Clinical trial results:
Randomized, Double-Blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Placebo for Women in Spontaneous Preterm Labor

Summary

EudraCT number	2014-003326-41
Trial protocol	GB IT
Global end of trial date	24 July 2017

Results information

Result version number	v5 (current)
This version publication date	30 August 2018
First version publication date	07 February 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	200719

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, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000162-PIP20-16
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of retosiban to prolong pregnancy and improve neonatal outcomes compared with placebo

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	25
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

NEWBORN-1 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to investigate efficacy and safety of retosiban in female participants aged 12 to 45 years with an uncomplicated singleton pregnancy in preterm labor with intact membranes between 24 0/7 and 33 6/7 weeks gestation. The study was conducted in 3 countries.

Pre-assignment

Screening details:

Twenty-five participants were randomly assigned to study treatments: 12 participants to retosiban intravenous (IV) infusion and 13 participants to matched placebo IV infusion. Two participants randomized to retosiban arm did not receive study treatment. The study was terminated early due to feasibility of recruiting the study in a timely manner.

Pre-assignment period milestones

Number of subjects started	25
Intermediate milestone: Number of subjects	Treated: 23
Number of subjects completed	23

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized and not treated: 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo was 0.9 percent sodium chloride infusion matched for retosiban volume, 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 type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was 0.9 percent sodium chloride matched for retosiban loading dose and continuous infusion rates.

Arm title	Retosiban

Arm description:

Participants were administered 6 milligram (mg) IV loading dose of retosiban over 5 minutes followed by a 6 milligram per hour (mg/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/hour continuous infusion for remainder of 48-hour treatment period.

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 a clear, colorless solution for infusion at a concentration of 15 milligrams per milliliter (mg/mL).

Number of subjects in period 1[1]	Placebo	Retosiban
Started	13	10
Completed	13	10

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two participants randomized to retosiban arm did not receive study treatment due to labor progression.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo was 0.9 percent sodium chloride infusion matched for retosiban volume, 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.	
Reporting group title	Retosiban
Reporting group description:	
Participants were administered 6 milligram (mg) IV loading dose of retosiban over 5 minutes followed by a 6 milligram per hour (mg/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/hour continuous infusion for remainder of 48-hour treatment period.	

Reporting group values	Placebo	Retosiban	Total
Number of subjects	13	10	23
Age categorical Units: Subjects			
Age continuous			
Maternal intent-to-treat (ITT) Population comprised of all mothers randomly assigned to treatment who have been exposed to study treatment irrespective of their compliance to the planned course of treatment.			
Units: years			
arithmetic mean	26.5	27.7	
standard deviation	± 6.78	± 6.73	-
Gender categorical			
Maternal intent-to-treat (ITT) Population comprised of all mothers randomly assigned to treatment who have been exposed to study treatment irrespective of their compliance to the planned course of treatment.			
Units: Subjects			
Female	13	10	23
Male	0	0	0
Race/Ethnicity, Customized			
Maternal intent-to-treat (ITT) Population comprised of all mothers randomly assigned to treatment who have been exposed to study treatment irrespective of their compliance to the planned course of treatment.			
Units: Subjects			
African American/African Heritage	2	2	4
Asian-Central/South Asian Heritage	0	1	1
Asian-East Asian Heritage	1	0	1
Asian-Japanese Heritage	4	2	6
Asian-South East Asian Heritage	1	0	1
White-White/Caucasian/European Heritage	5	5	10

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo was 0.9 percent sodium chloride infusion matched for retosiban volume, 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.

Reporting group title	Retosiban

Reporting group description:

Participants were administered 6 milligram (mg) IV loading dose of retosiban over 5 minutes followed by a 6 milligram per hour (mg/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/hour continuous infusion for remainder of 48-hour treatment period.

Subject analysis set title	Retosiban
Subject analysis set type	Safety analysis set

Subject analysis set description:

Participants were administered 6 milligram (mg) IV loading dose of retosiban over 5 minutes followed by a 6 milligram per hour (mg/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/hour continuous infusion for remainder of 48-hour treatment period. Data is a combined data set. Data is presented for 10 participants from retosiban arm of study 200719 (NCT02377466) and 43 participants from retosiban arm of study 200721 (NCT02292771). Actual total participants analyzed is 53 and not 10. 53 cannot be added due to system limitation.

Primary: Time to delivery or treatment failure, whichever occurs first

End point title	Time to delivery or treatment failure, whichever occurs first[1]

Time to delivery or treatment failure is the number of days from the first dose of study treatment until delivery or treatment failure whichever occurs first. Treatment failure is defined as the administration of any putative tocolytic medication for treatment of preterm labor or as prophylaxis of preterm labor. Maternal intent-to-treat (ITT) Population comprised of all mothers randomly assigned to treatment who have been exposed to study treatment irrespective of their compliance to the planned course of treatment. The mean number of days to delivery or treatment failure along with standard deviation has been presented. Statistical analysis was not performed due to early termination of the study.

Participants were not delivered or had early failure at the end of the study, so the number of days from the first treatment

Statistical analyses

No statistical analyses for this end point

Primary: Number of neonates with any diagnosis from the neonatal morbidity and mortality composite component

End point title	Number of neonates with any diagnosis from the neonatal morbidity and mortality composite component[4]

End point description:

The neonatal composite endpoint was determined from review of medical records and included the following components: fetal or neonatal death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia, necrotizing enterocolitis or isolated perforation, sepsis based on positive blood culture with clinical features of sepsis, meningitis based on positive results for cerebrospinal fluid culture performed as part of infection workup, retinopathy of prematurity, intraventricular hemorrhage (IVH), white matter injury and cerebellar hemorrhage. Neonates with any of the composite component has been presented. Statistical analysis was not performed due to early termination of study and resultant small sample size. Neonatal ITT Population comprised of all neonates whose mothers were the randomized participants who have been exposed to study treatment, that is, mothers from the ITT Population.

End point type	Primary

End point timeframe:

Up to 28 days after the estimated date of delivery (EDD) of 40 0/7 weeks

Notes:

[4] - 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: Statistical analysis was not performed due to early termination of the study and resultant small sample size.

