The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: OTA105256

Title : A randomized, double-blind, placebo-controlled, dose ranging study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK221149A administered intravenously and the pharmacokinetics of GSK221149A administered orally in healthy, pregnant females, with uncomplicated preterm labor between $30^{0/7}$ - $35^{6/7}$ weeks gestation

Rationale: GSK221149A is an oxytocin receptor antagonist, which is being developed for the treatment of preterm labor (PTL) without premature rupture of membranes. Preterm birth (PTB), frequently preceeded by PTL, is the largest single cause of infant morbidity and mortality and is frequently associated with long-term disability. Preterm births (24 to 37 weeks gestation) affect 6 to 12% of pregnancies in developed countries. They are the cause of 70% of neonatal deaths not associated with congenital malformations, and are associated with long-term neurocognitive, respiratory and ophthalmic morbidity. The clinical diagnosis of PTL is based on the rate and duration of uterine contractions and cervical changes. The aim of this study was to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of intravenous (IV) and oral administration of GSK221149A in pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks' gestation in Parts A and B. The aim of Part C was to investigate the safety, tolerability, PK and PD of IV administration of GSK221149A in pregnant women in PTL between $30^{0/7}$ and $35^{6/7}$ weeks' gestation.

Phase: IIA

Study Period: Initiation Date: 03 Dec 2007
Completion Date: 22 Jun 2011

Study Design: Parts A and B used a multicenter, randomized, double-blind, placebo-controlled, dose ranging design. Part C of the study used a randomized, double-blind, parallel group, placebo controlled design.

Centres: Multi Center study. Sites were located in the United States, United Kingdom, Singapore, France, Bulgaria, Spain, Argentina, South Korea, and Colombia.

Indication: Pre-term Labor

Treatment: For Parts A and B, subjects between $34^{0/7}$ and $35^{6/7}$ weeks' gestation in preterm labor were randomly assigned to receive either an IV infusion of GSK221149A followed by a single oral placebo dose, or an IV infusion of placebo followed by a single oral dose of 125 mg GSK221149A. The retosiban loading dose and infusion rate were increased in a stepwise fashion every 3 hours to achieve plasma concentrations of 10, 30, 75, and 150 ng/mL. In Part A, subjects were randomized in a 3:1 ratio for GSK221149A:placebo treatment. In Part B, subjects were randomized in a 2:1 ratio for GSK221149A:placebo treatment.

In Part C, subjects between $30^{0/7}$ and $35^{6/7}$ weeks' gestation in preterm labor were randomly assigned 1:1 to receive either an IV infusion of GSK221149A as 6 mg loading dose followed by a 6 mg/hour continuous infusion or placebo infusion for 48 hours. Subjects were stratified based on gestational age into two groups: Group 1 consisted subjects from $30^{0/7}$ weeks through $32^{6/7}$ weeks and Group 2 consisted subject from $33^{0/7}$ weeks through $35^{6/7}$ weeks gestational age. If, after one hour, subjects did not exhibit a satisfactory response the infusion rate could be increased to 12 mg/hour following a 6 mg loading dose. A satisfactory response was defined as a "clinically relevant reduction in the frequency of contractions with no increase in cervical dilation".

Objectives: Primary Objectives

Parts A and B:

- To describe the maternal safety and tolerability of GSK221149A administered IV to healthy pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks gestation
- To describe the fetal safety and tolerability of GSK221149A administered IV to healthy pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks gestation
- To evaluate the PD of GSK221149A in pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks gestation
- To characterize the PK of GSK221149A administered IV to pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks gestation

Part C

- To describe the maternal safety and tolerability of GSK221149A administered IV to healthy pregnant women in PTL between $30^{0/7}$ and $35^{6/7}$ weeks gestation

- To describe the fetal safety and tolerability of GSK221149A administered IV to healthy pregnant women in PTL between $30^{0/7}$ and $35^{6/7}$ weeks gestation
- To evaluate the PD of GSK221149A in pregnant women in PTL between $30^{0/7}$ and $35^{6/7}$ weeks gestation
- To characterize the PK of GSK221149A administered IV to pregnant women in PTL between $30^{0/7}$ and $35^{6/7}$ weeks gestation

Secondary

Parts A and B

- To describe the effect of maternal treatment with GSK221149A on short term neonatal growth and development
- To characterize the PK of GSK221149A administered orally to pregnant women in PTL between $34^{0/7}$ and $35^{6/7}$ weeks gestation as data permit

Part C

- To describe the effect of maternal treatment with GSK221149A on short term neonatal growth and well-being

Tertiary

Parts A and B:

- To assess fetal drug exposure, if parturition occurs within 24 hrs of therapy
- To determine to what extent GSK221149A is excreted in the breast milk if parturition occurs within 24 hrs of therapy (if the mother is lactating)
- To characterize the effect of acute therapy with GSK221149A on time to parturition

Part C

- To assess fetal drug exposure, if parturition occurs within 24 hrs of therapy
- To determine to what extent GSK221149A is excreted in the breast milk if parturition occurs within 24 hrs of therapy (if the mother is lactating)
- To characterize the effect of acute therapy with GSK221149A on time to parturition

Statistical Methods: Part A: A sample size of 16 subjects (12 GSK221149A, 4 placebo) was chosen to estimate the maximal response rate and dose-response relationship to select the dose for Part B of the study. Part B: A sample size of 63 subjects (42 GSK221149A, 21 placebo) was chosen to provide at least 80% power to detect an absolute increase of 40% in the proportion of patients achieving uterine quiescence (65% vs 25%, GSK221149A vs placebo). Part C: A sample size of 64 subjects (32 GSK221149A, 32 placebo) was chosen to provide at least 85% power to detect an absolute increase of 40% in the proportion of patients achieving quiescence (65% vs 25%, GSK221149A vs placebo). Statistical analyses were performed to compare the proportion of women achieving quiescence between GSK221149A and placebo using Bayesian methods for inference. Based on the available data and the defined prior, a posterior distribution for the relative risk was determined. The mean of this distribution provided an estimate of the relative risk and the corresponding 2.5th and 97.5th percentiles of the distribution provided a 95% Bayesian credible interval for the relative risk. For Part A, a non-informative prior was used; for Part B, an informative prior based on data from Part A was used and for Part C, a partially informative prior based on data from Parts A and B was used.

In Part B, a planned interim analysis was conducted after the first 12 subjects completed the study, after which time the decision was made to stop Part B and initiate Part C of the study. In Part C, planned interim analyses were conducted following the completion of each of 4 cohorts of 16 subjects. Pre-defined criteria for stopping for futility and for stopping for success were evaluated at each interim analysis.

In Part C, supportive analysis of time to delivery and proportion of births prior to $37^{0/7}$ weeks were conducted at each interim analysis using Bayesian methods for inference. Time to delivery was analysed as a function of both treatment and gestational age at study entry using a partially informative prior based on data from Parts A and B. The mean difference and associated 95% Bayesian credible interval was calculated from the posterior distribution. The proportion of births prior to $37^{0/7}$ weeks was analyzed using the same methods for proportion of women achieving quiescence using a non-informative prior.

Study Population:

Number of Subjects:	Parts A and B	Part C	Total
Planned N	79	64	143
Completed N	29	64	93
Demographics			
N (ITT)	29	64	93
Mean Age in Years (sd)	26.2 (5.3)	26.5 (6.1)	26.4 (5.8)
Mean Weight in Kg (sd)	a	68.9 (12.4)	68.9 (12.4)

White n (%)	25 (86%)	47 (73%)	72 (80%)	

a. Mean weight was not recorded in Parts A and B of the study.

