



Clinical trial results:

Randomized, Double-blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Atosiban Therapy for Women in Spontaneous Preterm Labor

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2014-001826-13 |
| Trial protocol | BE GB SE ES DE IT FR |
| Global end of trial date | 25 August 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v4 (current) |
| This version publication date | 23 September 2018 |
| First version publication date | 10 March 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 200721 |
|-----------------------|--------|

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) | EMA-001359-PIP01-12 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 13 December 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 25 August 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 compared with atosiban

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 16 March 2015 |
| 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 | Belgium: 6 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Israel: 35 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Mexico: 24 |
| Country: Number of subjects enrolled | Korea, Republic of: 13 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Worldwide total number of subjects | 97 |
| EEA total number of subjects | 25 |

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) | 3 |
| Adults (18-64 years) | 94 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

ZINN was a randomized, double-blind, double-dummy multicenter study to compare efficacy and safety of retosiban versus atosiban 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.

Pre-assignment

Screening details:

From 330 planned participants 97 were randomized to receive either retosiban or atosiban intravenous (IV) infusion in a ratio of 1:1. The study was terminated early due to feasibility.

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 | 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).

| | |
|------------------|----------|
| Arm title | Atosiban |
|------------------|----------|

Arm description:

Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution.

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

Dosage and administration details:

Atosiban was available as a clear, colorless solution for injection at a concentration of 6.75 mg/0.9 mL and 7.5 mg/mL solution for infusion

| Number of subjects in period 1 | Retosiban | Atosiban |
|---------------------------------------|-----------|----------|
| Started | 47 | 50 |
| Completed | 43 | 48 |
| Not completed | 4 | 2 |
| Consent withdrawn by subject | 2 | 1 |
| Lost to follow-up | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| 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 title | Atosiban |
|-----------------------|----------|

Reporting group description:

Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution.

| Reporting group values | Retosiban | Atosiban | Total |
|------------------------------------|-----------|----------|-------|
| Number of subjects | 47 | 50 | 97 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|----|
| Age continuous Units: years arithmetic mean standard deviation | 27.7 ± 6.15 | 27.1 ± 5.66 | - |
| Gender categorical Units: Subjects | | | |
| Female | 47 | 50 | 97 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|-----------------|
| 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 title | Atosiban |
| Reporting group description: | |
| Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution. | |
| Subject analysis set title | Retosiban |
| Subject analysis set type | Safety analysis |
| 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). | |

Primary: Time to delivery from the start of investigational product (IP) administration

| | |
|--|--|
| End point title | Time to delivery from the start of investigational product (IP) administration |
| End point description: | |
| Time to delivery is the number of days from the first dose of study treatment until delivery. 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 adjusted mean number of days to delivery along with standard error has been presented. 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. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 17 weeks | |

| End point values | Retosiban | Atosiban | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[1] | 50 ^[2] | | |
| Units: Days | | | | |
| arithmetic mean (standard error) | | | | |
| Days | 32.51 (± 2.990) | 33.71 (± 2.531) | | |

Notes:

[1] - Maternal ITT Population

[2] - Maternal ITT Population

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Retosiban v Atosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3797 |
| Method | Finite mixture model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.879 |
| upper limit | 6.479 |

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 (GA) at birth (weeks) is defined as the GA when the baby is born. Participants were considered to have delivered prior to 37 0/7 weeks, that is preterm , if the GA 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. Logistic regression model was used to calculate p-values. | |
| End point type | Secondary |
| End point timeframe: Up to 13 weeks | |

| | | | | |
|-----------------------------|-------------------|-------------------|--|--|
| End point values | Retosiban | Atosiban | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[3] | 50 ^[4] | | |
| Units: Participants | | | | |
| Participants | 25 | 28 | | |

Notes:

[3] - Maternal ITT Population

[4] - Maternal ITT Population

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Atosiban v Retosiban |

| | |
|---|----------------------|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.952 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 2.18 |

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. Logistic regression model was used to calculate p-values. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 17 weeks | |

| End point values | Retosiban | Atosiban | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[5] | 50 ^[6] | | |
| Units: Participants | | | | |
| Participants | 21 | 22 | | |

Notes:

[5] - Maternal ITT Population

[6] - Maternal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Atosiban v Retosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.952 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 2.29 |

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. Log of length of stay was calculated as treatment plus GA at randomization plus established progesterone use based on Analysis of covariance (ANCOVA) model. The p-value was calculated using t-test method. 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 | Secondary |
| End point timeframe: | |
| Up to 28 days post estimated date of delivery (EDD) of 40 0/7 weeks gestation | |

| End point values | Retosiban | Atosiban | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[7] | 50 ^[8] | | |
| Units: Days | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Days | 4.98 (3.54 to 6.99) | 4.38 (3.15 to 6.09) | | |

Notes:

[7] - Neonatal ITT Population

[8] - Neonatal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Retosiban v Atosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5672 |
| Method | ANCOVA |
| Parameter estimate | Ratio |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.76 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.222 |

Secondary: Number of neonates with composite neonatal morbidity and mortality

| | |
|-----------------|--|
| End point title | Number of neonates with 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, Respiratory Distress Syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) 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 (ROP), Intraventricular Hemorrhage (IVH), white matter injury and cerebellar hemorrhage.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 weeks after EDD (40 weeks gestation)

| End point values | Retosiban | Atosiban | | |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[9] | 50 ^[10] | | |
| Units: Participants | | | | |
| Participants | 3 | 2 | | |

Notes:

[9] - Neonatal ITT Population

[10] - Neonatal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Retosiban v Atosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5066 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 11.71 |

Secondary: Number of neonates with any composite neonatal morbidity and mortality, excluding RDS

| | |
|--|---|
| End point title | Number of neonates with any 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, BPD, NEC 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, ROP, IVH, white matter injury and cerebellar hemorrhage. Number of neonates with any 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[11] | 50 ^[12] | | |
| Units: Participants | | | | |
| Participants | 0 | 1 | | |

Notes:

[11] - Neonatal ITT Population

[12] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Number of neonates with each individual component of 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, BPD, NEC 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, ROP, IVH, cerebellar hemorrhage and white matter injury included Periventricular Leukomalacia PVL), porencephalic cyst, and persistent ventriculomegaly. Number of neonates with with each individual component of the composite neonatal morbidity and mortality has been presented. | |
| End point type | Secondary |
| End point timeframe: Up to 28 weeks after EDD (40 weeks gestation) | |

| End point values | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[13] | 50 ^[14] | | |
| Units: Participants | | | | |
| Fetal death | 0 | 0 | | |
| Neonatal death | 0 | 1 | | |
| RDS | 3 | 1 | | |

| | | | | |
|-----------------------------|---|---|--|--|
| BPD | 0 | 0 | | |
| NEC or isolated perforation | 0 | 0 | | |
| Sepsis | 0 | 0 | | |
| Meningitis | 0 | 0 | | |
| ROP | 0 | 0 | | |
| IVH | 0 | 0 | | |
| PVL | 0 | 0 | | |
| Porencephalic Cyst | 0 | 0 | | |
| Persistent Ventriculomegaly | 0 | 0 | | |
| Cerebellar Hemorrhage | 0 | 0 | | |

Notes:

[13] - Neonatal ITT Population

[14] - Neonatal ITT 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: | |
| Length of neonatal stay in specialized care unit like Intensive Care Unit (ICU) or Neonatal Intensive Care Unit (NICU) are reported. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 28 days post EDD (40 0/7 weeks gestation) | |

| End point values | Retosiban | Atosiban | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[15] | 50 ^[16] | | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Days | 13.65 (3.5 to 57.5) | 12.49 (7.6 to 21.8) | | |

Notes:

[15] - Neonatal Safety Population

[16] - 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 obtained from the newborn's medical records. Only those participants with data available at the specified data points were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 28 days of EDD (40 0/7 weeks gestation) | |

| End point values | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[17] | 50 ^[18] | | |
| Units: Participants | | | | |
| Participants | 2 | 3 | | |

Notes:

[17] - Neonatal Safety Population

[18] - Neonatal Safety 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 | Retosiban | Atosiban | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 50 | | |
| Units: Participats | | | | |
| Participants | 0 | 0 | | |

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: 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[19] | 50 ^[20] | | |
| Units: Participants | | | | |
| Participants | 3 | 3 | | |

Notes:

[19] - Maternal ITT Population

[20] - Maternal ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|------------------------|
| Comparison groups | Atosiban v Retosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.779 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.12 |
| upper limit | 4.84 |

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:

Number of participants who delivered prior to 35 0/7 weeks gestation has been presented. Only those maternal participants who were randomized prior to 35 0/7 week's gestation and delivered were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 11 weeks

| End point values | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[21] | 50 ^[22] | | |
| Units: Participants | | | | |
| Participants | 14 | 14 | | |

Notes:

[21] - Maternal ITT Population

[22] - Maternal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Retosiban v Atosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6646 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 2.9 |

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

| | |
|---|--|
| End point title | Number of participants with births <=7 days from the first study treatment |
| End point description: | |
| 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 | Retosiban | Atosiban | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[23] | 50 ^[24] | | |
| Units: Participants | | | | |
| Participants | 10 | 7 | | |

Notes:

[23] - Maternal ITT Population

[24] - Maternal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Retosiban v Atosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1432 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 7.24 |

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

| | |
|------------------------|---|
| End point title | Number of participants with births <=48 hours from the first study treatment |
| End point description: | 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[25] | 50 ^[26] | | |
| Units: Participants | | | | |
| Participants | 6 | 6 | | |

Notes:

[25] - Maternal ITT Population

[26] - Maternal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Atosiban v Retosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.525 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 5.15 |

Secondary: Number of participants with births ≤ 24 hours from the first study treatment

| | |
|---|--|
| End point title | Number of participants with births ≤ 24 hours from the first study treatment |
| End point description: 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[27] | 50 ^[28] | | |
| Units: Participants | | | | |
| Participants | 3 | 6 | | |

Notes:

[27] - Maternal ITT Population

[28] - Maternal ITT Population

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Atosiban v Retosiban |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4682 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 2.58 |

Secondary: Number of maternal participants with non-serious adverse events (AEs) and serious adverse events (SAEs)

| | |
|---|---|
| End point title | Number of maternal participants with non-serious adverse events (AEs) and serious adverse events (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. Maternal Safety Population comprised of all mothers randomly assigned to treatment who have been exposed to study treatment. The number of maternal participants who experienced at least one non-serious AE and one SAE has been presented. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 6 weeks after delivery | |

| End point values | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[29] | 50 ^[30] | | |
| Units: Participants | | | | |
| Non-serious AE | 34 | 25 | | |
| SAE | 7 | 9 | | |

Notes:

[29] - Maternal Safety Population

[30] - 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) in maternal participants

| | |
|--|---|
| End point title | Change from Baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP) in maternal participants |
| End point description: | |
| 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 1 week | |

| End point values | Retosiban | Atosiban | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[31] | 50 ^[32] | | |
| Units: Millimeter of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| DBP; Day 1: 15 to 30 minutes, n=42,45 | -3.6 (± 10.96) | -0.7 (± 8.95) | | |
| DBP; Day 1: 4 to 8 hours, n=42,43 | -4.3 (± 11.07) | -3.7 (± 10.28) | | |
| DBP; Day 1: 20 to 24 hours, n=38,41 | -5.7 (± 9.31) | -4.1 (± 9.90) | | |
| DBP; Day 2, n=40,42 | -4.4 (± 9.57) | -2.6 (± 9.93) | | |
| DBP; Post-infusion assessment, n=35,41 | -1.6 (± 8.63) | 1.3 (± 10.12) | | |
| SBP; Day 1: 15 to 30 minutes, n=42,45 | -2.5 (± 9.53) | -0.4 (± 11.02) | | |
| SBP; Day 1: 4 to 8 hours, n=42,43 | -4.3 (± 9.05) | -3.3 (± 12.21) | | |
| SBP; Day 1: 20 to 24 hours, n=38,41 | -4.1 (± 10.16) | -5.2 (± 13.03) | | |
| SBP; Day 2, n=40,42 | -3.9 (± 11.53) | -3.0 (± 11.35) | | |
| SBP; Post-infusion assessment, n=35,41 | -1.5 (± 11.04) | -2.1 (± 11.37) | | |

Notes:

[31] - Maternal Safety Population

[32] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate in maternal participants

| | |
|-----------------|---|
| End point title | Change from Baseline in heart rate in maternal participants |
|-----------------|---|

End point description:

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 1 week

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[33] | 50 ^[34] | | |
| Units: Beats per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: 15 to 30 minutes, n=42,46 | -3.0 (± 12.65) | -0.8 (± 10.45) | | |
| Day 1: 4 to 8 hours, n=42, 43 | -5.0 (± 13.69) | -3.0 (± 13.65) | | |
| Day 1: 20 to 24 hours, n=38, 41 | -1.2 (± 14.44) | -3.1 (± 13.82) | | |
| Day 2, n=39, 41 | -2.2 (± 11.81) | -2.3 (± 13.44) | | |
| Post-infusion assessment, n=35, 41 | -2.7 (± 12.90) | -1.8 (± 13.83) | | |

Notes:

[33] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in respiratory rate in maternal participants

| | |
|--|---|
| End point title | Change from Baseline in respiratory rate in maternal participants |
| End point description: 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 | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[35] | 50 ^[36] | | |
| Units: breaths per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: 15 to 30 minutes, n=25, 28 | 0.3 (± 2.82) | -0.6 (± 1.93) | | |
| Day 1: 4 to 8 hours, n=23, 24 | 0.0 (± 1.65) | -0.8 (± 2.33) | | |
| Day 1: 20 to 24 hours, n=21, 21 | 0.2 (± 1.87) | -0.6 (± 2.40) | | |
| Day 2, n=23, 24 | -0.3 (± 1.64) | 0.2 (± 3.45) | | |
| Post-infusion assessment, n=22, 23 | -0.3 (± 2.15) | -1.3 (± 2.70) | | |

Notes:

[35] - Maternal Safety Population

[36] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in temperature in maternal participants

| | |
|---|--|
| End point title | Change from Baseline in temperature in maternal participants |
| End point description: 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 | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[37] | 50 ^[38] | | |
| Units: degree Celsius | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: 15 to 30 minutes, n=41, 43 | -0.02 (± 0.379) | 0.02 (± 0.467) | | |
| Day 1: 4 to 8 hours, n=40, 42 | -0.06 (± 0.359) | 0.00 (± 0.507) | | |
| Day 1: 20 to 24 hours, n=37, 41 | -0.07 (± 0.366) | -0.03 (± 0.486) | | |
| Day 2, n=40, 42 | -0.07 (± 0.467) | -0.06 (± 0.353) | | |
| Post-infusion assessment, n=35, 41 | -0.18 (± 0.334) | -0.20 (± 0.422) | | |

Notes:

[37] - Maternal Safety Population

[38] - 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 in maternal participants

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

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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[39] | 50 ^[40] | | |
| Units: Billion cells per liter (L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Basophils;Day2,n=21,23 | 0.003 (± 0.0362) | 0.010 (± 0.0304) | | |

| | | | | |
|--|-------------------|-------------------|--|--|
| Basophils;Post-infusion assessment,n=24,28 | 0.001 (± 0.0315) | 0.007 (± 0.0181) | | |
| Basophils;early withdrawal,n=1,1 | -0.020 (± 99999) | 0.030 (± 99999) | | |
| Eosinophils;Day2,n=21,23 | -0.010 (± 0.0626) | -0.037 (± 0.1181) | | |
| Eosinophils;Post-infusion assessment,n=24,28 | 0.023 (± 0.0442) | 0.066 (± 0.1535) | | |
| Eosinophils;early withdrawal,n=1,1 | 0.030 (± 99999) | 0.050 (± 99999) | | |
| Lymphocytes;Day2,n=21,23 | 0.186 (± 0.9115) | 0.067 (± 0.6017) | | |
| Lymphocytes;Post-infusion assessment,n=24,28 | 0.348 (± 0.8611) | 0.233 (± 0.8047) | | |
| Lymphocytes;early withdrawal,n=1,1 | 0.270 (± 99999) | -1.770 (± 99999) | | |
| Monocytes;Day2,n=21,23 | 0.082 (± 0.2222) | 0.044 (± 0.2702) | | |
| Monocytes;Post-infusion assessment,n=24,28 | 0.222 (± 0.1904) | 0.133 (± 0.3467) | | |
| Monocytes;early withdrawal,n=1,1 | -0.160 (± 99999) | 0.410 (± 99999) | | |
| Neutrophils;Day2,n=21,23 | 0.102 (± 2.6712) | 0.559 (± 3.3890) | | |
| Neutrophils;Post-infusion assessment,n=24,28 | -1.865 (± 2.9246) | -0.670 (± 2.7063) | | |
| Neutrophils;early withdrawal,n=1,1 | -0.710 (± 99999) | -3.550 (± 99999) | | |
| Platelets;Day2,n=22,25 | 0.0 (± 25.95) | -2.4 (± 36.59) | | |
| Platelets;Post-infusion assessment,n=24,31 | 21.5 (± 63.14) | 20.6 (± 43.74) | | |
| Platelets;early withdrawal,n=1,1 | -33.0 (± 99999) | -58.0 (± 99999) | | |
| Leukocytes;Day2,n=23,25 | 0.17 (± 2.785) | 0.72 (± 2.905) | | |
| Leukocytes;Post-infusion assessment,n=25,30 | -1.18 (± 2.492) | -0.05 (± 2.756) | | |
| Leukocytes;early withdrawal,n=1,1 | -0.60 (± 99999) | -4.80 (± 99999) | | |

Notes:

[39] - Maternal Safety Population

[40] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocytes in maternal participants

| | |
|-----------------|---|
| End point title | Change from Baseline in erythrocytes in maternal participants |
|-----------------|---|

End point description:

Blood samples were collected for the evaluation of change in erythrocytes 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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[41] | 50 ^[42] | | |
| Units: Trillion cells per liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 2, n=23, 27 | -0.22 (± 0.284) | -0.29 (± 0.261) | | |
| Post-infusion assessment, n=25, 31 | 0.06 (± 0.257) | 0.05 (± 0.236) | | |
| Early withdrawal, n =1, 1 | -0.20 (± 99999) | -0.70 (± 99999) | | |

Notes:

[41] - Maternal Safety Population

[42] - 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) in maternal participants

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

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. 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[43] | 50 ^[44] | | |
| Units: grams per liter (g/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Hemoglobin; Day2, n=23, 27 | -5.4 (± 7.81) | -8.4 (± 6.86) | | |
| Hemoglobin; Post-infusion assessment, n=25, 31 | 0.8 (± 7.55) | 0.5 (± 5.37) | | |
| Hemoglobin; early withdrawal, n=1, 1 | -8.0 (± 99999) | -19.0 (± 99999) | | |
| MCHC; Day 2, n=23, 27 | 1.0 (± 9.41) | 0.9 (± 6.85) | | |
| MCHC; Post-infusion assessment, n=25, 31 | 1.0 (± 7.36) | 0.4 (± 8.98) | | |
| MCHC; early withdrawal, n=1, 1 | -3.0 (± 99999) | 24.0 (± 99999) | | |

Notes:

[43] - Maternal Safety Population

[44] - 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) in maternal participants

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

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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[45] | 50 ^[46] | | |
| Units: femtoliter (fL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| MCV; Day 2, n=23, 27 | 0.3 (± 2.67) | -0.4 (± 1.82) | | |
| MCV; Post-infusion assessment, n=25, 31 | -1.2 (± 2.17) | -1.0 (± 2.22) | | |
| MCV; early withdrawal, n=1, 1 | -1.0 (± 99999) | -5.0 (± 99999) | | |
| MPV; Day 2, n=22, 25 | 0.05 (± 0.607) | 0.06 (± 0.553) | | |
| MPV, Post-infusion assessment, n=24, 31 | -0.10 (± 0.639) | -0.03 (± 0.803) | | |
| MPV, early withdrawal, n=1, 1 | 0.00 (± 99999) | -1.40 (± 99999) | | |

Notes:

[45] - Maternal Safety Population

[46] - 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 in maternal participants

| | |
|-----------------|---|
| End point title | Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), |
|-----------------|---|

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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[47] | 50 ^[48] | | |
| Units: International Units per liter (IU/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| ALP; Day 2, n=35, 35 | -10.1 (± 12.12) | -12.6 (± 13.07) | | |
| ALP; Post-infusion assessment, n=30, 35 | 14.1 (± 39.85) | 5.9 (± 15.87) | | |
| ALP; early withdrawal, n=1, 1 | -6.0 (± 99999) | -19.0 (± 99999) | | |
| AST; Day 2, n=34, 35 | -0.9 (± 4.82) | -1.7 (± 3.07) | | |
| AST; Post-infusion assessment, n=29, 35 | -1.3 (± 4.87) | -1.3 (± 4.09) | | |
| AST; early withdrawal, n=1, 1 | -3.0 (± 99999) | 1.0 (± 99999) | | |
| ALT; Day 2, n= 35, 35 | -0.2 (± 2.53) | 0.0 (± 2.40) | | |
| ALT; Post-infusion assessment, n= 30, 35 | 0.0 (± 6.34) | 0.8 (± 6.19) | | |
| ALT; early withdrawal, n= 1, 1 | -2.0 (± 99999) | 5.0 (± 99999) | | |
| GGT; Day 2, n= 35, 35 | -0.4 (± 2.44) | -0.9 (± 3.08) | | |
| GGT; Post-infusion assessment, n=30, 35 | 17.6 (± 79.05) | 2.3 (± 4.39) | | |
| GGT; early withdrawal, n=1, 1 | 0.0 (± 99999) | 0.0 (± 99999) | | |
| LDH; Day 2, n=34, 35 | -9.7 (± 50.58) | -20.0 (± 29.18) | | |
| LDH; Post-infusion assessment, n=29, 35 | -2.4 (± 22.08) | -5.4 (± 30.93) | | |
| LDH; early withdrawal, n=1, 1 | -18.0 (± 99999) | -59.0 (± 99999) | | |

Notes:

[47] - Maternal Safety Population

[48] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and protein levels in maternal participants

| | |
|-----------------|---|
| End point title | Change from Baseline in albumin and protein levels in maternal participants |
|-----------------|---|

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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[49] | 50 ^[50] | | |
| Units: grams per liter (g/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Albumin; Day 2, n=35, 35 | -1.9 (± 2.28) | -2.0 (± 1.95) | | |
| Albumin; Post-infusion assessment, n=30, 35 | 0.3 (± 2.39) | -0.2 (± 2.26) | | |
| Albumin; early withdrawal, n=1, 1 | -4.0 (± 99999) | -8.0 (± 99999) | | |
| Protein; Day 2, n=35, 35 | -3.7 (± 4.18) | -3.3 (± 3.69) | | |
| Protein; Post-infusion assessment, n=30, 35 | 0.5 (± 4.73) | 0.0 (± 4.05) | | |
| Protein; early withdrawal, n=1, 1 | -5.0 (± 99999) | -12.0 (± 99999) | | |

Notes:

[49] - Maternal Safety Population

[50] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Change from Baseline in calcium, chloride, carbon dioxide, glucose, potassium, magnesium, phosphate and sodium level in maternal participants |
|-----------------|---|

End point description:

Blood samples were collected for the evaluation of change from Baseline in levels of 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). 99999 indicates standard deviation was not calculable for a single data point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[51] | 50 ^[52] | | |
| Units: millimoles per liter (mmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Calcium; Day 2, n=34, 35 | -0.097 (± 0.1125) | -0.078 (± 0.0884) | | |
| Calcium; Post-infusion assessment, n=29, 35 | 0.018 (± 0.0953) | 0.023 (± 0.0861) | | |
| Calcium; early withdrawal, n=1, 1 | -0.120 (± 99999) | -0.230 (± 99999) | | |
| Chloride; Day 2, n=35, 35 | 1.5 (± 2.02) | 1.4 (± 2.03) | | |
| Chloride; Post-infusion assessment, n=30, 35 | -1.5 (± 1.83) | -1.3 (± 2.63) | | |
| Chloride; early withdrawal, n=1, 1 | 2.0 (± 99999) | 8.0 (± 99999) | | |
| Carbon dioxide; Day 2, n=34, 35 | 0.7 (± 2.34) | 0.3 (± 2.63) | | |
| Carbon dioxide, Post-infusion assessment, n=29,35 | 1.9 (± 2.06) | 1.9 (± 2.67) | | |
| Carbon dioxide, early withdrawal, n=1, 1 | -2.0 (± 99999) | 6.0 (± 99999) | | |
| Glucose; Day 2, n=35,35 | 0.13 (± 2.013) | 1.51 (± 2.156) | | |
| Glucose; Post-infusion assessment, n=30, 35 | -0.70 (± 1.994) | -0.35 (± 2.283) | | |
| Glucose; early withdrawal, n= 1, 1 | 0.70 (± 99999) | -5.20 (± 99999) | | |
| Potassium; Day 2, n= 34, 35 | 0.06 (± 0.392) | -0.06 (± 0.346) | | |
| Potassium; Post-infusion assessment, n= 29, 35 | 0.21 (± 0.362) | 0.18 (± 0.355) | | |
| Potassium; early withdrawal, n= 1,1 | -0.10 (± 99999) | 0.50 (± 99999) | | |
| Magnesium; Day 2, n= 35,35 | 0.073 (± 0.2098) | -0.003 (± 0.0657) | | |
| Magnesium, Post-infusion assessment, n= 30,35 | 0.026 (± 0.0760) | 0.009 (± 0.0772) | | |
| Magnesium; early withdrawal, n= 1,1 | -0.060 (± 99999) | 0.030 (± 99999) | | |
| Phosphate; Day 2, n= 35,35 | -0.101 (± 0.2684) | -0.170 (± 0.2357) | | |
| Phosphate; Post-infusion assessment, n= 30,35 | 0.041 (± 0.2267) | 0.094 (± 0.2864) | | |
| Phosphate; early withdrawal, n= 1,1 | 0.100 (± 99999) | -0.120 (± 99999) | | |
| Sodium; Day 2, n= 35,35 | 0.7 (± 2.13) | 0.1 (± 1.69) | | |
| Sodium; Post-infusion assessment, n= 30,35 | -1.1 (± 2.05) | -0.2 (± 2.11) | | |
| Sodium; early withdrawal, n= 1,1 | -1.0 (± 99999) | 3.0 (± 99999) | | |

Notes:

[51] - Maternal Safety Population

[52] - 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 in maternal participants

| | |
|-----------------|---|
| End point title | Change from Baseline in direct bilirubin, bilirubin, indirect |
|-----------------|---|

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). 99999 indicates standard deviation was not calculable for a single data point.

End point type Secondary

End point timeframe:

Baseline and up to 1 week

| End point values | Retosiban | Atosiban | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[53] | 50 ^[54] | | |
| Units: micromoles per liter (µmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Direct Bilirubin; Day2, n=35,35 | -0.3 (± 0.85) | -0.3 (± 0.66) | | |
| Post-infusion assessment, n=30,35 | -0.5 (± 3.41) | -0.1 (± 0.73) | | |
| Direct Bilirubin;early withdrawal, n=1,1 | 0.0 (± 99999) | 0.0 (± 99999) | | |
| Bilirubin;Day2, n= 35,35 | -0.7 (± 2.52) | -1.3 (± 2.03) | | |
| Bilirubin; Post-infusion assessment, n= 30, 35 | -1.1 (± 8.24) | -0.5 (± 2.01) | | |
| Bilirubin; early withdrawal, n= 1,1 | -2.0 (± 99999) | -3.0 (± 99999) | | |
| Indirect Bilirubin; Day2, n=35,35 | -0.4 (± 2.35) | -1.1 (± 1.98) | | |
| Indirect Bilirubin;Postinfusion assessment,n=30,35 | -0.6 (± 5.06) | -0.4 (± 2.03) | | |
| Indirect Bilirubin; early withdrawal, n=1,1 | -2.0 (± 99999) | -3.0 (± 99999) | | |
| Creatinine; Day2, n=35,34 | 1.75 (± 6.765) | 0.04 (± 5.336) | | |
| Creatinine; Post-infusion assessment, n=30,33 | 2.19 (± 4.437) | 0.72 (± 4.680) | | |
| Creatinine; early withdrawal, n=1,1 | -0.90 (± 99999) | -6.10 (± 99999) | | |

Notes:

[53] - Maternal Safety Population

[54] - 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[55] | 50 ^[56] | | |
| Units: Participants | | | | |
| Participants | 4 | 7 | | |

Notes:

[55] - Maternal Safety Population

[56] - 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[57] | 50 ^[58] | | |
| Units: Participants | | | | |
| Participants | 5 | 5 | | |

Notes:

[57] - Maternal Safety Population

[58] - Maternal Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with fetal non-serious AEs and SAEs

| | |
|-----------------|--|
| End point title | Number of participants with fetal non-serious 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 non-serious AE and one SAE has been presented.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 17 weeks | |

| End point values | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[59] | 50 ^[60] | | |
| Units: Participants | | | | |
| Non-serious AE | 6 | 6 | | |
| SAE | 4 | 2 | | |

Notes:

[59] - Maternal Safety Population

[60] - 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[61] | 50 ^[62] | | |
| Units: Participants | | | | |
| Participants | 5 | 5 | | |

Notes:

[61] - Maternal Safety Population

[62] - 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. Only those participants with data available at the specified data points were analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 5 minutes after birth

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[63] | 50 ^[64] | | |
| Units: Score on APGAR scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| one minute, n=46, 50 | 8.2 (± 1.35) | 8.4 (± 1.14) | | |
| five minutes, n=46, 50 | 9.1 (± 0.96) | 9.4 (± 0.67) | | |

Notes:

[63] - Neonatal ITT Population

[64] - 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. Only those participants with data available at the specified data points were analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 17 weeks

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[65] | 49 ^[66] | | |
| Units: grams (g) | | | | |
| arithmetic mean (standard deviation) | | | | |
| grams (g) | 2761.9 (± 567.84) | 2844.4 (± 664.80) | | |

Notes:

[65] - Neonatal ITT Population

[66] - 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. Only those participants with data available at the specified data points were analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 17 weeks

| End point values | Retosiban | Atosiban | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 ^[67] | 42 ^[68] | | |
| Units: centimeters (cm) | | | | |
| arithmetic mean (standard deviation) | | | | |
| centimeters (cm) | 32.95 (± 2.179) | 33.00 (± 1.892) | | |

Notes:

[67] - Neonatal ITT Population

[68] - Neonatal ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of neonatal participants with non-serious AEs and SAEs

| | |
|-----------------|---|
| End point title | Number of neonatal participants with non-serious 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 non-serious 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[69] | 50 ^[70] | | |
| Units: Participants | | | | |
| Non-serious AEs | 23 | 17 | | |
| SAEs | 10 | 11 | | |

Notes:

[69] - Neonatal Safety Population

[70] - 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[71] | 50 ^[72] | | |
| Units: Participants | | | | |
| Participants | 19 | 16 | | |

Notes:

[71] - Neonatal Safety Population

[72] - 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 | Retosiban | Atosiban | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[73] | 50 ^[74] | | |
| Units: Participants | | | | |
| Participants | 5 | 3 | | |

Notes:

[73] - Neonatal Safety Population

[74] - 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: The length of hospital stay associated with hospital admission for preterm labor and term labor/term delivery was collected from review of medical records. 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: Up to 28 days post EDD (40 0/7 weeks gestation) | |

| End point values | Retosiban | Atosiban | | |
|-------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[75] | 50 ^[76] | | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Preterm labor, n=13, 10 | 5.549 (1.32 to 72.00) | 7.487 (0.87 to 37.82) | | |
| Term labor, n=25, 28 | 3.146 (0.17 to 62.71) | 3.398 (0.41 to 36.74) | | |

Notes:

[75] - Maternal Safety Population

[76] - 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 and normal term delivery were collected from the review of medical records. The number of participants who were admitted to a particular hospital unit like general ward, private/semi-private room, recovery, and other has been presented. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 28 days post EDD (40 0/7 weeks gestation) | |

| End point values | Retosiban | Atosiban | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 ^[77] | 50 ^[78] | | |
| Units: Participants | | | | |
| Preterm labor, general ward | 9 | 7 | | |
| Preterm labor, private/semi-private room | 1 | 0 | | |
| Preterm, Other | 3 | 4 | | |
| Normal term labor, general ward | 16 | 12 | | |
| Normal term labor, ward-not specified | 2 | 0 | | |
| Normal term labor,private/semi-private room | 1 | 7 | | |
| Normal term labor, recovery | 1 | 2 | | |
| Normal term labor, Other | 5 | 7 | | |

Notes:

[77] - Maternal Safety Population

[78] - 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 | 53 ^[79] | | | |
| Units: Microgram per liter | | | | |
| geometric mean (geometric coefficient of variation) | 83.4 (± 5.25) | | | |

Notes:

[79] - 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 | 53 ^[80] | | | |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 68.6 (± 109) | | | |

Notes:

[80] - 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:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study treatment and until Day 894

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. One participant was withdrawn prior to delivery and was not included in the summary.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Retosiban (Maternal) |
|-----------------------|----------------------|

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 title | Atosiban (Maternal) |
|-----------------------|---------------------|

Reporting group description:

Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution.

| | |
|-----------------------|-------------------|
| Reporting group title | Retosiban (Fetal) |
|-----------------------|-------------------|

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 title | Atosiban (Fetal) |
|-----------------------|------------------|

Reporting group description:

Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution.

| | |
|-----------------------|----------------------|
| Reporting group title | Retosiban (Neonatal) |
|-----------------------|----------------------|

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 title | Atosiban (Neonatal) |
|-----------------------|---------------------|

Reporting group description:

Participants were administered atosiban in 3 successive stages. An initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 milliliter (mL) solution for injection, followed by continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg/5 mL concentrate for solution.

| Serious adverse events | Retosiban (Maternal) | Atosiban (Maternal) | Retosiban (Fetal) |
|---|----------------------|---------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 9 / 50 (18.00%) | 4 / 47 (8.51%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Foetal monitoring abnormal | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Injury, poisoning and procedural complications | | | |
| Abdominal wound dehiscence | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Congenital, familial and genetic disorders | | | |
| Congenital hydronephrosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Ankyloglossia congenital | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Atrial septal defect | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Cataract congenital | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Pyloric stenosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Ventricular septal defect | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 | | | |
| Foetal heart rate disorder | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal heart rate deceleration abnormality | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Preterm premature rupture of membranes | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Normal labour | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Pre-eclampsia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Premature labour | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Premature separation of placenta | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Oligohydramnios | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrops foetalis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice neonatal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| General disorders and administration site conditions | | | |
| Sudden infant death syndrome | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Immune system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Milk allergy | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Hyperbilirubinaemia neonatal | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Choking | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 aspiration syndrome | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 | | | |
| Amniotic cavity infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Haematoma infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (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 | Atosiban (Fetal) | Retosiban (Neonatal) | Atosiban (Neonatal) |
|---|------------------|----------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 10 / 46 (21.74%) | 11 / 50 (22.00%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Foetal monitoring abnormal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Injury, poisoning and procedural complications | | | |
| Abdominal wound dehiscence | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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, familial and genetic disorders | | | |
| Congenital hydronephrosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Ankyloglossia congenital | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial septal defect | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cataract congenital | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |
| Pyloric stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |
| Ventricular septal defect | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Foetal heart rate disorder | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Foetal heart rate deceleration abnormality | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 | | | |
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Preterm premature rupture of membranes | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Normal labour | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Pre-eclampsia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Premature labour | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Premature separation of placenta | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |

| | | | |
|--|----------------|----------------|----------------|
| Oligohydramnios | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Hydrops foetalis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Jaundice neonatal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Sudden infant death syndrome | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune system disorders | | | |
| Milk allergy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Pancreatitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Hyperbilirubinaemia neonatal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 4 / 46 (8.70%) | 3 / 50 (6.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 3 |
| 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 / 50 (0.00%) | 1 / 46 (2.17%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choking | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Meconium aspiration syndrome | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Amniotic cavity infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Haematoma infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (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 |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (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 |

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

| Non-serious adverse events | Retosiban (Maternal) | Atosiban (Maternal) | Retosiban (Fetal) |
|---|----------------------|---------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 47 (72.34%) | 25 / 50 (50.00%) | 6 / 47 (12.77%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Eyelid haemangioma | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Foetal hypokinesia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 2 |
| Oligohydramnios | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Gestational hypertension | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Polyhydramnios | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Premature labour | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Preterm premature rupture of membranes | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Jaundice neonatal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cephalhaematoma | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral swelling | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Suprapubic pain subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Scrotal oedema subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Testicular retraction subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 4 | 1 / 50 (2.00%) 2 | 0 / 47 (0.00%) 0 |
| Breast engorgement subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Uterine atony subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Vulval oedema subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Neonatal respiratory distress syndrome subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Transient tachypnoea of the newborn subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Apnoea | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Choking | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory disorder neonatal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Use of accessory respiratory muscles | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Agitation | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Escherichia test positive | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Psychiatric evaluation abnormal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Candida test positive | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Klebsiella test positive | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Abdominal wound dehiscence | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Congenital hydronephrosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Foetal heart rate disorder | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foetal heart rate deceleration | | | |

| | | | |
|--------------------------------------|-----------------|----------------|----------------|
| abnormality | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 15 |
| Bradycardia foetal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 1 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia foetal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 3 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 8 / 47 (17.02%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Polycythaemia neonatorum | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anaemia | | | |

| | | | |
|--|------------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 2 / 50 (4.00%) 2 | 0 / 47 (0.00%) 0 |
| Anaemia of pregnancy subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Ear and labyrinth disorders Auditory disorder subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Gastrointestinal disorders Infantile colic subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 10 / 47 (21.28%) 12 | 5 / 50 (10.00%) 5 | 0 / 47 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Inguinal hernia subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Regurgitation subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Umbilical hernia subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Vomiting | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal rigidity | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia neonatal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne infantile | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blister | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Macule subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Renal and urinary disorders Renal pain subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 50 (4.00%) 2 | 0 / 47 (0.00%) 0 |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Flank pain subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 50 (2.00%) 1 | 0 / 47 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 50 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Infections and infestations | | | |

| | | | |
|---|----------------|----------------|----------------|
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Bacterial vaginosis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Cervicitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 3 / 50 (6.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 50 (4.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vaginitis gardnerella | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Genital candidiasis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Pulpitis dental | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyuria | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin candida | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Ureaplasma infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 50 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 50 (2.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | Atosiban (Fetal) | Retosiban (Neonatal) | Atosiban (Neonatal) |
|--|------------------|----------------------|---------------------|
| Total subjects affected by non-serious | | | |

| | | | |
|---|-----------------|------------------|------------------|
| adverse events | | | |
| subjects affected / exposed | 6 / 50 (12.00%) | 23 / 46 (50.00%) | 17 / 50 (34.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Eyelid haemangioma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Foetal hypokinesia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oligohydramnios | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gestational hypertension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Polyhydramnios | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Premature labour | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Preterm premature rupture of membranes | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Jaundice neonatal | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Cephalhaematoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Suprapubic pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Scrotal oedema | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Testicular retraction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Breast engorgement | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Uterine atony | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulval oedema | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Neonatal respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Transient tachypnoea of the newborn | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Apnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Choking | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory acidosis | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory disorder neonatal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Use of accessory respiratory muscles | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Agitation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mood swings | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Escherichia test positive | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric evaluation abnormal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida test positive | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Klebsiella test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Abdominal wound dehiscence subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Congenital, familial and genetic disorders | | | |
| Congenital hydronephrosis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Hydrocele subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Cardiac disorders | | | |
| Foetal heart rate disorder subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Foetal heart rate deceleration abnormality subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Bradycardia foetal subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Tachycardia foetal subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Nervous system disorders Cerebral haemorrhage subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Burning sensation subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Blood and lymphatic system disorders Polycythaemia neonatorum subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Anaemia of pregnancy subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Auditory disorder subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Gastrointestinal disorders Infantile colic subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 1 / 50 (2.00%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Inguinal hernia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Regurgitation subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Umbilical hernia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Abdominal rigidity subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Dental caries | | | |

| | | | |
|--|----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia neonatal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 10 / 46 (21.74%) | 8 / 50 (16.00%) |
| occurrences (all) | 0 | 10 | 8 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 46 (4.35%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne infantile | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blister | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 46 (2.17%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Macule | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Renal and urinary disorders Renal pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Bacterial vaginosis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Cervicitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginitis gardnerella | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital candidiasis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyuria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 46 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Skin candida | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Ureaplasma infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Vaginal infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypernatraemia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 46 (2.17%) 1 | 0 / 50 (0.00%) 0 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Metabolic acidosis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Iron deficiency subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 46 (0.00%) 0 | 0 / 50 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 January 2015 | Amendment No. 1 The following changes are reflected in the Country-Specific Protocol Amendment for Applicable Sites in France: Inclusion criteria 1 and 2 were amended to specify that subjects must be at least 18 years of age to participate in Study 200721, and subjects who participate in Study 200721 must also agree to participate in Study 200722, a separate infant follow-up study. Text was revised throughout to reflect the change in the subject age criterion and the requirement to enroll in the infant follow-up study. Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki. Finally, an appendix was added that categorizes laboratory samples into those supporting study conduct and those that may be analyzed at a later date. |
| 29 January 2015 | Amendment No. 2 The following changes are reflected in the Country-Specific Protocol Amendment for Applicable United Kingdom Sites: The text from Section 5.3 has been clarified. The intent of the language remains the same, but the clarification confirms there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind treatment for a study subject if needed. In addition, Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki |
| 04 February 2015 | Amendment No. 3 The following changes are reflected in the Country-Specific Protocol Amendment for Applicable Swedish Sites: An appendix was added to list the medications considered strong, moderate, and weak CYP3A4 (cytochrome P450 3A4 enzyme) inhibitors and inducers. |
| 22 August 2016 | Amendment No. 4: Clarified the methods for documenting Screening GA. Clarified that co-morbid conditions would exclude a subject with known or suspected maternal Zika infection. Revised guidance regarding adequate treatment response and defined inadequate treatment response. Added procedures to be followed for managing dose interruptions; and allowed pessary use if started before the current episode of preterm labor. Revised the requirements for continuous fetal heart rate monitoring to a minimum of 6 hours from the start of the infusion or from the start of a dose increase, provided the heart rate pattern was consistently reassuring. Clarified that confirmation of uterine contraction eligibility criterion must occur within 60 minutes before study drug dosing. Removed the follow-up amniotic fluid index (AFI) by abdominal ultrasound as a fetal safety endpoint. Removed the requirement for an ultrasound for AFI determination within 12 hours of completion of study treatment. Revised the method used for adjusting multiplicity of the key secondary endpoints from a stepwise Holm's test to a sequential testing method. |
| 21 December 2016 | Amendment No. 5: Remove the 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 or before retreatment unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization or the date of retreatment. Update the list of maternal drug-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. Remove changes detailed in the country-specific amendment for sites in France (dated 29 Jan 2015). Incorporate other administrative changes. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported