DRUGS IN PREGNANCY AND LACTATION

Treatment of spontaneous preterm labour with retosiban: a phase II pilot dose-ranging study

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AIMS

The aims of the present study were to investigate the maternal, fetal and neonatal safety and tolerability, pharmacodynamics and pharmacokinetics of intravenous (IV) retosiban in pregnant women with spontaneous preterm labour (PTL) between $34^{0/7}$ and $35^{6/7}$ weeks' gestation.

METHODS

In parts A and B of a three-part, double-blind, placebo-controlled, multicentre study, women were randomized 3:1 (Part A) or 2:1 (Part B) to either 12-h IV retosiban followed by a single dose of oral placebo (R-P) or 12-h IV placebo followed by single-dose oral retosiban (P-R).

RESULTS

A total of 29 women were randomized; 20 to R-P and nine to P-R. An integrated analysis found that adverse events were infrequent in mothers/newborns and consistent with events expected in the population under study or associated with confounding factors. Retosiban was rapidly absorbed after oral administration, with an observed half-life of 1.45 h. Efficacy analyses included 19 women. While not statistically significant, those receiving R-P more frequently achieved uterine quiescence in 6 h (R-P, 63%; 95% credible interval [CrI]: 38, 84; P-R, 43%; 95% CrI: 12, 78) and more achieved a reduction of ≥50% in uterine contractions in 6 h (R-P, 63%; 95% CrI: 38, 84; P-R, 29%; 95% CrI: 4, 64). The number of days to delivery was increased in women receiving R-P (median 26 days for R-P *vs.* 13 days for P-R).

CONCLUSIONS

Intravenous retosiban has a favourable safety and tolerability profile and might prolong pregnancies in women with PTL. The study provides the rationale and dosing strategy for further evaluation of the efficacy of retosiban in the treatment of PTL.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Preterm birth is the leading cause of infant morbidity and mortality and is associated with increased healthcare costs.
• Current tocolytic agents have not conclusively demonstrated improved neonatal outcomes.
• There is a need for agents that can prolong pregnancy in preterm labour (PTL) and improve outcomes for mothers and infants.

WHAT THIS STUDY ADDS
• Preliminary evidence suggests that intravenous retosiban might prolong pregnancy in spontaneous PTL and reduce uterine contraction frequency.
• Adverse events were infrequent in mothers/newborns and consistent with events expected in the patient population or associated with confounding factors.
• The study provided a rationale for further evaluation of the efficacy of retosiban in the management of spontaneous PTL.

Introduction

Preterm birth (PTB), defined as delivery before 37 weeks' gestation, is a leading cause of morbidity and mortality in newborns and infants [1–4]. PTB rates range from 6–12% in developed countries [5, 6]. The earlier the gestational age at delivery, the higher the risk of adverse neonatal outcomes [7–9].

Oxytocin is a potent stimulant of myometrial contractility, and a role for this hormone and its receptor is established in parturition [10, 11]. Atosiban, an oxytocin and vasopressin antagonist, is approved for use in Europe [12]. No drugs are currently approved for tocolysis in the United States [12–14], although a number of drugs are used off-label throughout the world for the treatment of spontaneous preterm labour (PTL) [1, 13, 15–18].

Retosiban is an oxytocin receptor antagonist developed for tocolysis. It is an oxazole diketopiperazine, highly selective for the oxytocin receptor (more than 1400-fold) over the human vasopressin receptors V_{1a}, V_{1b} and V_2 [19]. *In vitro* pharmacological studies demonstrated that retosiban significantly reduced the contractile activity of both spontaneously active and oxytocin-stimulated human myometrial strips [20]. *In vivo* preclinical studies showed that intravenous (IV) retosiban resulted in a dose-dependent decrease in oxytocin-induced contractions in anaesthetized rats and reduced spontaneous activity in late-term pregnant rats [21]. In phase I clinical studies of single and repeat oral or IV doses of retosiban in healthy nonpregnant women of child-bearing potential, retosiban was well tolerated and showed a favourable safety and pharmacokinetic (PK) profile (unpublished data, Study OTA 103772; Mindy Magee, PharmD, Director, Clinical Pharmacology Modelling and Simulation – US, RD Projects Clinical Platforms & Sciences, GSK, 709 Swedeland Road, Mail Stop UMW 2290, King of Prussia, PA, USA).