Pharmacokinetics Results:

The oral pharmacokinetics of a single 125 mg dose of retosiban to patients in the placebo group of Part A were analyzed using non-compartmental methods.. The peak and total exposure in pregnant women is comparable to what has been observed in healthy volunteers. The oral half-life of retosiban in pregnant women is in line with previous data. The intravenous pharmacokinetics of retosiban were evaluated using a mixed-effects modelling approach. NONMEM version 7.2 was used for the analysis. As noted in previous studies, the clearance of retosiban increased over the dosing period by 29%, suggesting significant auto-induction. The high volume of distribution indicates extensive distribution into peripheral tissues. The variability in clearance between patients is low (17%).

Per protocol, 4 breast milk samples and 7 umbilical cord samples were analyzed for retosiban. All samples were below the limit of quanitation (1.0 ng/mL).

Oral Pharmacokinetics of Retosiban

	AUC(0-inf) (ng*hr/mL)	AUC(0-t) (ng*hr/mL)	Cmax (ng/mL)	[1]Tmax (hrs)	Half-life (hrs)
N	8	8	8	8	8
Geometric Mean	429.7	419.1	126.9	13.69	1.45
CV%	39.6%	41.4%	62.1%	6.23%	34.8%

1. Oral dose was given 12 hours after the start of the intravenous infusion

Intravenous Pharmacokinetics

Parameter	Mean (% precision)	Variability (%)
CLinitial (L/hr)	66.9 (5.1%)	17.3%
CLss (L/hr)	86.5 (4.1%)	17.3%
Vcentral (L)	19.0 (26.8%)	65.9%
Vperipheral (L)	48.0 (11.8%)	Not estimated
Q (L/hr)	39.8 (17.9%)	Not estimated
Residual Error	18.8%	

Safety results:

The investigator or site staff was responsible for detecting, documenting, and reporting events that met the definition of an AE or SAE. AEs were collected from the start of Investigation Product until the follow-up contact and entered into the eCRF. If they had occurred, SAEs would have been collected over the same time period as stated for the AEs. An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An "on therapy" serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication

Adverse Events: Maternal	GSK221149[a] N=50	Placebo [b] N=43
No. subjects with AEs n (%)	25 (50%)	19 (44%)
Most Frequent AEs		
Headache, including tension headache	7 (14%)	1 (2%)
Labor pain	4 (8%)	1 (2%)
Back pain	3 (6%)	0 (0%)
Dyspepsia	3 (6%)	2 (5%)
Nausea	3 (6%)	1 (2%)
Upper abdominal pain, including abdominal pain	2 (4%)	2 (5%)
Post partum hemorrhage	2 (4%)	0 (0%)
Anemia of pregnancy	2 (4%)	0 (0%)
Urinary tract infection	2 (4%)	0 (0%)
Constipation	1 (2%)	1 (2%)
Premature rupture of membranes	1 (2%)	2 (5%)
Amniotic fluid decreased	1 (2%)	1 (2%)

Polyhydramnios	0 (0%)	2 (5%)
Paraesthesia	0 (0%)	2 (5%)
Post partum depression, including depression	0 (0%)	3 (7%)

a. The Retosiban group includes subjects from OTA105256 Parts A/B and C (those randomized to active IV infusion over 12 hours, plus one oral placebo tablet, and those randomized to active IV infusion over 48 hours)
b. The placebo group includes subjects from Parts A/B and C (those randomized to placebo IV infusion over 12 hours, plus one oral active tablet, and those randomized to placebo IV infusion over 48 hours)

Adverse Events: Neonatal	GSK221149[a]	Placebo [b]
Neonatal, any event	7 (14%)	8 (19%)
Hyperbilirubinemia and Jaundice	4 (8%)	6 (14%)
Hypoglycemia	3 (6%)	1 (2%)
Hypercalcemia	0 (0%)	2 (5%)
Malnutrition	0 (0%)	2 (5%)
Anemia	0 (0%)	2 (5%)

a. The Retosiban group includes neonates born to maternal subjects from OTA105256 Parts A/B and C (those randomized to active IV infusion over 12 hours, plus one oral placebo tablet, and those randomized to active IV infusion over 48 hours)
b. The placebo group includes neonates born to maternal subjects from Parts A/B and C (those randomized to placebo IV infusion over 12 hours, plus one oral active tablet, and those randomized to placebo IV infusion over 48 hours)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

Serious Adverse Event Maternal	GSK221149[a] N=50	Placebo[b] N=43
Any SAE n (%) [n (%)]	4 (8%) [2 (4%)]	2 (4%)
Postpartum hemorrhage	2 (4%) [1 (2%)]	0
Retained Placenta	1 (2%) [1 (2%)]	0
Musculoskeletal pain	1 (2%)	0
Amniotic Fluid Volume Decrease	0	1 (2%)
Hypertension	0	1 (2%)

a. The Retosiban group includes subjects from OTA105256 Parts A/B and C (those randomized to active IV infusion over 12 hours, plus one oral placebo tablet, and those randomized to active IV infusion over 48 hours)
b. The placebo group includes subjects from Parts A/B and C (those randomized to placebo IV infusion over 12 hours, plus one oral active tablet, and those randomized to placebo IV infusion over 48 hours)

Serious Adverse Events: Neonatal	GSK221149[a] N=50	Placebo[b] N=43
Any SAE n (%) [n (%)]	7 (14%)	7 (16%)
Hypoglycemia	2 (4%)	0
Hyperbilirubinemia/Jaundice	2 (4%)	2 (4%)
Cerebral atrophy	1 (2%)	0
Congenital heart disease (ASD)	1 (2%)	0
Meconium in amniotic fluid	1 (2%)	0
Malnutrition	0	2 (4%)
Tachypenia	0	1 (2%)
Apnea	0	1 (2%)
Respiratory Distress	0	1 (2%)

a. The Retosiban group includes neonates born to maternal subjects from OTA105256 Parts A/B and C (those randomized to active IV infusion over 12 hours, plus one oral placebo tablet, and those randomized to active IV infusion over 48 hours)
b. The placebo group includes neonates born to maternal subjects from Parts A/B and C (those randomized to placebo IV infusion over 12 hours, plus one oral active tablet, and those randomized to placebo IV infusion over 48 hours)

Efficacy Data: Summary of Statistical Analysis Results of Uterine Contraction Data (Quiescence)

Study Part	GSK221149	Placebo		
	Response Rate (n, %)	Response Rate (n, %)	Relative Risk	95 % Credible Intervals
Parts A/B	8/14 (57%)	1/5 (20%)	2.34	(0.74, 13.24)

Part C	15/30 (50%)		12/34 (35%)	1.61	(0.97, 2.77)

Summary of Statistical Analysis Results for Days Delay to Birth

Study Part	GSK221149 N	Placebo N	Posterior Treatment Effect in Days (A to P)*	95% Credible Intervals
Part A/B	14	5	11.8	(-5.00, 28.60)
Part C	30	34	8.2	(2.70, 13.80)

*In Part A/B, the treatment effect is the mean difference. In Part C, the treatment effect is the coefficient of treatment in the Bayesian linear model fitting days delay to treatment and gestational age at entry. Part A/B results are used as a partial informative prior in the Bayesian model.

Summary of Statistical Analysis of Proportion of Pre-term Births

Study Part	GSK221149	Placebo		
	Proportion of Pre-term Births (n, %)	Proportion Pre-term Births (n,%)	Post Relative Risk of Pre-term Birth	95% Credible Interval
Part C	5/30 (16.7%)	16/34 (47.1%)	0.38	(0.15, 0.81)

Conclusion:

In Parts A/B, patients receiving retosiban were more likely to achieve uterine quiescense and have a longer delay until delivery as compared to placebo. These results supported the further investigation of retosiban in Part C of the study. In Part C, patients receiving retosiban had a significant increase in the time to delivery and reduction in preterm births. Additionally, retosiban resulted in an increase in uterine quiescence and a reduction in the proportion of women required to withdraw or to receive rescue tocolytics.

Retosiban, given over a 48 hour period, to 59 women in preterm labor in Study OTA105256 was well-tolerated. There were no apparent treatment differences across all safety parameters evaluated for the mother, fetus, and neonate. All reported adverse events were generally consistent with the population under study.