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[5]	10[6]		
Units: Participants				
Participants	4	2		

Notes:

[5] - Neonatal ITT Population

[6] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to delivery

End point title	Time to delivery

End point description:

The time to delivery was calculated as the days between the delivery and start time of the study treatment infusion using the formula: Time to delivery (days) = (date and time of delivery minus date and time of start of infusion) divided by (24 multiplied by 60). The mean number of days to delivery along with standard deviation has been presented.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[7]	10[8]		
Units: Days				
arithmetic mean (standard deviation)				
Days	16.32 (± 18.595)	19.18 (± 22.770)		

Notes:

[7] - Maternal ITT Population

[8] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births prior to 37 0/7 Weeks gestation

End point title	Number of participants with births prior to 37 0/7 Weeks gestation

End point description:

Gestational age at birth (weeks) is defined as the gestational age when the baby is born. Participants were considered to have delivered prior to 37 0/7 weeks, that is preterm, if the gestational age at birth is less than 37 0/7 weeks. The number of participants who delivered prior to 37 0/7 weeks gestation has been presented.

End point type	Secondary

End point timeframe:

Up to 13 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[9]	10[10]		
Units: Participants				
Participants	9	8		

Notes:

[9] - Maternal ITT Population

[10] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births at term

End point title	Number of participants with births at term

End point description:

Participants were considered to have delivered at term if the gestational age was >=37 0/7. The number of participants who delivered at term, that is, 37 0/7 to 41 6/7 weeks gestation has been presented.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[11]	10[12]		
Units: Participants				
Participants	4	2		

Notes:

[11] - Maternal ITT Population

[12] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Length of neonatal hospital stay

End point title	Length of neonatal hospital stay

End point description:

The length of stay was collected from medical records and was calculated as the days between the delivery date and time and discharge date and time.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD of 40 0/7 weeks gestation

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[13]	10[14]		
Units: Days				
arithmetic mean (standard deviation)				
Days	37.50 (± 34.537)	26.05 (± 32.689)		

Notes:

[13] - Neonatal ITT Population

[14] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births prior to 35 0/7 weeks gestation

End point title	Number of participants with births prior to 35 0/7 weeks gestation

End point description:

The number of participants who delivered prior to 35 0/7 weeks gestation has been presented.

End point type	Secondary

End point timeframe:

Up to 11 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[15]	10[16]		
Units: Participants				
Participants	9	7		

Notes:

[15] - Maternal ITT Population

[16] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births prior to 32 0/7 weeks gestation

End point title	Number of participants with births prior to 32 0/7 weeks gestation

End point description:

The number of participants who delivered prior to 32 0/7 weeks gestation has been presented. Only those maternal participants who were randomized prior to 32 0/7 week's gestation and delivered were included.

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[17]	6[18]		
Units: Participants				
Participants	6	2		

Notes:

[17] - Maternal ITT Population

[18] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births prior to 28 0/7 weeks gestation

End point title	Number of participants with births prior to 28 0/7 weeks gestation

End point description:

The number of participants who delivered prior to 28 0/7 weeks gestation has been presented. Only those maternal participants who were randomized prior to 28 0/7 week's gestation and delivered were included.

End point type	Secondary

End point timeframe:

Up to 4 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[19]	2[20]		
Units: Participants				
Participants	2	1		

Notes:

[19] - Maternal ITT Population

[20] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births at <=7 days from the first study treatment

End point title	Number of participants with births at <=7 days from the first study treatment

End point description:

The number of participants who delivered in less than or equal to 7 days from first dose of study treatment has been presented.

End point type	Secondary

End point timeframe:

Up to 7 days

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[21]	10[22]		
Units: Participants				
Participants	5	5		

Notes:

[21] - Maternal ITT Population

[22] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births at <=48 hours from the first study treatment

End point title	Number of participants with births at <=48 hours from the first study treatment

End point description:

The number of participants who delivered in less than or equal to 48 hours from first dose of study treatment has been presented.

End point type	Secondary

End point timeframe:

Up to 48 hours

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[23]	10[24]		
Units: Participants				
Participants	3	3		

Notes:

[23] - Maternal ITT Population

[24] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with births at <=24 hours from the first study treatment

End point title	Number of participants with births at <=24 hours from the first study treatment

End point description:

The number of participants who delivered in less than or equal to 24 hours from first dose of study treatment has been presented.

End point type	Secondary

End point timeframe:

Up to 24 hours

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[25]	10[26]		
Units: Participants				
Participants	3	1		

Notes:

[25] - Maternal ITT Population

[26] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonates with any of the co-primary composite neonatal morbidity and mortality, excluding RDS

End point title	Number of neonates with any of the co-primary composite neonatal morbidity and mortality, excluding RDS

End point description:

The neonatal composite endpoint was determined from review of medical records and included the following components: fetal or neonatal death, RDS, bronchopulmonary dysplasia, necrotizing enterocolitis or isolated perforation, sepsis based on positive blood culture with clinical features of

sepsis, meningitis based on positive results for cerebrospinal fluid culture performed as part of infection workup, retinopathy of prematurity, IVH, white matter injury and cerebellar hemorrhage. The number of neonates with any co-primary composite neonatal morbidity and mortality component, excluding RDS has been presented.

End point type	Secondary

End point timeframe:

Up to 28 weeks after EDD (40 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[27]	10[28]		
Units: Participants				
Participants	3	0		

Notes:

[27] - Neonatal ITT Population

[28] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonates with each individual component of the composite neonatal morbidity and mortality

End point title	Number of neonates with each individual component of the composite neonatal morbidity and mortality

End point description:

The neonatal composite endpoint was determined from review of medical records and included the following components: fetal or neonatal death, RDS, bronchopulmonary dysplasia, necrotizing enterocolitis or isolated perforation, sepsis based on positive blood culture with clinical features of sepsis, meningitis based on positive results for cerebrospinal fluid culture performed as part of infection workup, retinopathy of prematurity, IVH, white matter injury and cerebellar hemorrhage. The number of neonates with each individual component of the composite component has been presented.