The present phase II study represented the first use of retosiban in pregnant women. The study consisted of three parts, the third of which (Part C) has been published [22]. Here, we present the results from Part A, a pilot phase to describe the maternal and fetal safety and tolerability, pharmacodynamics (PD) and PK of retosiban given intravenously to women in spontaneous PTL from $34^{0/7}$ to $35^{6/7}$ weeks' gestation, and Part B, which was designed to extend these observations and to demonstrate proof of mechanism based on the suppression of uterine contractions. Both parts also determined the PK of retosiban following a single oral dose. As the retosiban dose and treatment sequence were the same in both parts of the study, data for Parts A and B below are combined unless otherwise stated.

Methods

Study design

Parts A and B of this three-part, double-blind, placebo-controlled study were conducted at multiple centres (Table S1) and included women with a singleton pregnancy who experienced spontaneous PTL between $34^{0/7}$ and $35^{6/7}$ weeks' gestation. The study population was restricted to this gestational age range owing to the lower risk for neonatal complications compared with women of earlier gestational ages. It was therefore reasonable to undertake the study without rescue tocolysis, albeit with all women receiving retosiban (either immediately by infusion or after 12 h by mouth).

Part A aimed to recruit 12 eligible subjects to be randomized 3:1 to either IV retosiban followed by single-dose oral placebo [retosiban-placebo (R-P)], or IV placebo followed by 125 mg single-dose oral retosiban [placebo-retosiban (P-R)]. The retosiban loading dose and infusion rates were both increased in a stepwise fashion every 3 h to achieve mean plasma concentrations of 10, 30, 75 and 150 ng ml^{-1}, for a total of 12 h (Table S2). The IV loading and infusion doses were based on PK data from healthy nonpregnant women, within the therapeutic range of 10–60 ng ml^{-1} derived from preclinical models of PTL (unpublished data on file, see citation above).

In Part B, the safety, tolerability, PK and PD data from Part A were used to inform the dose and the duration of the infusion; however, no changes were made to the stepwise increase in the retosiban loading dose and infusion rates, as the retosiban concentrations during Part A matched the target concentrations. Part B aimed to recruit 63 subjects to be randomized 2:1 to the R-P or P-R treatment sequences.

For part B, a group sequential design was used with up to five planned cohorts, analysed in a cumulative manner with prespecified stopping rules based on the Bayesian predictive approach [23]. Criteria were defined for early stopping based on uterine contractions. The stopping criteria were based on the predictive probability of success at the final stage, given the data available at the interim analysis. If the predicted

probability of success exceeded the prespecified efficacy threshold (90%), the study was to be stopped early for success. If the predicted probability of success was below the prespecified futility threshold (20%), the study was to be stopped early for futility.

At the first planned interim analysis of 14 subjects, which was reviewed by a GSK Scientific Review Board, a decision was made to terminate Part B of the study. Although the predefined stopping rule for success was not met, the data at the interim analysis provided the first indication that IV retosiban acutely suppresses uterine contractions in women diagnosed with spontaneous PTL, with strong evidence to suggest that retosiban was effective in prolonging pregnancy. Moreover, meeting recruitment targets for Parts A and B, in women between $34^{0/7}$ and $35^{6/7}$ weeks' gestation, had been difficult and it was thought to be important to generate efficacy and safety information in women who were more likely to receive tocolysis in clinical practice. Based on the preliminary evidence of efficacy, along with a favourable safety profile, the Review Board decided that additional data supporting retosiban efficacy were required in a population that included women at earlier gestational ages. Part C recruited women between $30^{0/7}$ and $35^{6/7}$ weeks' gestation.

Written informed consent was obtained from all of the women. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki (2008) and was approved by the institutional review boards listed in the Supporting Information.

Subjects

Eligible subjects were 18–41 years of age, had a singleton pregnancy between $34^{0/7}$ to $35^{6/7}$ weeks' gestation based on the most reliable estimate available (usually the first-trimester ultrasound but, in keeping with standard clinical practice, using the date of the last menstrual period if the ultrasound was not available). All women had six or more uterine contractions per hour of at least 30 s duration by external cardiotocography, with cervical dilatation ≤3 cm and intact fetal membranes.

Subjects were excluded if they had any of the following: maternal or fetal indications for delivery, such as pre-eclampsia or fetal compromise; contraindication to tocolysis, such as clinically apparent intrauterine infection or placental abruption; and comorbid conditions with the potential to complicate pregnancy and outcomes, such as hypertension, pre-existing diabetes or substance abuse. Subjects could voluntarily withdraw from the study at any time or could be withdrawn at the discretion of the clinical investigator.

Endpoints and assessments

Safety. Primary safety endpoints included maternal safety and tolerability [vital signs, electrocardiograms (ECGs), clinical laboratory tests and adverse events (AEs)] during acute therapy and for the 24 h following treatment initiation. Continuous fetal heart rate (FHR) and amniotic fluid index monitoring were performed prior to and throughout therapy. These were used to determine a modified biophysical profile (BPP) score. Secondary neonatal safety endpoints included Apgar scores, weight, head circumference and length at birth. The infant weight,

head circumference, length and gross development were determined at a 4- to 6-week follow-up visit. Safety was assessed in the safety population, which included all randomized subjects who received at least one dose of study drug.

PK. PK endpoints included those after IV and oral dosing. Plasma samples were taken at baseline and approximately 2, 4, 8, 10, 12, 13, 14, 16, 20 and 24 h after the start of the infusion. Exact sampling times were recorded for each sample. For subjects who received IV placebo followed by a single 125 mg oral dose of retosiban, sample times at 12, 13, 14, 16, 20 and 24 hours correspond to pre-dose and 1, 2, 4, 8 and 12 h after oral dosing, respectively.

Efficacy. The primary PD endpoint assessed the number of contractions per hour and was made up of two components: the proportion of patients with fewer than four contractions per hour with no cervical change (uterine quiescence) and the proportion of women with at least a 50% reduction in the number of contractions (>30 s), with no cervical change at 6 h post-treatment initiation, maintained until 12 h post-treatment. Time to delivery was assessed as a tertiary clinical endpoint.

PD endpoints were assessed in the PD population, which consisted of all subjects from the safety population who provided PD data. Time to delivery was assessed in the clinical population, which included all subjects for whom birth data were available.

Statistics. The sample size and 3:1 randomization pattern for Part A were based on feasibility and were anticipated to be sufficient to characterize the safety/tolerability, PD and PK of the IV administration of retosiban. In Part B, the sample size and 2:1 randomization pattern provided at least 80% power to detect a difference in the proportion of patients achieving fewer than four uterine contractions per hour with no cervical change (uterine quiescence), assuming success rates of 25% and 65%, respectively, for placebo and retosiban, using a two-sided alpha of 0.05 and a continuity-corrected chi-square test with a null hypothesis of equal proportions. The randomization patterns aimed to ensure that as few women as possible were exposed to a delay in tocolysis.

Safety and tolerability data were summarized and no formal statistical analyses were performed.

For PK analyses, the IV data, together with data from Part C of the study, were fitted to a two-compartment model with auto-induction using NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD, USA). Details of this analysis have been presented elsewhere [24]. The model accounted for auto-induction of retosiban metabolism using the following equation:

$$CL = CL_{SS} - (CL_{SS} - CL_{initial})e^{(-k_{induction} \cdot Time)}$$

where CL_{SS} is the steady-state clearance after induction, $CL_{initial}$ is the initial clearance at the start of the infusion and $k_{induction}$ is a first-order rate constant describing the rate of induction. Model qualification was performed with bootstrapping, followed by a visual predictive check.

The PK data resulting from oral administration of retosiban were analysed using standard noncompartmental methods using WinNONLIN, version 6.3 (Pharsight Corporation, Cary, NC, USA).

For PD endpoints, statistical analyses were performed using Bayesian methods for inference. At the end of each stage, a posterior distribution for the relative risk of achieving uterine quiescence for retosiban *vs.* placebo was determined on the basis of prior and observed data. The mean of this posterior distribution provided an estimate of the relative risk, with the corresponding 2.5th and 97.5th percentiles of the posterior distribution, providing a 95% Bayesian credible interval (CrI) for the relative risk.

The predictive probability of success at each interim stage was also calculated. This was the probability of getting a 'significant result' at the end of the study, given the current observed data. A significant result was defined as the 95% Bayesian CrI for the posterior distribution for the relative risk that does not contain 1.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [25], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [26].

Results

Subject disposition and demographics

The numbers of randomized subjects, exclusions and subjects in each analysis population are given in Figure 1. Of the 29 subjects who were randomized, 20 were assigned to the R-P sequence and nine to the P-R sequence. One subject assigned to the P-R sequence did not receive the single oral retosiban dose. The PD and clinical populations excluded 10 subjects owing to protocol violations. Nine of these violations were related to evidence or concerns that screening assessments had not been performed, and occurred in subjects who were recruited by two investigators. One subject did not meet the entry criterion of having at least six contractions longer than 30 s in duration over the course of an hour. These 10 subjects were excluded from all efficacy analyses but were retained in the safety analysis. The efficacy analyses therefore included a total of 19 subjects (14 R-P and five P-R). The treatment groups were generally well matched with regard to demographic characteristics (summarized in Table 1).

Safety

Maternal AEs reported in two or more subjects are summarized in Table 2. Seven (35%) AEs were reported in the R-P group compared with one (11%) in the P-R group. There were more subjects randomized to R-P, and overall the numbers were small, which made it difficult to draw any conclusions. One woman who received the R-P treatment sequence experienced a postpartum haemorrhage with a retained placenta approximately 48 h after completion of the retosiban infusion. There was a maternal obstetric history of retained placenta, which increased the risk of recurrence. The ECGs, vital signs and clinical laboratory assessments were comparable in both groups.

FHR at comparable time points throughout dosing and modified BPP assessed before and after IV and oral administration were not significantly different in women treated in the R-P or P-R groups (Figure 2). No fetal AEs were reported. Neonatal Apgar scores; weight, length and head
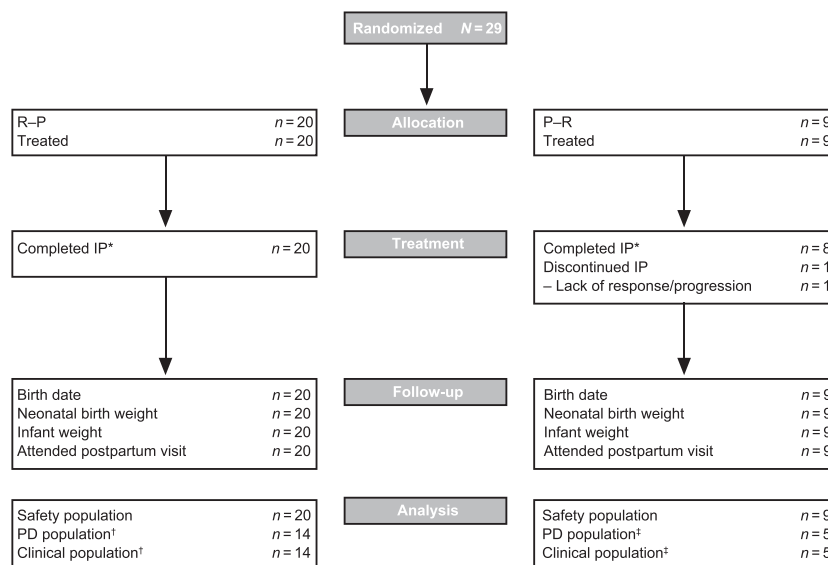

Figure 1

Subject disposition. *Completed investigational product (IP), defined as having received at least 95% of the infusion. †Six subjects excluded owing to protocol violation. ‡Four subjects excluded owing to protocol violation. PD, pharmacodynamics; P-R, placebo infusion over 12 h followed by a single oral dose of retosiban 125 mg; R-P, retosiban infusion over 12 h followed by a single oral placebo dose

Table 1

Summary of subject demographic and baseline characteristics

Treatment group	R-P	P-R
Number randomized, n	20	9
Age in years, mean (SD) [min–max]	25.6 (5.0) [19–37]	26.7 (5.7) [18–36]
Race, n (%)		
Black	1 (5)	0
Asian	2 (10)	1 (11)
White	17 (85)	8 (89)
Ethnicity, n (%)		
Hispanic or Latino	3 (15)	0
Non-Hispanic or non-Latino	17 (85)	9 (100)
Cervical dilatation, median (cm)	1.5	1.0
Contraction frequency, mean (SD)	11.3 (5.8)	11.8 (4.5)

P-R, placebo infusion over 12 h followed by a single oral dose of retosiban 125 mg; R-P, retosiban infusion over 12 h followed by a single oral placebo dose; SD, standard deviation

Table 2

Summary of adverse events occurring in two or more maternal subjects across all treatments

System organ class preferred term, n (%)	R-P n = 20	P-R n = 9	Total N = 29
Any event	7 (35)	1 (11)	8 (28)
Anaemia	2 (10)	0	2 (7)
Urinary tract infection	1 (5)	1 (11)	2 (7)
Headache	2 (10)	0	2 (7)

P-R, placebo infusion over 12 h followed by a single oral dose of retosiban 125 mg; R-P, retosiban infusion over 12 h followed by a single oral placebo dose

circumference at birth and follow-up; and an assessment of gross general development at follow-up (at ~40 weeks' adjusted gestational age) were consistent with those expected for the population, taking into account the gestational age at delivery. Three neonatal serious AEs (SAEs) were reported, two in one male infant with congenital anomalies diagnosed after birth, who was born at 36 weeks' gestation, in the R-P treatment sequence group; however, the mother had epilepsy, abnormal glucose tolerance and a pre-existing diagnosis of polyhydramnios. The investigator and sponsor concluded that the congenital abnormalities were unrelated to treatment, as they occurred during organogenesis in the first trimester, whereas retosiban was given in the third

trimester. The other neonatal SAE was hypoglycaemia, reported in a male infant in the R-P treatment arm. The investigator considered the hypoglycaemia to be possibly due to prematurity.

PK

Oral administration. PK data from the eight women who received single-dose oral retosiban are shown in Table 3. Retosiban was rapidly absorbed, with peak concentrations occurring 2 h postdose. The observed mean half-life (1.45 h) was similar to that previously observed in nonpregnant women (unpublished data on file, Study OTA 105101; Mindy Magee, PharmD, Director, CPMS – US, RD Projects Clinical Platforms & Sciences, GSK, 709 Swedeland Road, Mail Stop UMW 2290, King of Prussia, PA 19406, USA).

IV administration. Empirical Bayes estimates of clearance ($CL_{initial}$, CL_{ss}), volume of central compartment (V_1), volume of peripheral compartment (V_2) and intercompartmental clearance (Q) are summarized in Table 4. The predicted mean concentration–time plot, predicted by the model (with observed data superimposed), is shown in Figure 3. The initial clearance of retosiban (69.7 l h^{-1}) was high, suggesting extensive metabolism. Over the 24-h treatment period, clearance further increased by about 25%. The volumes of distribution were large, suggesting extensive distribution in the body, consistent with the low protein binding (33%) seen in human plasma.

Efficacy outcomes. Although the results were not statistically significant, there was preliminary evidence that IV retosiban suppresses uterine contractions and prolongs pregnancy in women in spontaneous PTL.

The proportion of women achieving uterine quiescence within 6 h of treatment was 63% (95% CrI: 38, 84) following R-P treatment compared with 43% (95% CrI: 12, 78) following P-R treatment, with a relative risk (RR) of 1.59 (95% CrI: 0.68, 5.44). The predictive probability of success (i.e. the probability of getting a 'significant result' at the end of the study, given the current observed data) was 52.7%. The proportion of women achieving at least a 50% reduction in the number of contractions, with no cervical change at 6 h and a maintained reduction until 12 h, was 63% (95% CrI: 38, 84) for R-P compared with 29% (95% CrI: 4, 64) for P-R. The RR of achieving ≥50% reduction in the number of contractions was 2.61 (95% CrI: 0.86, 14.66), with a predictive probability of success of 81.2%.

Women administered R-P had a mean 12-day increase in the number of days to delivery compared with women administered P-R. The median time to delivery was 26 days for R-P compared with 13 days for P-R (Figure 4).

Although a formal sensitivity analysis was not performed, examination of the 10 excluded subjects' data suggested that the inference would not have changed if the data had been included in the final analyses.
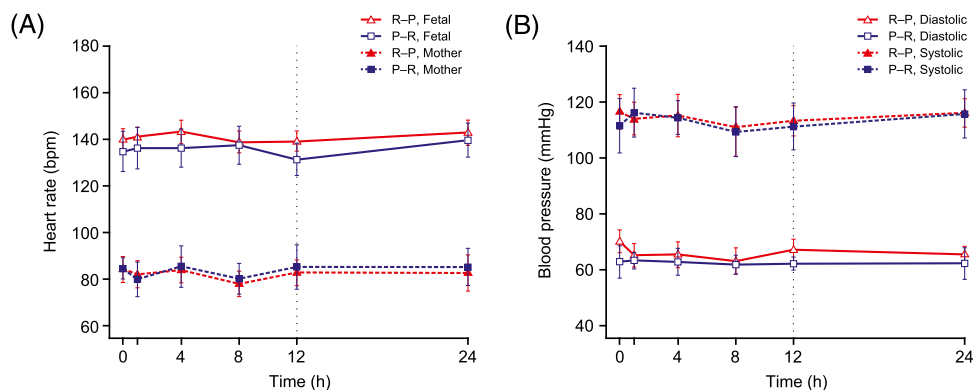
Figure 2

Maternal and fetal heart rate and maternal blood pressure. (A) Maternal and fetal heart rate. The dotted vertical line represents the end of the 12-h intravenous (IV) retosiban infusion or administration of the oral dose. (B) Maternal blood pressure. The dotted vertical line represents the end of the 12-h IV infusion and administration of the oral dose. Error bars represent the 95% Confidence interval

Table 3

Summary of the pharmacokinetics of a single 125 mg tablet of retosiban given to eight subjects in preterm labour

Parameter	Geometric mean CV% (min, max)
AUC$_{(0-t)}$ (ng*h ml^{-1})	419.1
	43.2
	(243.7, 743.1)
AUC$_{(0-\infty)}$ (ng*h ml^{-1})	429.7
	41.1
	(263.7, 748.2)
C$_{max}$ (ng ml^{-1})	126.9
	68.6
	(57.8, 340.5)
T$_{max}$^{a} (h)	2
	(0.07, 2.78)
Half-life (h)	1.45
	35.8
	(1.05, 2.79)

AUC$_{(0-t)}$, area under the plasma concentration–time curve from zero to the time of the last quantifiable concentration; AUC$_{(0-\infty)}$, area under the curve of the plasma concentrations from zero to infinity; C$_{max}$, maximum plasma concentration; CV%, coefficient of variation, percent; T$_{max}$, time to maximum plasma concentration
^{a}Median (min–max)

Table 4

Empirical Bayes estimates of intravenous retosiban pharmacokinetic parameters ($n = 14$)

Parameter	Geometric mean CV% (min, max)
CL$_i$ (l h^{-1})	69.7
	15.8
	(50.7, 93.8)
CL$_{ss}$ (l h^{-1})	86.9
	15.8
	(63.3, 117.1)
V$_1$ (l)	20.2
	38.5
	(11.9, 34.1)
V$_2$ (l)	47.9^a
Q (l h^{-1})	39.8^a

CL$_i$, initial clearance; CL$_{ss}$, clearance at end of treatment; CV, coefficient of variation; Q, intercompartmental clearance; V$_1$, volume of central compartment; V$_2$, volume of peripheral compartment
^{a}Interindividual variability for these parameters was not estimated

Discussion

The purpose of the present phase II dose-ranging study was to characterize maternal, fetal and neonatal safety and tolerability, and to assess the PD and PK profile of 12-h IV retosiban and the PK profile of oral retosiban in women with spontaneous PTL.

Protocol-specified maternal, fetal and neonatal safety assessments, as well as maternal, fetal and neonatal AEs, were consistent with those expected for the study population or were associated with confounding risk factors. Postpartum haemorrhage is a potential concern with the use of retisoban, given the effect of oxytocin antagonism on uterine tone and postpartum bleeding. Postpartum haemorrhage with retained placenta was reported in one subject treated with 12-h IV retosiban followed by oral placebo; however, several factors confounded the relationship between the event and retosiban exposure. Neonatal SAEs were generally associated with known complications of PTB or identified confounders unrelated to study drug administration.
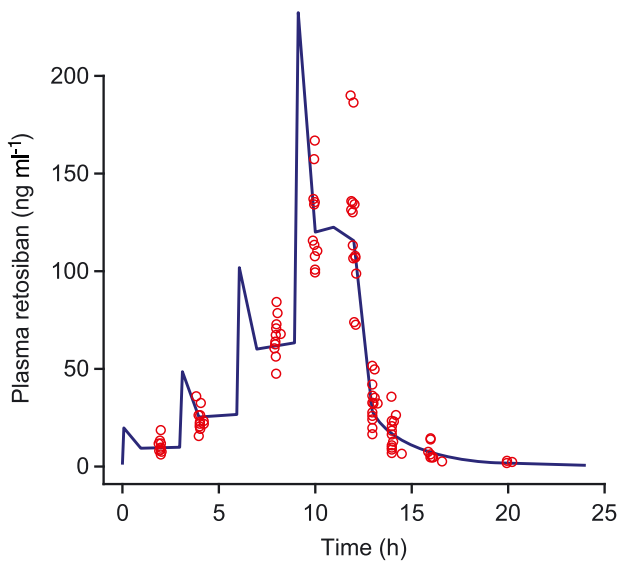
Figure 3

Mean plasma retosiban concentration–time plot. The solid line is the mean predicted from the pharmacokinetic model, and the open circles are the observed concentration data from the 14 patients who received the 12-h intravenous infusion of retosiban and were included in the pharmacokinetic analysis
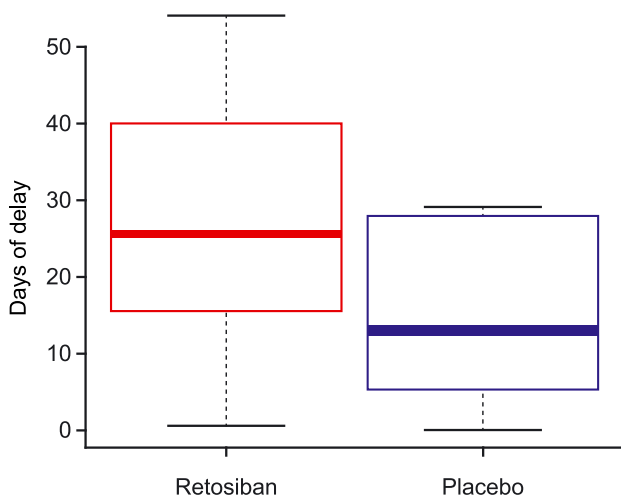

Figure 4

Number of days to delivery following treatment initiation. Middle line is the median, outer edge of box is the 25th and 75th quantile and the whiskers represent the min and max values

Although subject numbers were low, the efficacy analysis provided preliminary evidence that IV retosiban suppresses uterine contractions in women in spontaneous PTL, as demonstrated by a nonsignificant reduction in both the proportion of women achieving uterine quiescence (defined as four or fewer contractions per hour) and the proportion of women with a ≥50% reduction in the number of uterine contractions. The initial finding that IV retosiban infusion over 12 h followed by a single oral placebo dose might be associated with a difference in the number of days to delivery

was an important observation. The latter finding is interesting because both groups were exposed to retosiban, albeit by different administration modes and at different time periods. These results might imply that retosiban is more effective in prolonging pregnancies when given to women immediately as an IV infusion than when administration is delayed for 12 h and it is given as a single oral dose. It remains to be determined whether this is because of the timing, mode of administration or the duration of the effective plasma concentration. However, the result is consistent with the hypothesis that immediate IV retosiban could improve neonatal outcome by prolonging gestation.

Although the oral PK population analysed was small, the data indicated that retosiban is rapidly absorbed after oral administration, with peak concentrations about 2 h postdose. The observed half-life (1.45 h) was similar to that observed in our phase I study in nonpregnant women of child-bearing age. After IV administration, the initial clearance of retosiban (69.7 $l\ h^{-1}$) was significantly higher than that found in healthy women of child-bearing potential [50–63.6 $l\ h^{-1}$ (unpublished data on file, Study OTA 103772: Mindy Magee, PharmD, Director, CPMS – US, RD Projects Clinical Platforms & Sciences, GSK, 709 Swedeland Road, Mail Stop UMW 2290, King of Prussia, PA 19406, USA)]. This was not an unexpected finding, as pregnancy has been found to increase the clearance of many drugs, particularly cytochrome P450 (CYP) 3A4 substrates [27].

Based on a planned interim analysis of 14 subjects, a decision was made to stop Part B of the study and initiate a third, proof-of-concept, Part C, as reported recently [22]. Although the predefined stopping criteria (predictive probability of success greater than 90%) were not met, this decision was based on the preliminary evidence that retosiban might be effective in prolonging pregnancy in women in spontaneous PTL at $34^{0/7}$ to $35^{6/7}$ weeks' gestation, highlighting a requirement for efficacy data in women at earlier gestational ages (30–35 weeks).

There are several challenges to conducting clinical research in PTL in addition to those challenges usually encountered during the development of new drugs. Pregnancy results in significant physiological changes, including increased plasma volume, CYP450 activity, and hepatic and renal blood flow [27]; phase I studies in nonpregnant females cannot be wholly extrapolated. Another challenge is the evaluation of the clinical outcomes. The interpretation of the effects on uterine contractions is complicated by the difficulty in diagnosing PTL, and, even with strict diagnostic criteria, there is a marked placebo response. Furthermore, the contraction frequency does not necessarily correlate with the strength of effective contractions, so contraction frequency may not be a reliable indicator for PTL progression. Our results were also limited by the relatively small number of women included in the study, particularly in the efficacy analyses. This can be partly attributed to the high proportion of women excluded because of protocol violations. These were mainly due to the failure of two investigators to undertake the screening assessments and were not related to the study drug.

The present dose-ranging pilot study provided evidence of the safety and tolerability of retosiban, as well as preliminary evidence of its effect on uterine contractility, a

prerequisite for the proof-of-concept study to evaluate efficacy in the treatment of PTL.

Competing Interests

Contributors

All authors met the International Committee for Medical Journal Editors criteria for authorship, were fully involved in manuscript development and assume responsibility for the direction and content. S.T. and D.S. had a major role in the study design, implementation, data review and interpretation; G.V., J.S., B.S. and L. C. were involved in study design, data analysis and interpretation; M.F. was involved in the pharmacological aspects of study design, data analysis and interpretation; C.B. and T.M. were involved in statistical aspects of study design, data analysis and interpretation.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13336/suppinfo

Table S1 List of investigators and sub-investigators
Table S2 Loading and maintenance dose schedule for Part A