Treatment of Spontaneous Preterm Labour with Retosiban:

A Phase 2 Proof-of-Concept Study

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Summary (246/250 max)

Aim: To investigate the efficacy and safety of intravenous retosiban in women with spontaneous preterm labour.

Methods: Randomised, double-blind, placebo-controlled, phase 2 trial. Retosiban was administered intravenously for 48 hours to women in spontaneous preterm labour between $30^{0/7}$ and $35^{6/7}$ weeks' gestation with an uncomplicated singleton pregnancy in an in-patient obstetric unit. Outcome measures were uterine quiescence (primary endpoint), days to delivery, preterm delivery, and safety.

Results: Uterine quiescence was achieved in 62% of women who received retosiban (n=30) compared with 41% who received placebo (n=34). The relative risk (RR) was 1.53 (95% credible interval [CrI]: 0.98, 2.48; NS). Retosiban resulted in a significant increase in time to delivery compared with placebo (mean difference, 8.2 days; 95% CrI: 2.7, 13.74); this difference was consistent across all gestational ages. The proportion of preterm births in the retosiban and placebo groups was 18.7% (95% CrI: 7.4%, 33.7%) and 47.2% (95% CrI: 31.4%, 63.4%), respectively. The RR of preterm birth in women treated with retosiban was 0.38 (95% CrI: 0.15, 0.81). There were no deliveries within 7 days in the retosiban group, but there were six (17.6%) births in the placebo group. Maternal, fetal, and neonatal adverse events were similar in the retosiban and placebo groups.

Conclusions: Intravenous administration of retosiban in women with spontaneous preterm labour was associated with a greater than 1-week increase in time to delivery compared with placebo, a significant reduction in preterm deliveries, a non-significant increase in uterine quiescence, and a favourable safety profile.

What is known about this subject

- Preterm birth is the largest single cause of infant morbidity and mortality; risks increase with earlier gestational age.
- Current tocolytics have not been demonstrated to improve neonatal outcome.
- A tocolytic that significantly prolongs pregnancy may improve neonatal and infant outcomes.

What this study adds

- Retosiban prolonged pregnancy and reduced preterm birth.
- Treatment was well tolerated and there was no indication of a safety issue for mother, fetus, or newborn.
- The results demonstrate proof-of-concept in the treatment of threatened spontaneous preterm labour.

INTRODUCTION

Preterm birth is the largest single cause of infant morbidity and mortality and is frequently associated with long-term disability [1–4]. Current tocolytics may not be effective in delaying delivery for a number of possible reasons [1, 5–7]: the drug target may be inappropriate, the plasma concentration may be ineffective, or redundant mechanisms may allow the process of labour to continue. Clinicians remain optimistic that an effective tocolytic will be developed which can significantly prolong pregnancy and improve neonatal and infant outcomes in appropriate pregnancies.

Atosiban, a mixed vasopressin (V_{1a})/oxytocin receptor antagonist, is licensed in the European Union as a tocolytic for parenteral administration [8]. There are no tocolytics currently approved in North America. Many therapies are used off-label throughout the world, including beta-sympathomimetics, prostaglandin synthase inhibitors, and calcium channel blockers [9], although none have been conclusively demonstrated to delay delivery and improve neonatal or infant outcomes. Retosiban, a specific, high-affinity oxytocin receptor antagonist, is now in development for the inhibition of uterine contractions in spontaneous preterm labour. Retosiban is an oxazole diketopiperazine oxytocin antagonist with good bioavailability and nanomolar affinity for the human oxytocin receptor (Ki=0.65 nM), with >1400-fold selectivity over the closely related vasopressin receptors [10]. Nomenclature for the vasopressin and oxytocin receptors is as specified in the Guide to Receptors and Channels (GRAC), 5th edition [11].

There is evidence from *in vitro* and *in vivo* studies that retosiban inhibits spontaneous and induced uterine contractions. Phase 1 studies have demonstrated safety in non-pregnant volunteers (unpublished data on file, study OTA 105101; Michael Fossler, PharmD, PhD, FCP, Senior Director, CPMS – US, RD Projects Clinical Platforms & Sciences,

GlaxoSmithKline, King of Prussia, PA, USA) and retosiban has been evaluated in pregnant women to determine the dose-range and confirm proof of mechanism based on suppression of uterine contractions [12,13]. The pilot dose ranging studies were done on 29 women in threatened preterm labour between 34 and 35^{+6} weeks' gestation. These studies (to be published separately) demonstrated rapid absorption of retosiban with plasma concentrations consistent with nonpregnant volunteers. The safety profile was similar to placebo. Retosiban was associated with a reduction in uterine activity and a marked increase in the number of days to delivery. In the current report, proof-of-concept was further extended to confirm the efficacy and safety of intravenous retosiban in women experiencing spontaneous preterm labour between $30^{0/7}$ and $35^{6/7}$ weeks' gestation with an uncomplicated singleton pregnancy.

METHODS

Study Design

This was a double-blind, placebo-controlled study in women admitted with spontaneous preterm labour between $30^{0/7}$ and $35^{6/7}$ weeks' gestation (registration number NCT00404768; http://clinicaltrials.gov/ct2/show/NCT00404768?term=be+NCT00404768&rank=1.) Eligible women were stratified by gestational age, $30^{0/7}$ to $32^{6/7}$ weeks or $33^{0/7}$ to $35^{6/7}$ weeks, and randomised 1:1 to intravenous retosiban or placebo. Magnesium sulphate for neuroprotection and antenatal steroids were allowed.

The retosiban dosing regimen was designed to achieve a mean steady-state concentration of 75 ng/ml (informed by pre-clinical data, the dose-ranging study, and studies in non-pregnant healthy volunteers) using a loading dose of 6 mg over 5 minutes and a continuous infusion of 6 mg/hour over 48 hours. At any point after 1 hour of receiving the 6-mg/hour rate, a single dose increase was permitted in women who did not respond to treatment. In this case, the infusion rate could be increased to 12 mg/hour after an additional 6-mg loading dose. An adequate treatment response was defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilatation. Women who did not respond to the dose increase could discontinue study medication and receive an alternative rescue tocolytic at the discretion of the investigator.

A group sequential design was used with up to three planned interim analyses (four planned cohorts of 16 women each). At each interim analysis, the study could have been stopped for success or futility based on *a priori* stopping rules.

Eligible Women

Eligible women were 18 to 45 years of age, had a singleton pregnancy between $30^{0/7}$ and $35^{6/7}$ weeks' gestation based on best available obstetric estimate, were having six or more uterine contractions per hour of at least 30 seconds' duration by external cardiotocography (CTG) with cervical dilatation ≥1 to ≤4 cm, and had intact fetal membranes.

Excluded were women with indications for delivery, such as pre-eclampsia or fetal compromise; women with contraindications to tocolysis, such as clinically apparent intrauterine infection or placental abruption; and women with comorbid conditions with the potential to complicate pregnancy and outcomes, such as hypertension, insulin-dependent diabetes, or substance abuse.

Procedure

Following confirmation of eligibility, maternal examination and investigations were done (vital signs; 12-lead electrocardiogram (ECG); biochemistry, haematology, and urinalysis). An ultrasound was done to determine amniotic fluid index (AFI) and a CTG for fetal heart rate monitoring. These tests were not repeated if they had been done in the 6 hours before consent. Within 1 hour before dosing, the contraction rate and duration were determined, a vaginal examination was done to assess cervical dilatation, and fetal heart rate was recorded. Dosing began at time zero. After the start of treatment, the following assessments were conducted at specified time points: maternal blood pressure, heart rate, ECG, uterine contractions, physical examination, clinical laboratory tests, AFI, and fetal heart rate. Women who discontinued study medication and their infants were followed for safety.

Study Endpoints

The primary pharmacodynamic endpoint (response rate) was the proportion of women who achieved and maintained uterine quiescence, defined as four or fewer contractions per hour and <1 cm change in cervical dilatation at hour 6. The principal efficacy endpoints were days to delivery (a tertiary endpoint) and preterm births (<37 weeks). The safety endpoints were aimed at detecting adverse drug effects based on maternal monitoring (ECG, laboratory results, vital signs, and adverse events), fetal monitoring (CTG, modified biophysical profile consisting of AFI and non-stress test, and adverse events), and neonatal observations (Apgar scores, growth parameters at birth and follow-up, gross development, and adverse events).

Follow-up

Women were discharged 6 hours after the end of the infusion or at the discretion of the investigator. Hospital records were reviewed to determine gestational age at birth; Apgar scores; and weight, length, and head circumference at birth. Infants were assessed approximately 1 month after birth. Neonatal adverse events were determined from either neonatal records or maternal reporting.

Statistical Analyses

The planned Bayesian statistical analysis declared statistical significance if the 95% credible interval (corresponding to the confidence interval) excluded 0 (for a difference) or 1 (for relative risk [RR]). Partially informative priors (probability distribution according to available data) from the dose-ranging study were used in the analyses of proportions of women achieving uterine quiescence and days to delivery. This was analogous to including data from a certain number of women from the prior study, as well as observed data from the present study, according to standard application of Bayes' theorem [14]. A non-informative prior (analogous to analysis of the observed data from the study) was used for the analysis of

the proportion of preterm births and a sensitivity analysis (i.e. to evaluate the influence of the partially informative priors) for the endpoints of uterine quiescence and days to delivery. The planned sample size (n = 64) provided at least 86% power to detect a 40% absolute difference, or RR of 2.6, in the proportion of women achieving uterine quiescence.

The safety and analysis populations were defined as all women who received at least one dose of study drug. For the primary endpoint of uterine quiescence, women who stopped the study drug within 6 hours of time zero were recorded as non-responders. For analyses of days to delivery and proportion of preterm births, actual birth data were used.

Uterine quiescence response rates for each treatment group and the relative risks (defined as the ratio of retosiban to placebo response rates) along with 95% credible intervals were estimated by using a Bayesian formulation of Fisher's exact test. The proportion of women delivering preterm was similarly analysed. The mean difference in days to delivery between treatment groups, along with the 95% credible interval, was estimated from a Bayesian formulation of an analysis of covariance model with gestational age at entry fit as a continuous covariate. No other hypothesis tests were performed, according to the protocol. All statistical analyses were performed with SAS/IML® (SAS Software, Cary, NC, USA) or the R open-source software environment for statistical computing.

Details of ethics approval: Written informed consent was obtained from all women. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki (2008) and was approved by the following institutional review boards: CPP Ile-de-France XI, Saint-Germain-en-Laye 78105, France, ref. 174142/063858; St. Joseph's Hospital and Medical Center Institutional Review Board for Human Research, Phoenix, AZ 85013, USA , ref. 105422/034702; Sandhills Multi-Institutional Review Board, Pinehurst, NC 28374, USA, ref. 135920/048485; University of Tennessee Graduate School of

Medicine Institutional Review Board, Knoxville TN 37920, USA, ref. 129343/045389; Asan Medical Center IRB, Seoul 138-736, Korea, ref. 170633/061966; Singhealth Office of Research169611, Singapore, ref. 136524/048769; Western Institutional Review Board, Olympia, WA 98502, USA, ref. 184592/069282; TMC Institutional Review, Tucson, AZ 85712, USA, ref. 166865/061308; Comite de Etica en Investigacion del Hospital Universitario Clinica San Rafael, Bogota/Cundinamarca, Colombia, ref. 205896/078327; Ethics Committee for Multicenter Trials, Sofia 1504, Bulgaria, ref. 171264/061999; Severance Hospital IRB, Seodaemun-gu, Seoul 120-752, Korea, ref. 170632/062795; Comite Etico de Investigacion Clinica, Hospital Universitario Vall d'Hebron 08035, Barcelona, Spain, ref. 171272/062160; CPP Ile-de-France XI, Saint-Germain-en-Laye 78105, France, ref 174154/063864; Forsyth Medical Center Institutional Review Board, Winston-Salem, NC 27103, USA, ref. 037174/048486; Comite de Etica Medica en Investigacion, Bogota, Colombia, ref. 205915/078324; ArrowHead Regional Medical Center IRB, Colton, CA 92324, USA, ref. 120625/040718; Ethics Committee for Multicenter Trials, Sofia 1303, Bulgaria, ref. 171265/062002; University of Texas Medical Branch IRB, Galveston, TX 77555, USA, ref. 126172/034700.

RESULTS

Seventeen centres enrolled, randomised, and treated 64 women (**Figure 1**). One additional subject was randomised but not dosed because of labour progression; her data are not included in this report. Six women did not complete the retosiban infusion due to lack of response (n = 2) or a decision on the part of the subject or investigator (n = 4). The principal reasons for discontinuation of the infusion in the placebo group (n = 12) were lack of response (n = 7), adverse event (n = 3), or subject or investigator decision (n = 2).

Demographic and baseline characteristics of women participating in the study are summarised in **Table 1**. The groups were well matched. Patients were primarily white women in their mid-to-late twenties, and ranging in age from 18 to 41 years. There was a slight imbalance in randomisation, with fewer retosiban patients (9/30 vs. 15/34) randomised to the earlier gestational age group, although the increased rate of discontinuation of drug in the placebo group resulted in a similar number of patients completing the infusion in each study arm (22 and 20 for retosiban and placebo, respectively). A protocol amendment was introduced after the first 12 women were enrolled for stratification by gestational age to ensure future balanced randomisation. Although there is an imbalance of the number of women in the early gestational age group across treatments, analyses indicated that the effect of retosiban versus placebo was similar across gestational ages.

Pharmacodynamic and Efficacy Outcomes

Uterine Contractions

Uterine quiescence was achieved in 62% of women who received retosiban compared with 41% who received placebo. The RR was 1.53 (95% CrI: 0.98, 2.48; NS). The mean baseline contraction rates were 12.5 and 12.9/hour in the retosiban and placebo groups, respectively. The rates at hour 6 were 3.7 and 5.3, respectively (**Figure 2**).

Intravenous infusion rates were increased in 37% (11/30) and 62% (21/34) of women assigned to retosiban and placebo, respectively. Ten women received rescue tocolysis: three (10%) in the retosiban group and seven (21%) in the placebo group. Rescue tocolytics included magnesium sulphate (n = 6), nifedipine (n = 3), fenoterol (n = 2), ritodrine (n = 1), atosiban (n = 1), and salbutamol (n = 1).

Time to Delivery and Preterm Births

The time to delivery was longer in women treated with retosiban compared with placebo (mean difference 8.2 days [95% CrI: 2.7, 13.74]; median time to delivery: 34.5 and 25 days, respectively). There were no deliveries within 7 days in the retosiban group, but six births (17.6%) in the placebo group. The time to delivery at each gestational age for women who received retosiban or placebo is shown in **Figure 3**.

The proportion of preterm births in the retosiban and placebo groups was 18.7% (95% CrI: 7.4%, 33.7%) and 47.2% (95% CrI: 31.4%, 63.4%), respectively. The RR of preterm birth in women treated with retosiban was 0.38 (95% CrI: 0.15, 0.81).

Statistical Inference

Partially informative priors from the dose-ranging study (data from 14 subjects treated with retosiban IV and 5 treated with placebo IV) were included in the evaluation of uterine quiescence and time to delivery. The analyses were repeated using non-informative priors, which indicated that the use of these partially informative priors from the dose-ranging study had no impact on the statistical inferences, although there were minor changes to the point estimates and 95% CrI, as shown in **Table 2**.

Safety

Maternal Assessments

Results from maternal ECGs, vital signs, and clinical laboratory assessments were comparable for both groups. There were no significant changes in maternal blood pressure with treatment; mean systolic and diastolic blood pressures following infusion of retosiban or placebo (0–48 hours) are shown in **Figure 4**. Maternal adverse events and serious adverse events were generally similar across treatment groups. There were 14/30 (47%) adverse

events and 2/30 (7%) serious adverse events reported in the retosiban group, compared with 17/34 (50%) and 2/34 (6%) in the placebo group. Adverse events are displayed in **Table 3** and a summary of serious adverse events is shown in **Table 4**. There was one report of postpartum haemorrhage that occurred more than 30 days after the completion of retosiban. The event was considered not related to treatment.

Fetal Assessments

There were no significant changes in the modified biophysical profile and values were similar across all treatment groups. Fetal heart rate parameters were not significantly different in women treated with retosiban or placebo. In one woman in the placebo group, there was a fetal heart rate deceleration that resolved spontaneously. Mean fetal and maternal heart rates following maternal administration of retosiban or placebo (0–48 hours) are shown in **Figure 5**.

Neonatal Assessments

Apgar scores and growth parameters were consistent with those expected for the estimated gestational age at birth and were similar across groups. Neonatal endpoints and gross developmental follow-up at approximately 1 month are summarised in **Table 5A, B**. Adverse events were reported in 4/30 (13%) and 7/34 (21%) of retosiban- and placebo-exposed neonates, respectively. Adverse events in newborns are summarised in **Table 6**. Two of 30 (7%) neonates whose mothers received retosiban had a serious adverse event reported compared with 3/34 (9%) of placebo-exposed neonates (**Table 7**). Neonatal adverse events and serious adverse events were generally associated with preterm birth complications or had confounding risk factors.

DISCUSSION

The results of this study demonstrate that short-term treatment with retosiban significantly prolongs pregnancy and reduces the incidence of preterm birth. Few, if any, placebo-controlled studies have demonstrated an effect of this magnitude [7, 15, 16]. This is encouraging, as data on the efficacy of current tocolytics are contradictory and adverse effects have been reported in mothers or offspring [17]. To date, no tocolytic has been demonstrated effectively to delay delivery and improve outcome, although some agents, such as the beta-sympathomimetics, have been demonstrated to delay delivery [18]. This represents a dilemma, since it is known that babies born at later gestational ages have lower morbidity and mortality, yet delaying delivery has not been shown to improve outcome [9]. There are many possible explanations, such as methodological issues in the clinical trials or failure to use the time to perform procedures that improve outcome. More worrying is the possibility that administration of a tocolytic could theoretically maintain the fetus in an adverse intrauterine environment. In light of this, it is important that patients are carefully selected for tocolysis, with exclusion of those having aetiological factors, such as abruption or intrauterine infection, which could adversely influence the outcome. The results of this study demonstrate a significant prolongation in time to delivery in women administered retosiban for the treatment of preterm labour and form the basis for phase 3 trials that will determine whether the prolongation of the pregnancy is associated with improved outcomes in the offspring.

Additional studies are in progress to further elucidate the mechanisms of retosiban action on the myometrium and other tissues, such as the amnion. Interestingly, in the present study there was a marked increase in the duration of pregnancy following a single, time-limited infusion. This observation raises questions about the pathophysiology of preterm labour, and

suggests that in this patient population the initiating stimulus may be discrete, self-limited, and non-recurrent.

The retosiban infusion was well tolerated, and there was no indication of a safety issue for mother, fetus, or newborn. A theoretical safety concern with retosiban is an increased risk of postpartum haemorrhage if delivery occurs within a few hours of infusion. A case of postpartum haemorrhage occurred more than 30 days after retosiban and was not considered related to treatment. Because of the mechanism of action of retosiban and the role of oxytocin in promoting haemostasis after delivery, it will be important to monitor similar events in subsequent trials.

Treatment discontinuations and dose escalations provide evidence that the initial retosiban dosing regimen, consisting of a 6-mg loading dose and 6-mg/hour infusion, is the lowest effective dose. More women discontinued study drug in the placebo group than in the retosiban group. In addition, more women taking placebo had their infusion rates increased compared with women taking retosiban (65% vs. 37%). As almost 40% of women on retosiban required a dose increase, it is unlikely that a dose lower than 6 mg/hour would provide adequate effect. Taken together, the data from this study support the initial 6-mg/hour infusion rate as the lowest effective dose for the majority of women, while recognising that a considerable number of women may require higher doses to attain a satisfactory response.

Strengths and Limitations

The strength of this study is that it provides evidence for the efficacy, safety, and tolerability of a specific oxytocin receptor antagonist for the treatment of spontaneous preterm labour,

and thus represents a proof-of-concept study in this population. It is perhaps surprising that the effects on time to delivery, preterm birth, and use of rescue tocolysis were so marked, given the heterogeneous population typical of such studies. The difference in the effect on uterine quiescence between active treatment and placebo groups was not statistically significant, although there was a markedly higher rate of quiescence in women who received retosiban (62% vs. 41%). A potential limitation of this study is that it was not, nor was it intended to be, a definitive trial to demonstrate the effectiveness of retosiban in clinical practice. Nor was it designed to demonstrate improved neonatal morbidity and mortality; there was no long-term neonatal follow-up. The inclusion criteria, similar to many prior trials investigating tocolytic agents, did not include fetal fibronectin or cervical ultrasound, which may be used in clinical practice. Furthermore, women at early gestational ages (<30 weeks) were not recruited.

The advent of a therapeutic intervention that could significantly prolong pregnancy in patients with spontaneous preterm labour would be invaluable. While the mode of action of retosiban in preterm labour is not fully understood, this placebo-controlled study found that the short-term administration of retosiban halted preterm labour and prolonged pregnancy to a degree that could have a positive impact on perinatal outcomes.

CONCLUSION

In conclusion, this phase 2 study provides proof-of-concept evidence for the efficacy and safety of retosiban, a prerequisite for investment in phase 3 clinical trials. Whether the tocolytic effect of retosiban results in improved neonatal and infant outcomes following preterm labour at early and late gestational ages remains to be determined.

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Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: ST received consultancy fees, travel reimbursement and/or honoraria payments with contract research and commercial organisations including GlaxoSmithKline; HM received grant funding for study administration, travel reimbursement, and consultancy fees from GlaxoSmithKline; GV received grant funding for study administration and consultancy fees from GlaxoSmithKline; JS, BS, MF, TM, MP, and KB are employees of GlaxoSmithKline and own shares of GlaxoSmithKline company stock.

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Valenzuela, Jerry Snidow, and Brendt Stier were involved in study design, data analysis, and data interpretation; Michael Fossler was involved in the pharmacological aspects of study design, data analysis, and data interpretation; Timothy Montague was involved in statistical aspects of study design, data analysis, and data interpretation; Marcy Powell and Kathleen Beach were involved in data analysis and data interpretation.

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FIGURE LEGENDS

Figure 1. Disposition of women in proof-of-concept study (IP=investigational product).

Figure 2. Mean uterine contraction frequency.

Figure 3. Scatter plot of days to delivery versus gestational age at randomisation. The solid line represents the time in days to achieve 37 weeks. Women falling below the solid line delivered before 37 weeks and those above the line delivered after 37 weeks. The dashed red and blue lines display the linear fit for time to delivery for the retosiban and placebo groups, respectively. The difference between the red and blue lines represents the difference between retosiban and placebo in mean days to delivery, which was consistent across gestational ages.

Figure 4. Maternal blood pressure (mean and 95% CrI) following administration of retosiban or placebo (0− 48 hours).

Figure 5. Maternal and fetal heart rate (mean and 95% CrI) following maternal treatment with retosiban or placebo (0− 48 hours).

Table 1. Summary of subject demographic and baseline characteristics

Treatment group	**Retosiban**	**Placebo**
Number treated	30	34
Age in years, mean (range)	25.2 (18-39)	27.8 (19-41)
BMI, mean (SD)	25.8 (4.4)	26.9 (4.3)
Race, n (%)		
African American	4 (13)	2 (6)
American Indian or Alaskan Native	1 (3)	2 (6)
Asian	2 (7)	6 (18)
White – Arabic/North African	1 (3)	0
White – White/Caucasian/European	22 (73)	24 (71)
Ethnicity, n (%)		
Hispanic or Latino	10 (33)	12 (35)
Non-Hispanic or Latino	20 (67)	22 (65)
Gestational age, n (%)		
$30^{6/7}$-$32^{6/7}$	9 (30)	15 (44)
$33^{0/7}$-$35^{6/7}$	21 (70)	19 (56)
Cervical dilatation, median cm	2	2
Contraction frequency, mean (SD)	12.5 (7.5)	12.9 (6.0)
Prior tocolytic, n (%)	6 (20)	10 (29)

BMI, body mass index; SD, standard deviation.

Table 2. Effect of partially informative versus non-informative prior

Prior	**Relative risk of uterine quiescence**	**Difference in time to delivery**
Partially informative prior using data from phase 2 dose-ranging study	1.53 (95% CrI: 0.98, 2.48)	8.2 (95% CrI: 2.7, 13.74)
Non-informative prior (phase 2a proof of concept study only)	1.54 (95% CrI: 0.94, 2.63)	7.3 (95% CrI: 1.0, 13.5)

CrI: credible interval.

Table 3. Maternal adverse events[a]

Adverse event	**Retosiban** ***n*** **= 30** ***n*** **(%)**	**Placebo** ***n*** **= 34** ***n*** **(%)**
Headache	4 (13)	1 (3)
Dyspepsia	3 (10)	1 (3)
Back pain	2 (7)	0
Nausea	2 (7)	1 (3)
Abdominal pain, upper	1 (3)	1 (3)
Amniotic fluid, decreased	1 (3)	1 (3)
Constipation	1 (3)	1 (3)
Premature rupture of membranes	1 (3)	2 (6)
Paraesthesia	0	2 (6)
Polyhydramnios	0	2 (6)
Postpartum depression	0	2 (6)

[a] Listed are all adverse events, regardless of treatment group. Women with more than one occurrence of the same type of adverse event are listed only once.

Table 4. Maternal serious adverse events[a]

Treatment	Adverse event	Investigator assessment of drug relatedness	Comments
Retosiban	Postpartum haemorrhage	No	The event occurred >30 days post discontinuation of retosiban
Retosiban	Musculoskeletal pain	No	The event was secondary to a motor vehicle accident and occurred >26 days post discontinuation of retosiban
Placebo	Amniotic fluid volume decreased	No	AFI decreased to 5.8 cm two days after completion of placebo infusion. Event resolved as AFI subsequently increased to 6.6 cm and 7.1 cm
Placebo	Hypertension	No	Elevated systolic and diastolic blood pressure at 3-week postpartum visit, approximately 5 weeks after completion of placebo infusion. Admitted to hospital and blood pressure normalised with antihypertensives

[a] A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, results in hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, is a congenital anomaly/birth defect, drug-induced liver injury, or any other event deemed medically important.

AFI, amniotic fluid index.

Table 5A,B. Neonatal Outcomes

A. Neonatal endpoints					
	Treatment	**Time point**	***N***	***n***	**Mean (SD)**
Apgar Score at 1minute	Retosiban	Birth	30	30	8.3 (0.88)
	PBO	Birth	34	34	8.2 (0.77)
Apgar Score at 5 minutes	Retosiban	Birth	30	30	9 (0.53)
	PBO	Birth	34	34	8.9 (0.34)
Length (cm)	Retosiban	Birth	30	28	47.8 (2.78)
	PBO	Birth	34	34	47.8 (3.39)
	Retosiban	Follow-up	30	22	50.6 (2.89)
	PBO	Follow-up	34	29	51.3 (3.3)
Neonatal weight (g)	Retosiban	Birth	30	30	3099 (512.6)
	PBO	Birth	34	34	2940 (585.0)
	Retosiban	Follow-up	30	22	3427 (635.5)
	PBO	Follow-up	34	30	3602 (659.5)
Neonatal head circumference (cm)	Retosiban	Birth	30	27	33.3 (1.78)
	PBO	Birth	34	34	33.1 (1.63)

	Retosiban	Follow-up	30	21	35.1 (1.75)
	PBO	Follow-up	34	27	35.2 (1.77)
Time to follow-up (days)	Retosiban	Follow-up	30	22	18.4 (15.67)
	PBO	Follow-up	34	31	25.1 (20.45)
B. Gross development reported at follow-up					
Gross development	Treatment	*n*	Normal	Abnormal	Not reported
	Retosiban	30	22	0	8
	PBO	34	30	1	3

Table 6. Adverse events occurring in neonates[a]

Adverse event	**Retosiban** ***n*=30 (%)**	**Placebo** ***n*=34 (%)**
Hypoglycaemia	2 (7)	1 (3)
Hyperbilirubinaemia	1 (3)	5 (15)
Jaundice	1 (3)	1 (3)
Anaemia	0	2 (6)
Hypercalcaemia	0	2 (6)
Malnutrition[b]	0	2 (6)

[a] Listed are all adverse events, regardless of treatment group. Neonates with more than one occurrence of the same type of adverse event are listed only once.

[b] Medical Dictionary for Regulatory Activities (MedDRA) preferred term for event reported as nutrition imbalance (infant).

Table 7. Neonatal serious adverse events[a]

Serious adverse event	Retosiban *n* = 30 (%) (events occurred in two neonates)	Placebo *n* = 34 (%) (events occurred in three neonates)
Hyperbilirubinaemia	1[b] (3)	2 [c,d] (6%)
Hypoglycaemia	1[e] (3)	0
Jaundice	1[e] (3)	0
Meconium in amniotic fluid	1[e] (3)	0
Apnoea	0	1[d] (3)
Malnutrition[f]	0	2[c,d] (6)
Respiratory distress	0	1[d] (3)
Tachypnoea	0	1[g] (3)

[a] A serious adverse event is any untoward medical occurrence that results in death, is life- threatening, results in hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, is a congenital anomaly/birth defect, drug-induced liver injury, or any other event deemed medically important.

[b] 37-week infant. Investigator noted a maternal/fetal blood group incompatibility (mother A+; infant O+).

[c] Delivered at 33 weeks' gestation.

[d] Delivered at 31 weeks' gestation.

[e] Infant born to a mother with gestational diabetes (risk of neonatal hypoglycaemia) following post-date induction (risk of meconium). Investigator attributed neonatal jaundice to maternal-fetal blood group incompatibility.

[f] Medical Dictionary for Regulatory Activities (MedDRA) preferred term for event reported as nutrition imbalance (infant).

[g] Delivered at $34^{6/7}$ weeks' gestation.

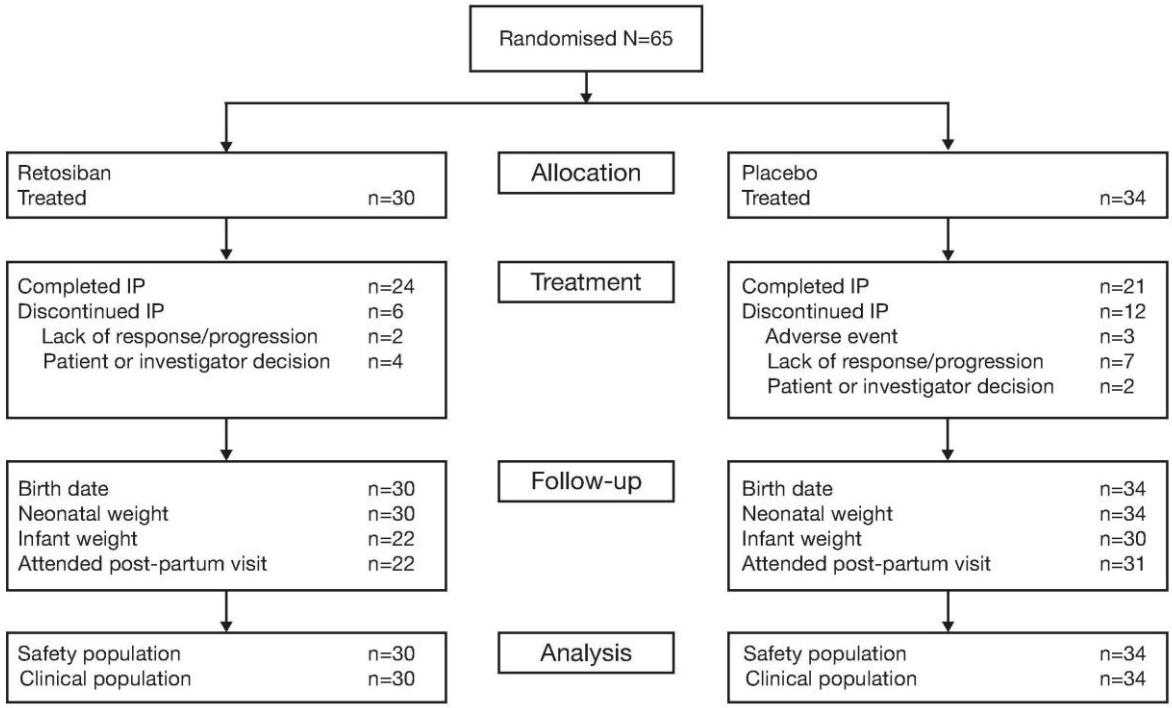


Figure 1

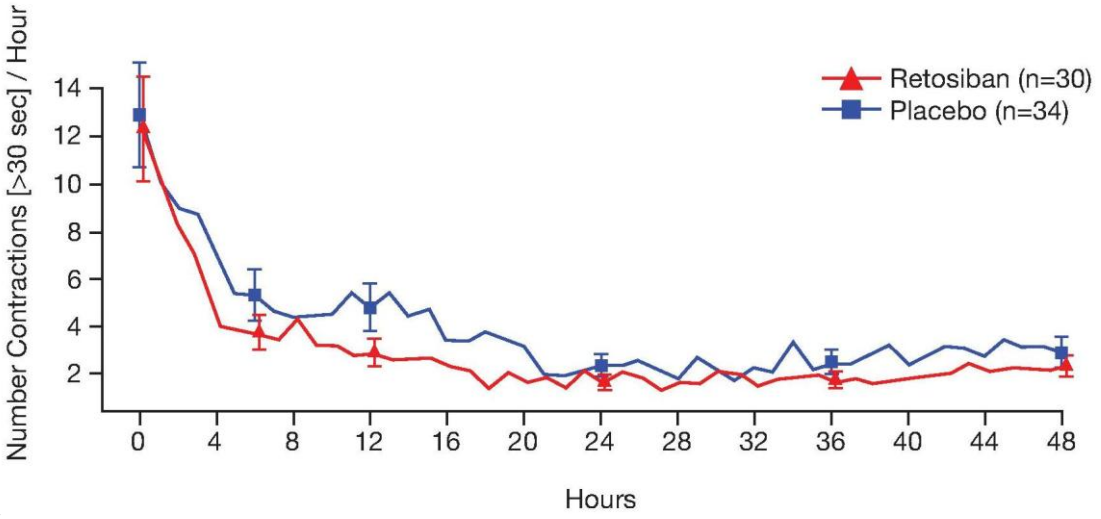
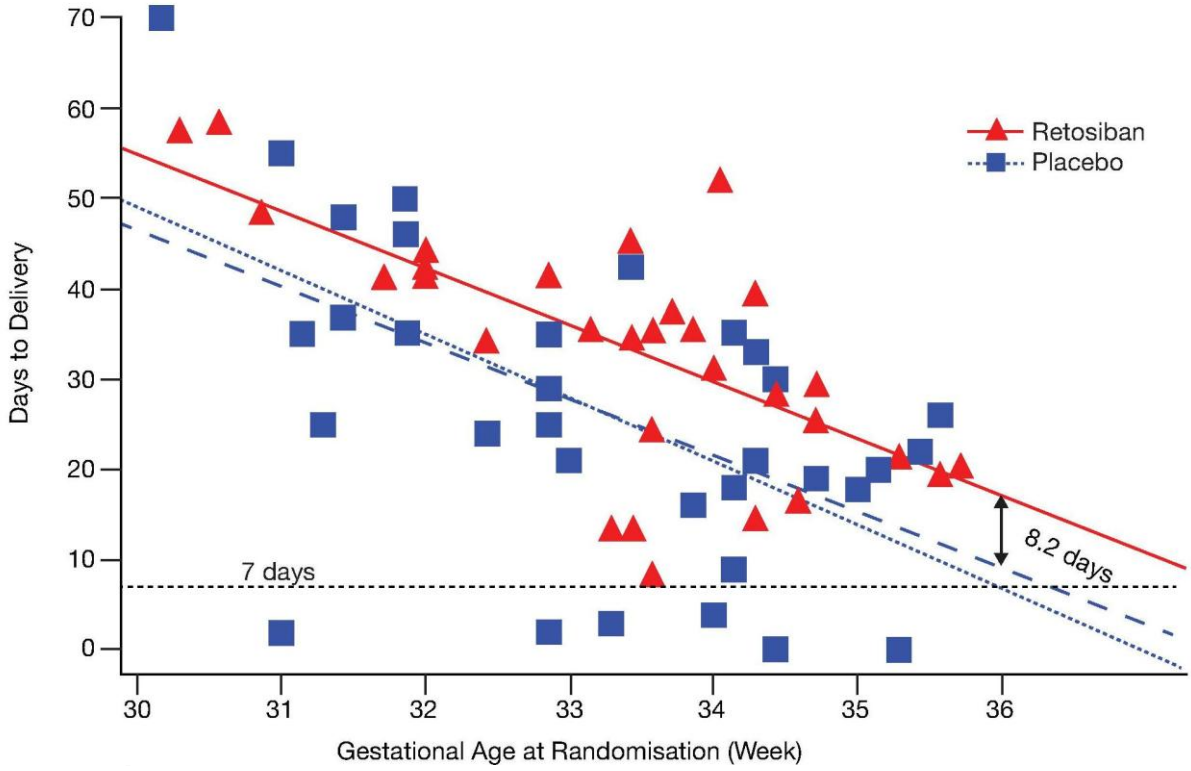


Figure 2



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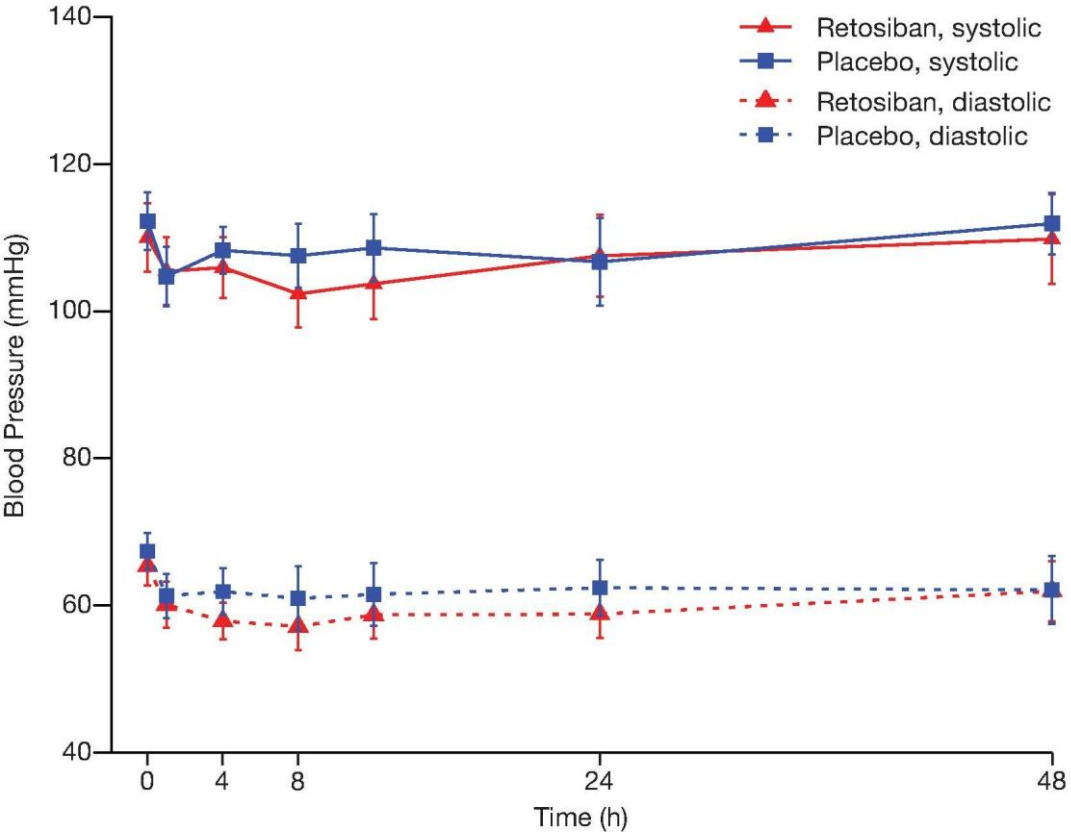

Figure 4

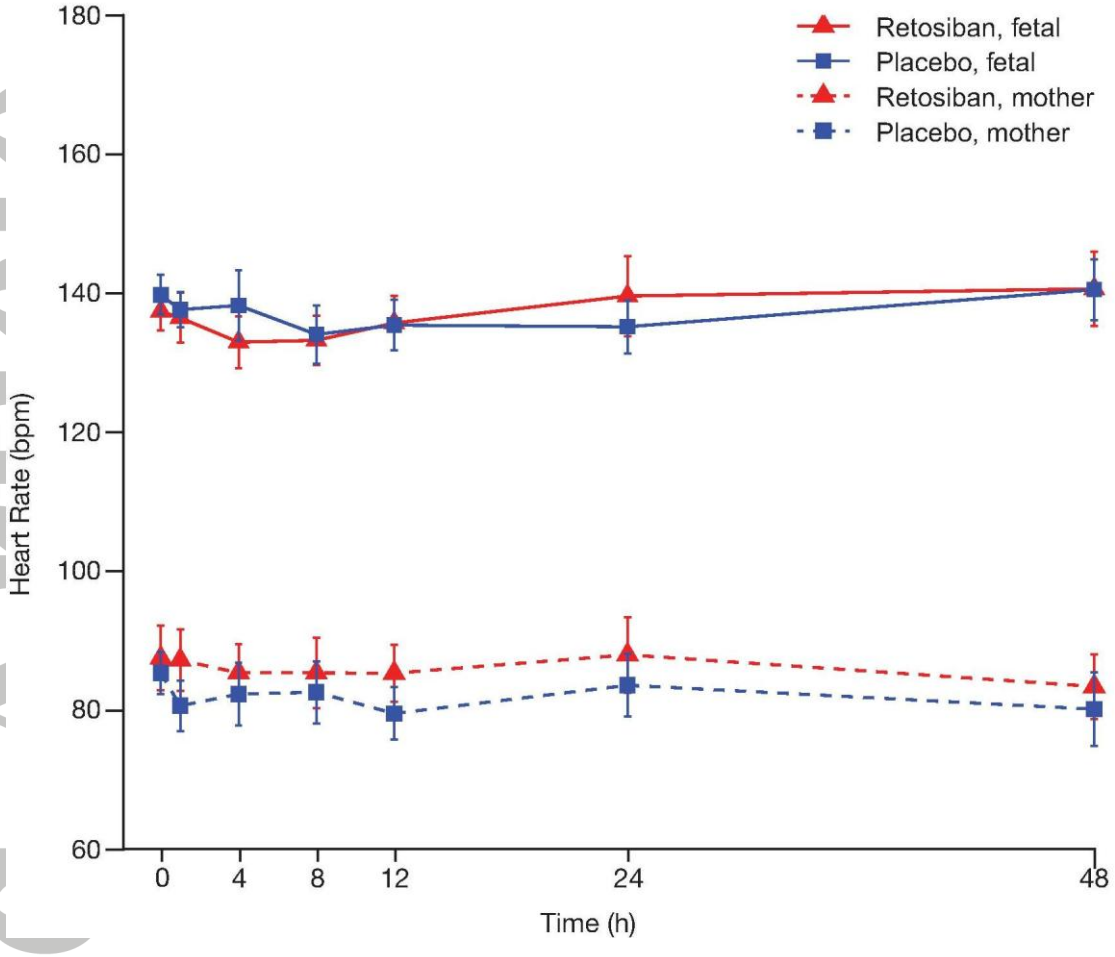

Figure 5