End point type	Secondary

End point timeframe:

Up to 28 days after the EDD of 40 0/7 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[29]	10[30]		
Units: Participants				
Fetal Death	0	0		
Neonatal Death	0	0		
RDS	3	2		
Bronchopulmonary dysplasia	3	0		
Necrotizing enterocolitis or Isolated Perforation	0	0		
Sepsis	0	0		
Meningitis	0	0		
Retinopathy of prematurity	0	0		

IVH	0	0		
White Matter Injury	0	0		
Cerebellar Hemorrhage	0	0		

Notes:

[29] - Neonatal ITT Population

[30] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonatal participants with admission to a particular hospital unit

End point title	Number of neonatal participants with admission to a particular hospital unit

End point description:

Neonatal healthcare resource utilization was collected from review of medical records. The number of neonatal participants who were admitted to a particular hospital unit that is, level III (or higher) intensive neonatal care (NICU), Intensive care unit (ICU), general ward, Level I - Basic Neonatal care, Well born nursery (SCBU) and Level II-Special Care Newborn nursery high dependency (NHDU) has been summarized. Neonatal Safety Population consisted of neonates whose mothers received study treatment.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[31]	10[32]		
Units: Participants				
Level III (or higher) NICU	5	6		
Intensive care unit	0	1		
General Ward	2	2		
Level II-Special Care NHDU	0	1		
Missing	1	0		
Multiple ward type	5	0		

Notes:

[31] - Neonatal Safety Population

[32] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay in specialized care unit

End point title	Length of stay in specialized care unit

End point description:

Neonatal healthcare resource utilization was collected from review of medical records. The length of stay in a specialized care unit (NICU or ICU) has been presented for neonatal participants with admission to ICU or NICU.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[33]	7[34]		
Units: Days				
arithmetic mean (standard deviation)				
Days	40.34 (± 35.475)	35.60 (± 35.308)		

Notes:

[33] - Neonatal Safety Population

[34] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of newborn participants with hospital readmission

End point title	Number of newborn participants with hospital readmission

End point description:

Newborn hospital readmission following hospitalization for birth was collected from the newborn's medical records. The number of newborn participants who had readmission to hospital is presented.

End point type	Secondary

End point timeframe:

Up to 28 days of EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[35]	10[36]		
Units: Participants				
Participants	0	0		

Notes:

[35] - Neonatal Safety Population

[36] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay following readmission to hospital

End point title	Length of stay following readmission to hospital

End point description:

Newborn hospital readmission following hospitalization for birth was collected from the newborn's medical records. Length of stay in hospital following readmission is presented for neonates.

End point type	Secondary

End point timeframe:

Up to 28 days after EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[37]	10[38]		
Units: Days				
median (full range (min-max))				
Days	0 (0 to 0)	0 (0 to 0)		

Notes:

[37] - Neonatal Safety Population

[38] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ambulatory surgery

End point title	Number of participants with ambulatory surgery

End point description:

Information regarding participants who had ambulatory surgery was collected from the newborn medical records. The number of neonatal participants with ambulatory surgery is presented.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[39]	10[40]		
Units: Participants				
Participants	0	0		

Notes:

[39] - Neonatal Safety Population

[40] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Treatment failure is defined as the administration of any putative tocolytic medication for treatment of preterm labor or as prophylaxis of preterm labor. Time to treatment failure is the number of days from the first dose of study treatment until treatment failure. The mean number of days to delivery or treatment failure along with standard deviation has been presented. Only those maternal participants with treatment failure were included in the analysis. 99999 indicates standard deviation could not be

calculated as only one participant was analyzed.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[41]	1[42]		
Units: Days				
arithmetic mean (standard deviation)				
Days	1.141 (± 1.4307)	0.899 (± 99999)		

Notes:

[41] - Maternal ITT Population

[42] - Maternal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who received any putative tocolytic

End point title	Number of participants who received any putative tocolytic

End point description:

A putative tocolytic medication was the medication administered for active preterm labor or as prevention of preterm labor and included calcium channel blockers, nonsteroidal anti-inflammatory drugs, or beta agonists, or magnesium sulfate doses that exceeded prespecified IV loading doses, infusion rates, or total duration of administration.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[43]	10[44]		
Units: Participants				
Participants	4	1		

Notes:

[43] - Maternal Safety Population

[44] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with subsequent preterm labor

End point title	Number of participants with subsequent preterm labor

End point description:

The participants who had not delivered after 48 hours post-infusion were contacted to determine if they had delivered or experienced any subsequent episodes of preterm labor. A subsequent episode of preterm labor was only recorded if the participant reported it to the Principal Investigator during one of the telephone follow-up calls but did not then go on to immediately deliver. However, if labor started and led to immediate delivery, then the only data collected would be the pre-specified delivery data and thus would not be counted as a subsequent episode of preterm labor. The number of participants who had a subsequent episode of preterm labor after administration of the study treatment has been presented. Maternal Safety Population comprised of all maternal participants randomly assigned to treatment who have been exposed to study treatment.

End point type	Secondary

End point timeframe:

Up to 11 weeks

End point values	Placebo	Retosiban		
		Reporting group		

Notes:

[47] - Maternal Safety Population

[48] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP)

End point title	Change from Baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP)

End point description:

SBP and DBP were measured with participants in a semirecumbent or seated position. SBP and DBP were measured during inpatient randomized treatment phase (15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the end of the infusion) and at the post-infusion assessment. Baseline is the last available assessment prior to first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 9 days

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[49]	10[50]		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
DBP; Day 1: 15 to 30 minutes; n=13, 10	-3.2 (± 10.64)	-6.8 (± 8.22)		
DBP; Day 1: 4 to 8 hours; n=11, 10	-9.0 (± 11.31)	-7.0 (± 10.14)		
DBP; Day 1: 20 to 24 hours; n=10, 8	-13.1 (± 11.05)	-6.5 (± 8.65)		
DBP; Day 2; n=11, 7	-10.2 (± 11.07)	-4.0 (± 6.66)		
DBP; Post infusion assessment; n=9, 5	-6.6 (± 12.69)	-2.8 (± 4.76)		
SBP; Day 1: 15 to 30 minutes; n=13, 10	-0.8 (± 7.50)	-3.1 (± 10.40)		
SBP; Day 1: 4 to 8 hours; n=11, 10	-7.1 (± 13.09)	-1.3 (± 9.06)		
SBP; Day 1: 20 to 24 hours; n=10, 8	-5.2 (± 12.47)	2.6 (± 14.56)		
SBP; Day 2; n=11, 7	-4.5 (± 11.86)	0.7 (± 10.21)		
SBP; Post infusion assessment; n=9, 5	-9.6 (± 8.69)	-7.0 (± 8.22)		

Notes:

[49] - Maternal Safety Population

[50] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate

End point title	Change from Baseline in heart rate

End point description:

Heart rate was measured with the participants in a semirecumbent or seated position. Heart rate was measured during inpatient randomized treatment phase (15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the end of the infusion) and at the post-infusion assessment. Baseline is the last available assessment prior to first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 9 days

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[51]	10[52]		
Units: beats per minute				
arithmetic mean (standard deviation)				
Day 1: 15 to 30 minutes; n=13, 10	-5.1 (± 12.37)	1.4 (± 8.13)		
Day 1: 4 to 8 hours; n=11, 10	-2.6 (± 10.82)	-0.3 (± 8.12)		
Day 1: 20 to 24 hours; n=9, 8	-4.1 (± 10.61)	6.5 (± 21.64)		
Day 2; n=11, 7	-5.6 (± 15.73)	-3.6 (± 13.91)		
Post infusion assessment; n=9, 5	-6.1 (± 17.80)	-3.8 (± 16.24)		

Notes:

[51] - Maternal Safety Population

[52] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in temperature

End point title	Change from Baseline in temperature

End point description:

Temperature was measured with the participants in a semirecumbent or seated position. Temperature was measured during inpatient randomized treatment phase (15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the end of the infusion) and at the post-infusion assessment. Baseline is the last available assessment prior to first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[53]	10[54]		
Units: degree Celsius				
arithmetic mean (standard deviation)				
Day 1: 15 to 30 minutes; n=12, 9	-0.028 (± 0.4123)	-0.111 (± 0.1900)		
Day 1: 4 to 8 hours; n=11, 10	0.087 (± 0.3947)	-0.144 (± 0.3594)		
Day 1: 20 to 24 hours; n=10, 8	0.104 (± 0.5413)	-0.043 (± 0.3174)		
Day 2; n=11, 7	0.105 (± 0.5067)	0.051 (± 0.2062)		
Post-infusion assessment; n=9, 5	-0.136 (± 0.4668)	0.072 (± 0.2234)		

Notes:

[53] - Maternal Safety Population

[54] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in respiratory rate

End point title	Change from Baseline in respiratory rate

End point description:

Respiratory rate was measured with the participants in a semirecumbent or seated position. Respiratory rate was measured during inpatient randomized treatment phase (15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the end of the infusion) and at the post-infusion assessment. Baseline is the last available assessment prior to first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[55]	10[56]		
Units: breaths per minute				
arithmetic mean (standard deviation)				
Day 1: 15 to 30 minutes; n=11, 8	0.5 (± 3.45)	-1.1 (± 2.90)		
Day 1: 4 to 8 hours; n=8, 9	1.1 (± 3.83)	-1.1 (± 2.15)		
Day 1: 20 to 24 hours; n=9, 7	0.3 (± 2.35)	-1.0 (± 2.77)		
Day 2; n=10, 6	0.9 (± 4.01)	0.0 (± 1.79)		
Post infusion assessment; n=8, 4	0.4 (± 4.27)	0.5 (± 2.52)		

Notes:

[55] - Maternal Safety Population

[56] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit levels

End point title	Change from Baseline in hematocrit levels

End point description:

Blood samples were collected for the evaluation of change in hematocrit levels from Baseline. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[57]	10[58]		
Units: Proportion of red blood cells in blood				
arithmetic mean (standard deviation)				
Day 2; n=9, 3	-0.0343 (± 0.04324)	-0.0470 (± 0.02773)		
Post-infusion assessment; n=7, 5	-0.0090 (± 0.02900)	-0.0078 (± 0.02928)		

Notes:

[57] - Maternal Safety Population

[58] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin and Erythrocyte Mean Corpuscular hemoglobin Concentration (MCHC)

End point title	Change from Baseline in hemoglobin and Erythrocyte Mean Corpuscular hemoglobin Concentration (MCHC)

End point description:

Blood samples were collected for the evaluation of change in hemoglobin levels and MCHC from Baseline. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[59]	10[60]		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin; Day 2; n=9, 3	-11.2 (± 11.20)	-15.7 (± 6.66)		
Hemoglobin; Post-infusion assessment; n=7, 5	-1.0 (± 9.76)	-1.6 (± 8.79)		
MCHC; Day 2; n=9, 3	-0.3 (± 17.27)	-2.7 (± 10.97)		
MCHC; Post-infusion assessment; n=7, 5	5.0 (± 8.52)	2.6 (± 5.41)		

Notes:

[59] - Maternal Safety Population

[60] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets and leukocytes count

End point title	Change from Baseline in basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets and leukocytes count

End point description:

Blood samples were collected for the evaluation of change in basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets and leukocytes count. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[61]	10[62]		
Units: Billion cells per liter (L)				
arithmetic mean (standard deviation)				
Basophils; Day 2; n=9, 3	-0.003 (± 0.0132)	0.000 (± 0.0458)		
Basophils; post-infusion assessment; n=7, 5	0.003 (± 0.0160)	0.058 (± 0.1103)		
Eosinophils; Day 2; n=9, 3	0.004 (± 0.0938)	-0.063 (± 0.0513)		
Eosinophils; post-infusion assessment; 7, 5	0.064 (± 0.1321)	-0.044 (± 0.1328)		
Lymphocytes; Day 2; n=9, 3	0.323 (± 0.6117)	0.877 (± 0.1914)		
Lymphocytes; post-infusion assessment; 7, 5	0.253 (± 1.0579)	1.006 (± 1.4223)		
Monocytes; Day 2; n=9, 3	0.008 (± 0.3389)	0.147 (± 0.5773)		

Monocytes; post-infusion assessment; 7, 5	0.141 (± 0.2535)	-0.082 (± 0.4135)		
Neutrophils; Day 2; n=9, 3	2.744 (± 6.9362)	-1.813 (± 3.3001)		
Neutrophils; post-infusion assessment; 7, 5	-2.246 (± 6.0323)	-1.910 (± 2.8497)		
Platelets; Day 2; n=8, 3	-6.4 (± 47.42)	-24.7 (± 32.58)		
Platelets; post-infusion assessment; 6, 5	-15.7 (± 60.48)	-5.4 (± 33.34)		
Leukocytes; Day 2; n=9, 3	3.10 (± 6.720)	-0.87 (± 2.914)		
Leukocytes; post-infusion assessment; 7, 5	-1.76 (± 5.358)	-0.98 (± 2.645)		

Notes:

[61] - Maternal Safety Population

[62] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocyte mean corpuscular volume (MCV) and mean platelet volume (MPV)

End point title	Change from Baseline in erythrocyte mean corpuscular volume (MCV) and mean platelet volume (MPV)

End point description:

Blood samples were collected for the evaluation of change in MCV and MPV from Baseline. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[63]	10[64]		
Units: femtoliter (fL)				
arithmetic mean (standard deviation)				
MCV; Day 2; n=9, 3	0.4 (± 2.79)	1.7 (± 4.73)		
MCV; Post-infusion assessment; n=7, 5	-1.9 (± 1.77)	-0.8 (± 1.30)		
MPV; Day 2; n=8, 3	-0.11 (± 0.455)	-0.20 (± 0.436)		
MPV; Post-infusion assessment; n=6, 5	0.02 (± 0.833)	0.48 (± 1.026)		

Notes:

[63] - Maternal Safety Population

[64] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocyte level

End point title	Change from Baseline in erythrocyte level

End point description:

Blood samples were collected for the evaluation of change in erythrocyte level from Baseline. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[65]	10[66]		
Units: Trillion cells per liter				
arithmetic mean (standard deviation)				
Day 2; n=9, 3	-0.39 (± 0.423)	-0.53 (± 0.153)		
Post-infusion assessment; n=7, 5	-0.03 (± 0.330)	-0.02 (± 0.303)		

Notes:

[65] - Maternal Safety Population

[66] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and lactate dehydrogenase (LDH) levels

End point title	Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and lactate dehydrogenase (LDH) levels

End point description:

Blood samples were collected for the evaluation of change in ALP, ALT, AST, GGT and LDH from Baseline. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[67]	10[68]		
Units: International Units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALP; Day 2; n=9, 5	-17.3 (± 17.56)	-11.8 (± 6.46)		
ALP; post-infusion assessment; n=8, 6	6.6 (± 31.14)	-2.8 (± 14.08)		
ALT; Day 2; n=9, 5	3.9 (± 19.60)	4.4 (± 10.64)		
ALT; post-infusion assessment; n=8, 6	-8.8 (± 20.04)	2.5 (± 5.50)		
AST; Day 2; n=9, 5	4.4 (± 15.69)	2.0 (± 10.20)		
AST; post-infusion assessment; n=8, 6	-9.1 (± 13.05)	-0.5 (± 7.45)		
GGT; Day 2; n=9, 5	-0.9 (± 1.69)	-0.8 (± 1.30)		
GGT; post-infusion assessment; n=7, 5	4.4 (± 2.57)	0.4 (± 2.07)		
LDH; Day 2; n=9, 5	-6.7 (± 33.51)	-26.4 (± 31.86)		
LDH; post-infusion assessment; n=7, 5	-8.1 (± 21.93)	-7.6 (± 31.76)		

Notes:

[67] - Maternal Safety Population

[68] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and protein levels

End point title	Change from Baseline in albumin and protein levels

End point description:

Blood samples were collected for the evaluation of change in albumin and protein levels from Baseline. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[69]	10[70]		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Albumin; Day 2; n=9, 5	-3.4 (± 3.68)	-2.6 (± 1.67)		
Albumin; post-infusion assessment; n=7, 5	-1.3 (± 2.21)	-1.0 (± 2.35)		
Protein; Day 2; n=9, 5	-5.8 (± 6.26)	-5.4 (± 3.58)		
Protein; post-infusion assessment; n=7, 5	-2.4 (± 3.41)	-1.8 (± 5.02)		

Notes:

[69] - Maternal Safety Population

[70] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in anion gap, calcium, chloride, carbon dioxide, glucose, potassium, magnesium, phosphate and sodium level

End point title	Change from Baseline in anion gap, calcium, chloride, carbon dioxide, glucose, potassium, magnesium, phosphate and sodium level

End point description:

Blood samples were collected for the evaluation of change from Baseline in levels of anion gap, calcium, chloride, carbon dioxide, glucose, potassium, magnesium, phosphate, and sodium. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[71]	10[72]		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Anion Gap; Day 2; n=8, 4	0.0 (± 4.72)	0.0 (± 1.83)		
Anion Gap; post-infusion assessment; n=7, 4	-1.6 (± 5.26)	0.3 (± 2.22)		
Calcium; Day 2; n=9, 5	-0.042 (± 0.2833)	-0.040 (± 0.1208)		
Calcium; post-infusion assessment; n=7, 5	0.091 (± 0.2052)	-0.048 (± 0.1016)		
Chloride; Day 2; n=9, 5	1.0 (± 5.17)	1.8 (± 2.17)		
Chloride; post-infusion assessment; n=7, 5	-0.7 (± 3.35)	-0.6 (± 2.30)		
Carbon Dioxide; Day 2; n=9, 5	-0.2 (± 3.63)	0.0 (± 2.35)		
Carbon Dioxide; post-infusion assessment; n=7, 5	2.3 (± 3.64)	-0.2 (± 2.77)		
Glucose; Day 2; n=9, 5	1.47 (± 1.639)	1.98 (± 1.064)		
Glucose; post-infusion assessment; n=7, 5	0.11 (± 2.497)	0.28 (± 2.109)		
Potassium; Day 2; n=9, 5	-0.16 (± 0.394)	0.10 (± 0.515)		
Potassium; post-infusion assessment; n=7, 5	-0.16 (± 0.237)	0.10 (± 0.283)		
Magnesium; Day 2; n=9, 5	-0.411 (± 0.9476)	-0.236 (± 0.5428)		
Magnesium; post-infusion assessment; n=7, 5	-0.449 (± 0.6473)	-0.056 (± 0.6199)		
Phosphate; Day 2; n=9, 5	-0.133 (± 0.1768)	0.030 (± 0.2928)		
Phosphate; post-infusion assessment; n=7, 5	0.021 (± 0.2018)	0.110 (± 0.1557)		
Sodium; Day 2; n=9, 5	1.4 (± 2.96)	0.4 (± 1.67)		
Sodium; post-infusion assessment; n=7, 5	0.1 (± 2.12)	-0.8 (± 1.64)		

Notes:

[71] - Maternal Safety Population

[72] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in direct bilirubin, bilirubin, indirect bilirubin, creatinine and urate levels

End point title	Change from Baseline in direct bilirubin, bilirubin, indirect bilirubin, creatinine and urate levels

End point description:

Blood samples were collected for the evaluation of change from Baseline in levels of direct bilirubin, bilirubin, indirect bilirubin, creatinine and urate. Baseline is defined as the last available assessment prior to the first dose of study treatment. Change from Baseline is the post-dose visit value minus Baseline. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline and up to 1 week

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[73]	10[74]		
Units: micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Direct Bilirubin; Day 2; n=9, 5	0.0 (± 1.00)	-0.4 (± 0.89)		
Direct Bilirubin; post-infusion assessment; n=7, 5	0.3 (± 0.76)	-0.4 (± 0.89)		
Bilirubin; Day 2; n=9, 5	-0.7 (± 1.41)	-0.8 (± 1.10)		
Bilirubin; post-infusion assessment; n=8, 6	-0.3 (± 1.28)	-2.0 (± 3.10)		
Indirect Bilirubin; Day 2; n=9, 5	-0.7 (± 1.41)	-0.4 (± 1.67)		
Indirect Bilirubin; post-infusion assessment;n=7,5	-0.6 (± 1.51)	-1.6 (± 3.85)		
Creatinine; Day 2; n=6, 3	-0.33 (± 6.812)	2.37 (± 1.429)		
Creatinine; post-infusion assessment; n=6, 3	1.92 (± 5.075)	-0.33 (± 2.695)		
Urate; Day 2; n=9, 5	1.1 (± 24.72)	-22.0 (± 13.04)		
Urate; post-infusion assessment; n=7, 5	12.9 (± 24.30)	-2.0 (± 40.25)		

Notes:

[73] - Maternal Safety Population

[74] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who discontinued study treatment due to clinical and laboratory toxicities

End point title	Number of participants who discontinued study treatment due to clinical and laboratory toxicities

End point description:

Number of maternal participants who discontinued study treatment due to clinical and laboratory toxicities is presented.

End point type	Secondary

End point timeframe:

Up to 48 hours post-infusion

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[75]	10[76]		
Units: Participants				
Participants	0	0		

Notes:

[75] - Maternal Safety Population

[76] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of maternal participants with a score of 12 or higher on the Edinburgh Postnatal Depression Scale (EPDS)

End point title	Number of maternal participants with a score of 12 or higher on the Edinburgh Postnatal Depression Scale (EPDS)

End point description:

The effect of preterm birth on maternal health status was assessed using the EPDS. The EPDS is a 10-item self-reported assessment of depression, validated for administration during both the antenatal and the post-natal periods. Items are rated on a 4-point variable Likert scale, ranging from 0 to 3. The total score was calculated by adding individual scores for each item and ranged from 0 to 30. A score of less than 8 indicates depression not likely; score of 9 to 11 indicates possible depression and a score of more than 12 indicates an increased probability of depression. Maternal participants were required to complete the EPDS at the maternal follow-up assessment 6 weeks post-delivery.

End point type	Secondary

End point timeframe:

Up to 6 weeks post delivery

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[77]	10[78]		
Units: Participants				
Participants	2	0		

Notes:

[77] - Maternal Safety Population

[78] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of maternal participants with AEs of special interest (AESI).

End point title	Number of maternal participants with AEs of special interest (AESI).

End point description:

Maternal AESI included: maternal death; chorioamnionitis and its complications (clinical chorioamnionitis, preterm premature rupture of membranes, endomyometritis, wound infection, pelvic abscess, bacteremia, septic shock, disseminated intravascular coagulation, and adult RDS); placental abruption; postpartum hemorrhage – postpartum hemorrhage and/or retained placenta and pulmonary edema. The number of participants with at least one AESI has been presented.

End point type	Secondary

End point timeframe:

Up to 6 weeks post-delivery

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[79]	10[80]		
Units: Participants				
Participants	0	1		

Notes:

[79] - Maternal Safety Population

[80] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of maternal participants with disease related AEs (DRE)

End point title	Number of maternal participants with disease related AEs (DRE)

End point description:

Maternal DREs included: signs and symptoms of labor discomfort (example, cramping, backache, muscle aches, nausea); subsequent episodes of preterm labor and hospitalization for delivery. The number of participants with at least one DRE has been presented.

End point type	Secondary

End point timeframe:

Up to 6 weeks post-delivery

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[81]	10[82]		
Units: Participants				
Participants	0	1		

Notes:

[81] - Maternal Safety Population

[82] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of fetal participants with AEs and SAEs prior to delivery

End point title	Number of fetal participants with AEs and SAEs prior to delivery

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; important medical events that may require medical or surgical intervention to prevent one of the other outcomes described before; is associated with liver injury and impaired liver function. Fetal AEs and SAEs included the adverse events that were experienced by the fetus prior to delivery. The number of participants who experienced at least one AE and one SAE has been presented.

End point type	Secondary

End point timeframe:

Up to 17 weeks post-infusion

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[83]	10[84]		
Units: Participants				
AE	3	5		
SAE	0	1		

Notes:

[83] - Maternal Safety Population

[84] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with fetal acidosis

End point title	Number of participants with fetal acidosis

End point description:

The number of participants with fetal acidosis is presented.

End point type	Secondary

End point timeframe:

Up to 16 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[85]	10[86]		
Units: Participants				
Participants	0	0		

Notes:

[85] - Maternal Safety Population

[86] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with fetal AESI

End point title	Number of participants with fetal AESI

End point description:

Fetal AESI included: intrauterine fetal demise; category II or III fetal heart rate tracing; and fetal inflammatory response syndrome characterized by cord blood interleukin-6 >11 picogram per milliliter (pg/mL), funisitis, or chorionic vasculitis. The number of participants who experienced at least one AESI has been presented.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[87]	10[88]		
Units: Participants				
Participants	3	5		

Notes:

[87] - Maternal Safety Population

[88] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal APGAR Scores

End point title	Neonatal APGAR Scores

End point description:

APGAR is a quick test to assess the health of new born children. The test is performed at 1 and 5 minutes after birth. APGAR scale is determined by evaluating the new born on five categories (appearance, pulse, grimace, activity and respiration) on a scale from zero to two, then summing up the five values obtained. APGAR score ranges from 0 to 10 where a score of 7 and above is normal. The mean and standard deviation of APGAR scores at one minute and at five minutes of birth has been presented.

End point type	Secondary

End point timeframe:

Up to 5 minutes after birth

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[89]	10[90]		
Units: Score on APGAR scale				
arithmetic mean (standard deviation)				
one minute at birth	7.3 (± 1.80)	7.5 (± 1.78)		
five minutes at birth	8.5 (± 1.05)	8.7 (± 1.06)		

Notes:

[89] - Neonatal ITT Population

[90] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Weight of neonates

End point title	Weight of neonates

End point description:

The weight of neonates was obtained from the neonate birth record. The mean weight of neonates and standard deviation has been presented.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[91]	10[92]		
Units: grams (g)				
arithmetic mean (standard deviation)				
grams (g)	2015.0 (± 805.67)	2121.2 (± 681.31)		

Notes:

[91] - Neonatal ITT Population

[92] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Head circumference of neonates

End point title	Head circumference of neonates

End point description:

The head circumference was determined from the neonate birth record.

End point type	Secondary

End point timeframe:

Up to 17 weeks

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[93]	10[94]		
Units: centimeters (cm)				
arithmetic mean (standard deviation)				
centimeters (cm)	29.57 (± 2.791)	30.13 (± 3.059)		

Notes:

[93] - Neonatal ITT Population

[94] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonatal participants with AEs and SAEs

End point title	Number of neonatal participants with AEs and SAEs

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; important medical events that may require medical or surgical intervention to prevent one of the other outcomes described before; is associated with liver injury and impaired liver function. The number of participants who experienced at least one AE and one SAE has been presented. Neonatal Safety Population consisted of neonates whose mothers received randomized treatment.

End point type	Secondary

End point timeframe:

Up to 28 days after the EDD of 40 weeks gestation

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[95]	10[96]		
Units: Participants				
AEs	8	7		
SAEs	3	5		

Notes:

[95] - Neonatal Safety Population

[96] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonatal participants with AESI

End point title	Number of neonatal participants with AESI

End point description:

Neonatal AESI included: Neonatal death; Asphyxia; Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis); RDS; Hypotension; IVH/periventricular leukomalacia; Bronchopulmonary dysplasia; Neonatal acidosis; Hyperbilirubinemia; Necrotizing enterocolitis; and Hypoxic ischemic encephalopathy. The number of neonatal participants who experienced at least one AESI has been presented.

End point type	Secondary

End point timeframe:

Up to 28 days after EDD of 40 weeks gestation

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[97]	10[98]		
Units: Participants				
Participants	8	5		

Notes:

[97] - Neonatal Safety Population

[98] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonatal participants with DRE

End point title	Number of neonatal participants with DRE

End point description:

The disease related neonatal events occurring in Infants born prior to 37 completed weeks included: apnea (severe), respiratory failure due to fatigue, hypoxia, or air leak from alveolar injury, patent ductus arteriosus, bradycardia, ventriculomegaly, cerebellar hemorrhage, hydrocephalus other than congenital, gastroesophageal reflux, aspiration pneumonia, anemia, retinopathy of prematurity (all stages), hearing disorder, temperature instability and hypoglycemia. The number of participants with at least one DRE has been presented.

End point type	Secondary

End point timeframe:

Up to 28 days after EDD of 40 weeks gestation

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[99]	10[100]		
Units: Participants				
Participants	4	2		

Notes:

[99] - Neonatal Safety Population

[100] - Neonatal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maternal length of stay in hospital

End point title	Maternal length of stay in hospital

End point description:

Details on maternal health care resource use (both for hospitalizations related to preterm labor not resulting in a delivery and hospitalizations related to preterm labor/normal labor resulting in a delivery) associated with an episode of preterm labor, preterm delivery and normal term delivery (>= 37 weeks gestation) were collected from review of medical records. Length of hospital stay associated with hospital admission for preterm labor and normal term labor/term delivery is presented. One participant in the retosiban arm did not have hospitalization data; hence, was excluded from the analysis at delivery. Only participants with data available at the specified time points were analyzed (indicated by n=X) in category titles. 99999 for dispersion indicates standard deviation could not be calculated as only one participant was analyzed. 99999 for retosiban arm indicates data was not available as the number of participants analyzed was zero.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[101]	10[102]		
Units: Days				
arithmetic mean (standard deviation)				
Preterm labor; n=1, 0	2.642 (± 99999)	99999 (± 99999)		
Preterm delivery; n=9, 7	10.177 (± 11.9312)	13.583 (± 20.7670)		
Normal term delivery; n=4, 2	3.719 (± 2.2309)	4.635 (± 2.7616)		

Notes:

[101] - Maternal Safety Population

[102] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hospital admissions related to preterm labor and preterm delivery

End point title	Number of participants with hospital admissions related to preterm labor and preterm delivery

End point description:

Maternal healthcare resource utilization associated with an episode of preterm labor and preterm delivery were collected from the review of medical records. One participant in the retosiban arm did not have hospitalization data; hence, was excluded from the analysis at delivery. The number of participants who had hospital admission for preterm labor and preterm delivery has been presented. Only those participants with data available at the specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Up to 28 days after EDD (40 0/7 weeks of gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[103]	10[104]		
Units: Participants				
Preterm labor; n=13, 10	1	0		
Preterm delivery; n=13, 9	9	7		

Notes:

[103] - Maternal Safety Population

[104] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants admitted to particular hospital unit

End point title	Number of participants admitted to particular hospital unit

End point description:

Maternal healthcare resource utilization associated with an episode of preterm labor, preterm delivery and normal term delivery were collected from the review of medical records. The number of participants who were admitted to a particular hospital unit has been presented.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[105]	10[106]		
Units: Participants				
General ward	9	2		
Private/Semi-private room	3	2		
Labor and delivery	2	3		
Labor and delivery to post-partum	0	1		
Post-partum	0	1		
Ward not specified	0	1		
Labor ward	0	1		
Antenatal ward	0	1		
Postnatal ward	0	1		

Notes:

[105] - Maternal Safety Population

[106] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with different modes of transportation to hospital

End point title	Number of participants with different modes of transportation to hospital

End point description:

The means by which the maternal participants were transported to the hospital i.e. ground ambulance/emergency vehicle (gr. amb/emer. veh), air ambulance, family member or other means were obtained from the review of medical records. The number of maternal participants with the corresponding mode of transportation is presented for preterm labor visit and delivery visit. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles). 99999 indicates data was not available as the number of participants analyzed is zero.

End point type	Secondary

End point timeframe:

Up to 28 days post EDD (40 0/7 weeks gestation)

End point values	Placebo	Retosiban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[107]	10[108]		
Units: Participants				
Preterm labor; gr. amb/emer. veh; n=1, 0	0	99999		
Preterm labor; air ambulance; n=1, 0	0	99999		
Preterm labor; family member; n=1, 0	1	99999		
Preterm labor; other; n=1, 0	0	99999		
Delivery; gr. amb/emer. veh; n=5, 5	2	1		
Delivery; air ambulance; n=5, 5	0	0		
Delivery; family member; n=5, 5	3	3		
Delivery; other; n=5, 5	0	1		
Preterm labor;<24 hour stay;gr. amb/emer.veh;n=1,0	0	99999		
Preterm labor; <24 hour stay;air ambulance; n=1, 0	0	99999		
Preterm labor; <24 hour stay;family member; n=1, 0	1	99999		
Preterm labor; <24 hour stay;other; n=1, 0	0	99999		

Notes:

[107] - Maternal Safety Population

[108] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Retosiban clearance

End point title	Retosiban clearance

End point description:

Maternal blood samples were collected at the indicated time points for pharmacokinetic analysis. Data is a combined data set. Data is presented for 10 participants from retosiban arm of study 200719 (NCT02377466) and 43 participants from retosiban arm of study 200721 (NCT02292771).

End point type	Secondary

End point timeframe:

Day 1 (2 to 4 hours, 10 to 14 hours) and Day 2 (22 to 26 hours, and 48 to 54 hours) post-infusion

End point values	Retosiban			
Subject group type	Subject analysis set			
Number of subjects analysed	10[109]			
Units: Liters per hour				
geometric mean (geometric coefficient of variation)				
Liters per hour	83.4 (± 5.25)			

Notes:

[109] - Maternal Safety Population. Number of participants is combined from 2 studies. Actual value is 53.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution of retosiban

End point title	Volume of distribution of retosiban

End point description:

Maternal blood samples were collected at the indicated time points for pharmacokinetic analysis. Data is a combined data set. Data is presented for 10 participants from retosiban arm of study 200719 (NCT02377466) and 43 participants from retosiban arm of study 200721 (NCT02292771).

End point type	Secondary

End point timeframe:

Day 1 (2 to 4 hours, 10 to 14 hours) and Day 2 (22 to 26 hours, and 48 to 54 hours) post-infusion

End point values	Retosiban			
Subject group type	Subject analysis set			
Number of subjects analysed	10[110]			
Units: Liters				
geometric mean (geometric coefficient of variation)				
Liters	68.6 (± 109)			

Notes:

[110] - Maternal Safety Population. Number of participants is combined from 2 studies. Actual value is 53.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) will be collected from the start of study treatment and until the follow up contact (Up to 6 weeks after delivery).

Adverse event reporting additional description:

SAEs and AEs were analyzed in Maternal Safety Population and Neonatal Safety Population which comprised of mothers randomly assigned to treatment who were exposed to study treatment and neonates whose mothers received randomized treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo (Maternal)

Placebo was 0.9 percent sodium chlori' hers received r do verse e ve t (U

Serious adverse events	Placebo (Maternal)	Retosiban (Maternal)	Placebo (Fetal)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Ankyloglossia congenital			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital hypothyroidism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Umbilical cord prolapse			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meconium plug syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Selective eating disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Group B streptococcus neonatal sepsis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Retosiban (Fetal)	Placebo (Neonatal)	Retosiban (Neonatal)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	3 / 13 (23.08%)	5 / 10 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Ankyloglossia congenital			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (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
Pregnancy, puerperium and perinatal conditions			
Umbilical cord prolapse			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meconium plug syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (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
Respiratory, thoracic and mediastinal disorders			
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Selective eating disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (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			
Group B streptococcus neonatal sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
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 (Maternal)	Retosiban (Maternal)	Placebo (Fetal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	6 / 10 (60.00%)	3 / 13 (23.08%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pregnancy, puerperium and perinatal conditions			
Oligohydramnios			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Uterine contractions abnormal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Granuloma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Oedema genital			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Respiratory acidosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood calcium decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood glucose decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Liver function test increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Body temperature fluctuation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vaccination complication			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Foetal heart rate disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	14
Foetal heart rate deceleration abnormality			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Intraventricular haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Motor dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Abdominal discomfort			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Necrotising colitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cholestasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus generalised			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Intertrigo			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Seborrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Amniotic cavity infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bacterial vulvovaginitis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Kidney infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Feeding intolerance			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Retosiban (Fetal)	Placebo (Neonatal)	Retosiban (Neonatal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	8 / 13 (61.54%)	7 / 10 (70.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pregnancy, puerperium and perinatal conditions			
Oligohydramnios			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Uterine contractions abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Granuloma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 13 (23.08%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory acidosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tachypnoea			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood calcium decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood glucose decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Liver function test increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Body temperature fluctuation			

Motor dysfunction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Haematochezia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Necrotising colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vomiting			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	6 / 13 (46.15%)	4 / 10 (40.00%)
occurrences (all)	0	6	4
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Cholestasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Seborrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Amniotic cavity infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Bacterial vulvovaginitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Kidney infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Feeding intolerance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2015	Amendment No. 1
14 September 2015	Amendment No. 2 Revise the guidance for administration of antenatal corticosteroids to read as follows: If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Clarify in the Time and Events Table (footnote 15) that hematology, chemistry, and liver function tests will only be determined through a central laboratory at the screening, Day 2, and the face-to-face post-infusion assessment visits. Incorporate other administrative changes
19 April 2016	Amendment No.3 The following changes are reflected in the Country-Specific Protocol Amendment for Italy: Amend inclusion criteria 1 and 2 to specify that participants must be at least 18 years of age to participate in Study 200719. Text was revised throughout to reflect the change in the participant age criterion. Revise text throughout to indicate that participants recruited into Study 200719 in Italy must not be dosed with the investigational product until the results of their chemical parameters have been reviewed by the Investigator and no indicators of altered liver function (AST and ALT values and bilirubinemia) are apparent. This check for altered liver function must be carried out before the study drug is administered, i.e., before initiating randomized treatment.
20 June 2016	Amendment No.4
05 January 2017	Remove screening urine drug and alcohol tests. Remove requirement that investigator confirm uterine contraction rate and cervical dilation after randomization and just before study drug administration. Add that after randomization and prior to study drug administration investigators will re-assess that tocolytic therapy is still indicated, according to their medical discretion. Clarify that an abdominal ultrasound to assess fetal growth is needed at Screening unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization. Update the list of maternal disease-related events to clarify the reporting process for events of subsequent preterm labor and hospitalization for delivery that are not worse than expected. Add that the amniotic fluid index should be measured using the 4-quadrant method. Incorporate other administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported