TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomized, open-label study to characterize the pharmacokinetics of inhaled oxytocin (GR121619) compared with IM oxytocin in women in the third stage of labour, and with IV oxytocin in non-pregnant, non-lactating women of childbearing potential

Compound Number: GR121619

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Effective Date: 30-MAY-2018

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N281575_00	2016-AUG-22	Original
2016N281575_01	2016-OCT-10	Amendment No. 1
Section 6.2: Inclusion of information on CE marking		
2016N281575_02	2018-JAN-04	Amendment No. 2
Update to PK collection procedures and implementation of in-stream PK data analysis. Update to location of Secondary Medical Monitor contact information		
2016N281575_03	30-MAY-2018	Amendment No. 3
Modification to informal interim and Group 2 analysis plans.		

SPONSOR SIGNATORY

PPD

30TH MAY 2018

Pauline Williams Date

Head of Global Health R&D

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK
Secondary Medical Monitor	Name and contact details available in Study Reference Manual				
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline (GSK) Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **EudraCT 2016-002672-27**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205920:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 205920

Rationale

Post-partum hemorrhage is one of the main causes of maternal mortality in the developing world. The World Health Organization (WHO) lists oxytocin on its list of 'Essential Medicines' for Humanity as a preventative treatment for post-partum hemorrhage; however, because of its cold-chain storage requirement and parenteral administration route, high-quality oxytocin is not always available in resource-poor settings. GlaxoSmithKline (GSK) has developed a stable, dry-powder formulation of oxytocin to address this unmet need, with the goal of reducing post-partum hemorrhage morbidity and mortality in these settings.

This study is being conducted to further assess safety and tolerability of inhaled oxytocin, and to characterize the pharmacokinetic (PK) profile of inhaled oxytocin compared to oxytocin administered as standard of care. Two groups of subjects will be enrolled. Group 1 will enroll pregnant women, who will be randomized to receive either inhaled (IH) or intramuscular (IM) oxytocin as active management of the third stage of labour. Group 2 will enroll non-pregnant women of childbearing potential, who will receive IH oxytocin and intravenous (IV) oxytocin in a cross over design over two dosing sessions.

Objectives/Endpoints

Group 1 – Women in Third Stage of Labour (TSL)

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 International Units (I.U.) IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events (AE); absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax, Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h])

Objectives	Endpoints
	will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

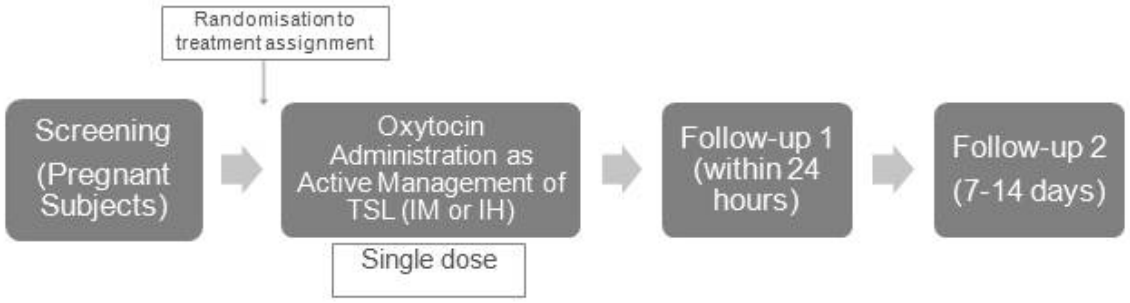
Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

Groups 1 and 2 – Women in TSL and Non-pregnant, non-lactating females of child bearing potential

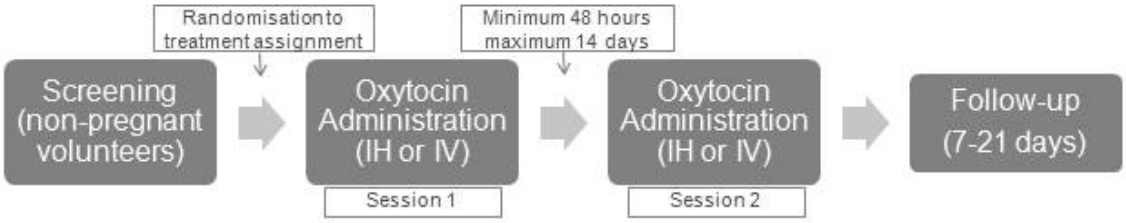
Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2	• Cp10, Cp20, Cp30, Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

Overall Design

Group 1 – Women in TSL



Group 2 – Non-pregnant, non-lactating females of child bearing potential



Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery). Group 2: All screening assessments to be completed within 28 days prior to the first dose.
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions.
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 micrograms (mcg) IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 h post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2).

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor. Replacement subjects will complete all study procedures.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for inhaled and intramuscular oxytocin. In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose.

Analysis

The primary objective of this study is to characterize pharmacokinetics of IH oxytocin and IM oxytocin in women in the third stage of labour.

No formal hypotheses will be tested, however, comparisons of interest, within Group 1, and between Group 1 and Group 2 and between Cohorts A and B in Group 2 will be made and the point estimates and corresponding two-sided 90% confidence intervals (CI) will be presented to provide the range of plausible values for the comparisons.

2. INTRODUCTION

Maternal mortality associated with postpartum hemorrhage (PPH) is one of the major public health problems in the developing world. Approximately half a million women worldwide die annually from causes directly related to pregnancy and childbirth, and up to one third of these deaths in Africa and Asia are caused by complications as a result of PPH [Khan, 2006; WHO, 2010]. A Cochrane Review meta-analysis of the data from multiple preventative trials with oxytocin at 10 international units (I.U.) given via the intramuscular (IM) route has confirmed this specific uterotonic, and this particular route of administration, to be the gold standard prophylactic therapy for PPH [Mousa, 2014]. For this reason, the World Health Organization (WHO) has designated oxytocin as one of its 'Essential Medicines' for humanity [WHO Model List of Essential Medicines 18th list, April 2013 (WHO, 2013); WHO Model List of Essential Medicines for Children 4th list, April 2013 (WHO, 2013)].

However, in resource-poor settings within the developing world, the effectiveness of prophylactic IM oxytocin is diminished by a lack of appropriate refrigeration facilities and availability of trained health care professionals (HCPs) to administer IM injections [Mousa, 2014]. Although single-use, oxytocin prefilled, syringes for IM injection are available in many developing countries (e.g. UNIJECT device), the development of a needle-free and self-administered inhaled (IH) oxytocin product, which delivers

comparable systemic exposure to 10 I.U. IM, would be a major step-change in the administration of this life-saving medicine to pregnant women in resource-poor regions of the developing world. This would be particularly relevant in rural areas where the mother has no routine access to a trained HCP and/or where there is no reliable electricity supply to permit refrigerated storage of oxytocin injection vials.

We have developed a stable, dry-powder formulation of oxytocin to be administered via the oral inhaled pulmonary route (compared to 10 I.U. of IM oxytocin) using a GlaxoSmithKline (GSK)-manufactured medical device (or device manufactured for GSK by a third party) which is a capsule-based inhaler (Modified Air Inlet ROTAHALER™ Dry Powder Inhaler (DPI) device, hereafter referred to as ROTAHALER). This formulation and delivery method has the potential to be used in settings where effective oxytocin is currently unavailable to women in the third stage of labour (TSL).

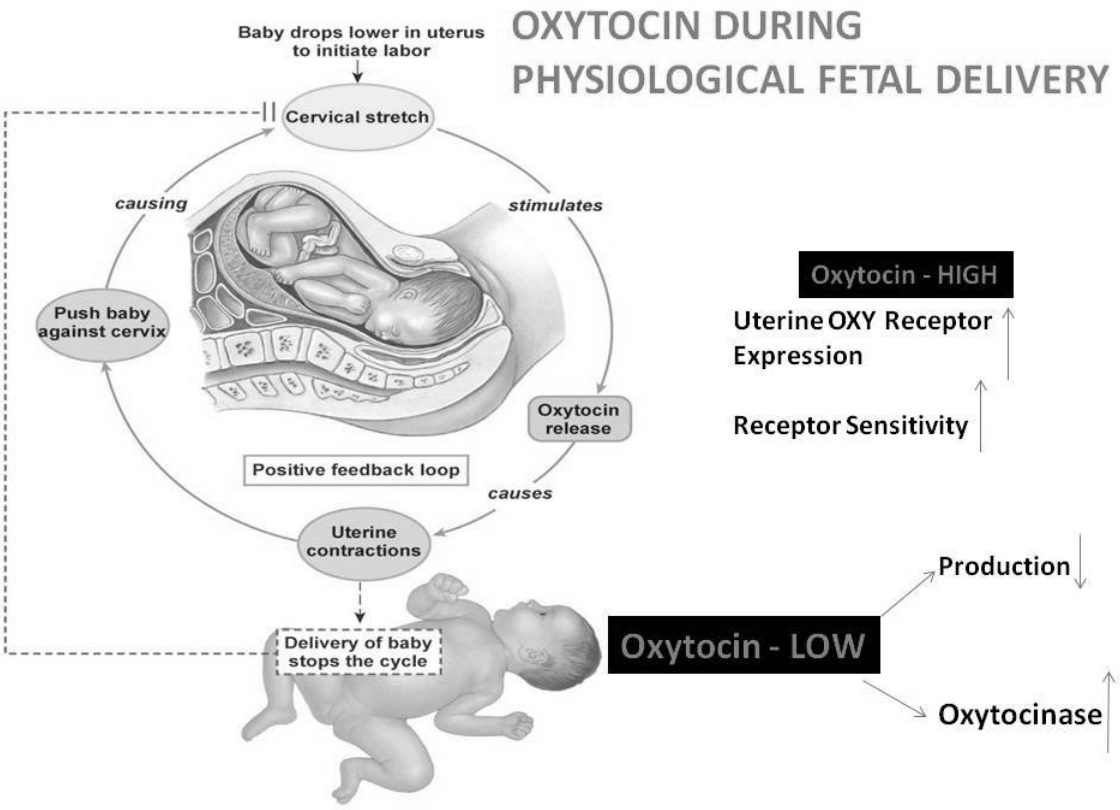
2.1. Study Rationale

This study will be the second investigation of oxytocin in humans via the IH route, which follows the first time in human (FTIH) study, 201558 [GlaxoSmithKline Document Number 2015N234711_01, 2015; see Section 2.2.1 for more information on the FTIH trial]. Published literature on the pharmacokinetics (PK) of oxytocin in non-pregnant and pregnant women is limited. There is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy; potentially related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy related changes in hepatic and renal function [Syntocinon Summary of Product Characteristics, Novartis, 2014; Thornton, 1990]. In addition, endogenous oxytocin plasma concentrations have been reported to either increase or remain constant after the delivery of the fetal anterior shoulder [Thornton, 1988]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in the TSL for a given dose and route of administration of oxytocin. To further understand the effect of pregnancy on the PK of oxytocin, this study will investigate the PK of oxytocin in pregnant women in TSL following either IH (400 micrograms [mcg]) or 10 I.U. IM (17 mcg) administration. A greater understanding of the PK of oxytocin in TSL will help facilitate extrapolation of data obtained in healthy non-pregnant women to women in TSL. An additional group of non-pregnant non-lactating female volunteers will also be included as a control group and will receive 400 mcg IH oxytocin and 5 I.U. intravenous (IV) oxytocin. This second group will enrol one cohort of subjects taking the combined oral contraceptive (COC), and another cohort using a non-hormonal form of contraception. This will assess if women need to be on an oral contraceptive vs. other methods of birth control in future clinical studies, since although the COC is believed to suppress endogenous oxytocin levels the literature is not consistent about this observation. As the requirement to be taking the COC makes recruitment more of a challenge it will be helpful to know if this inclusion is essential, or if women using non-hormonal forms of birth control might also have sufficiently low systemic oxytocin levels suitable for PK studies.

2.2. Brief Background

Oxytocin is a nonapeptide which is produced by the hypothalamus and released into the systemic circulation by the posterior pituitary gland. Within the brain, oxytocin, like most hypothalamic synthesized hormones, acts as a neurotransmitter. In human pregnancy, during the later phases of the third trimester, increasing circulating levels of oxytocin act as a potent endogenous uterotonic which facilitates the initiation of labour. Furthermore, a neurohormonal positive feedback loop exists between dilatation of the cervico-vaginal canal by fetal passage and the hypothalamus (i.e. Fergusson reflex) which augments oxytocin production, thus increasing uterine contraction intensity and frequency which facilitates vaginal delivery. However, once the fetus is delivered, plasma oxytocin levels rapidly diminish probably due to a combination of increased circulating levels of oxytocinase (the principal oxytocin deactivating enzyme), in the plasma, an overall reduction in hypothalamic oxytocin synthesis (Figure 1), and a reduction in uterine oxytocin receptor (OTR) density. This oxytocin-depleted, relatively auterotonic, physiological environment puts the mother at risk of PPH during the subsequent placental delivery phase (i.e. TSL).

Figure 1 Oxytocin During Physiological Fetal Delivery



Oxytocin receptors are constitutively expressed in smooth muscle cells (SMCs) in the uterine myometrium, muscular walls of the bronchi and upper digestive tract, myoepithelial cells of the breast duct which are essential for the oxytocin-dependent postpartum breast milk let-down reflex, and in different regions of the brain. Although

uterine OTR expression increases during the later stages of pregnancy, it is not known whether pregnancy increases OTR expression at non-uterine sites, such as the maternal brain, where neuronal oxytocin signalling has been implicated in postpartum bonding behaviour with the baby. Within the kidney, oxytocin is known to bind to vasopressin (V2) receptors, rather than OTR, in the medullary renal collecting duct which triggers an antidiuretic effect.

Binding of oxytocin to OTR triggers an increase in intracellular calcium (Ca2+), which is partly mediated through oxytocin-dependent up-regulation of prostaglandin F (PGF)2α synthesis, which in the uterine myometrium leads to physiological uterine contractions during 3rd-stage labour.

More recent research has shown oxytocin to be present in broncho-alveloar lavage fluid collected from the respiratory tract of adult humans of both sexes, but oxytocinase expression was not assessed. In an in vivo pharmacology study [Prankerd, 2013] in pregnant ewes intratracheal insufflation of a dry-powder formulation of oxytocin was associated with poor absolute bioavailability (ca 5%), but despite low systemic exposure, this still caused a pharmacodynamic response that was manifested by increased electrical uterine activity measured by electromyography, probably as a result of increased OTR stimulation in the pregnant uterus.

2.2.1. IH Oxytocin FTIH Study 201558

Study 201558 [GlaxoSmithKline Document Number 2016N277949_00] was the FTIH study to evaluate safety, tolerability, and characterize the PK profile of 4 dose strengths of IH oxytocin compared to oxytocin 10 I.U. IM. The study enrolled 16 healthy, non-pregnant, premenopausal female subjects. One subject was withdrawn prior to IH oxytocin dosing due to inability to cannulate. Subjects were administered 10 I.U. IM oxytocin, IH placebo containing (only) the excipients found in the IH oxytocin formulation, and IH oxytocin. A minimum washout period of 48 hours (h) was required between each dose of active drug. This dose escalation study evaluated 4 doses of IH oxytocin: 50 mcg, 200 mcg, 400 mcg, and 600 mcg. The most frequently reported Adverse Event (AE) was headache, and occurred in at least one subject in each treatment arm. In general, IH oxytocin was well-tolerated, no safety concerns with IH dosing were identified, no clinically significant effect on respiratory parameters were observed, and no Serious Adverse Events (SAEs) were reported. The PK profile of the 400 mcg IH oxytocin dose was similar to that of 10 I.U. IM, and has been selected for further evaluation. See Section 4.5 for further information on PK characteristics.

2.2.2. PK Specimen Stability as Observed in 205920

Prior to the initiation of the current trial, a sample-handling process was developed using blood from pregnant subjects of at least 37 weeks gestation to ensure ex-vivo oxytocin stability in specimens collected from Group 1 TSL subjects.

Per protocol, after 10 subjects had completed all procedures in Group 1, an informal interim PK analysis was conducted. It was observed that in the majority of the plasma samples collected from TSL subjects, oxytocin concentrations were below the limit of quantification (BLQ) or at very low concentrations (approximately 3pg/mL) approaching

the lower limit of quantification (LLQ) of the assay (2pg/mL). This was seen across both IM and IH routes of administration. This was an unexpected finding which has been confirmed by re-analysis of selected samples. As such, it is considered that it may be due to ex-vivo oxytocin instability related to uninhibited oxytocinase and peptidases, which are believed to be at increased concentrations in the plasma of postpartum women compared with non-pregnant women, and women at 37 weeks gestation. This finding resulted in a temporary halt to the trial.

3. OBJECTIVES AND ENDPOINTS

3.1. Group 1: Women in TSL

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h]) will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

3.2. Group 2: Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

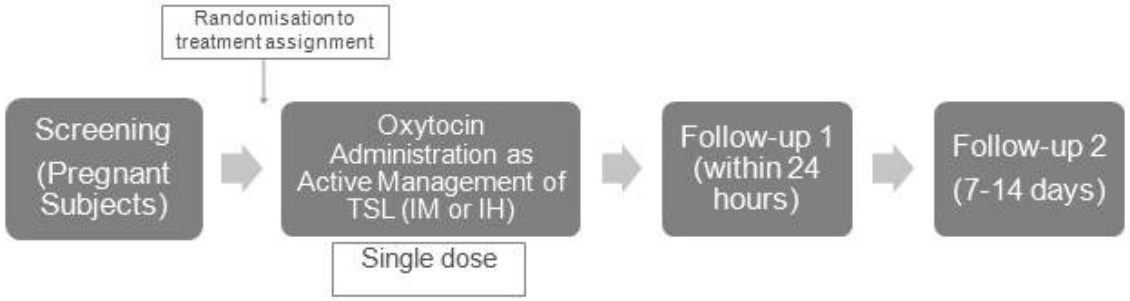
3.3. Groups 1 and 2: Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2.	• Cp10, Cp20, Cp30, Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Study Schematic Group 1: Women in TSL



4.1.2. Study Schematic Group 2: Non-pregnant, non-lactating females of child bearing potential

4.1.3. Study Design Detail

This study will enrol two groups.

Group 1 - Women in TSL

Group 1 will enrol women with an uncomplicated pregnancy, and main phase procedures will occur during TSL. Subjects will be randomized to receive either IH or IM oxytocin

as active management of TSL. The specific timing of this dose will be as per local standard of care.[1]

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Group 2 will enrol healthy, non-pregnant, non-lactating female subjects of childbearing potential, and each subject will participate in 2 dosing sessions. Group 2 will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive, and Cohort B will enrol women who are not using a hormonal form of contraceptive. Group 2 subjects will receive IH oxytocin at one dosing session, and IV oxytocin at the other dosing session; the order of IH versus IV oxytocin administration will be randomly assigned.

PK samples will be analysed periodically throughout the study duration to enable development of the population PK model and derivation of PK parameters via non-compartmental methods, as data permits.

No formal interim analysis is planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: IH, IM in Group 1 and IH in Group 2 Cohort A in order to assess if dose escalation is required.

4.1.3.1. Pregnant Females (Group 1)

Subjects will review the study information and if they agree to participate, sign the informed consent form. For most subjects this is expected to take place at an outpatient antenatal visit, or additional study-specific screening visit. If a subject meets all inclusion/exclusion criteria for the study, she will be eligible for enrolment in the study.

To facilitate recruitment, and provide subjects ample time to consider participation, screening may occur any time after 18 weeks gestation (based on estimated date of delivery). See time and events (T&E) table in Section 7.1 for details.

4.1.3.2. Non-pregnant Females (Group 2)

Subjects will review the study information and if they agree to participate, sign the informed consent form. If a subject meets all inclusion/exclusion criteria for the study, she will be enrolled in the study.

Screening may occur within 28 days prior to randomization for non-pregnant volunteers. If a subject falls outside this window prior to randomization and enrolment, she must be re-screened. Certain screening procedures may not be required to be repeated; see T&E (Section 7.1) for details.

[1] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

Group 2 subjects will take part in 2 dosing sessions, which must be conducted a minimum of 48 hours apart. It is recommended that subjects complete Session 2 within 14 days of Session 1. Subjects will be randomized to receive either IH or IV oxytocin during Session 1, and to receive the other treatment during Session 2, such that all subjects in Group 2 receive both treatments over the course of the 2 sessions.

4.1.4. ROTAHALER Inhaler Training

The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner (refer to Section 6.7). Subjects will be instructed by the investigator/designee to use an inspiration technique (2 inhalations) that enables maximal inhalation of the ROTACAPS powder capsule contents (refer to Section 6.7 for full details). This will ensure optimal and consistent drug delivery (full instructions available in the Study Reference Manual [SRM]).

4.1.5. Length of Stay for All Subjects

Group 1 - Women in TSL

Subjects in Group 1 will be admitted to hospital during labour as part of their routine care, and will be required to remain inpatient for a minimum of 4 hours after receiving any study-related dose of oxytocin. After final PK collection, subjects will be finished with study procedures and the main phase of the study will be considered complete. Discharge from hospital will be determined by the subject's medical provider.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Subjects in Group 2 will be admitted to the clinical unit prior to dosing on Day 1 and are to remain inpatient until at least 4 hours after dosing. Discharge will occur at the discretion of the investigator.

4.2. Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery) Group 2: All screening assessments to be completed within 28 days prior to the first dose
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 mcg IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 hours post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

[1] See Section 6.4 for possible dose adjustment to IH oxytocin.

4.3. Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2). Refer to Section 6.3 for treatment assignment information.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment at the discretion of the Sponsor. Replacement subjects will complete all study procedures as outlined in Section 7.1.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for IH and IM. In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose. See Section 6.4.1 for more details.

4.4. Design Justification

Group 1 - Women in TSL

This trial uses a randomized, single-dose approach to assign women in TSL to receive oxytocin by one of two routes: IM or IH. No placebo is being used, as the current standard of care is to administer oxytocin as active management of TSL to prevent PPH.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

A group of non-pregnant, non-lactating women of childbearing potential will receive IH and IV oxytocin. This group will be divided into two cohorts: Cohort A will enrol women on the combined oral contraceptive. This cohort will serve as a control group, as they most closely resemble the population enrolled in the FTIH study. Cohort B will enrol women using a non-hormonal form of contraception. This comparison group will help characterize the effect of oral contraceptives on endogenous oxytocin production and the PK profile of oxytocin.

Blinding

This study uses an open-label design.

4.5. Dose Justification

Single inhaled doses of oxytocin (50-600 mcg) have been generally well tolerated in the FTIH study, with no emerging safety signals, in healthy, non-pregnant, premenopausal female subjects (Study 201558) [GlaxoSmithKline Document Number 2016N277949_00; see also Section 2.2.1]. Following inhaled administration oxytocin was rapidly absorbed into the systemic circulation (tmax ranging from 0.05 to 0.50 h) with systemic exposure (Cmax and AUC) increasing with inhaled dose in an

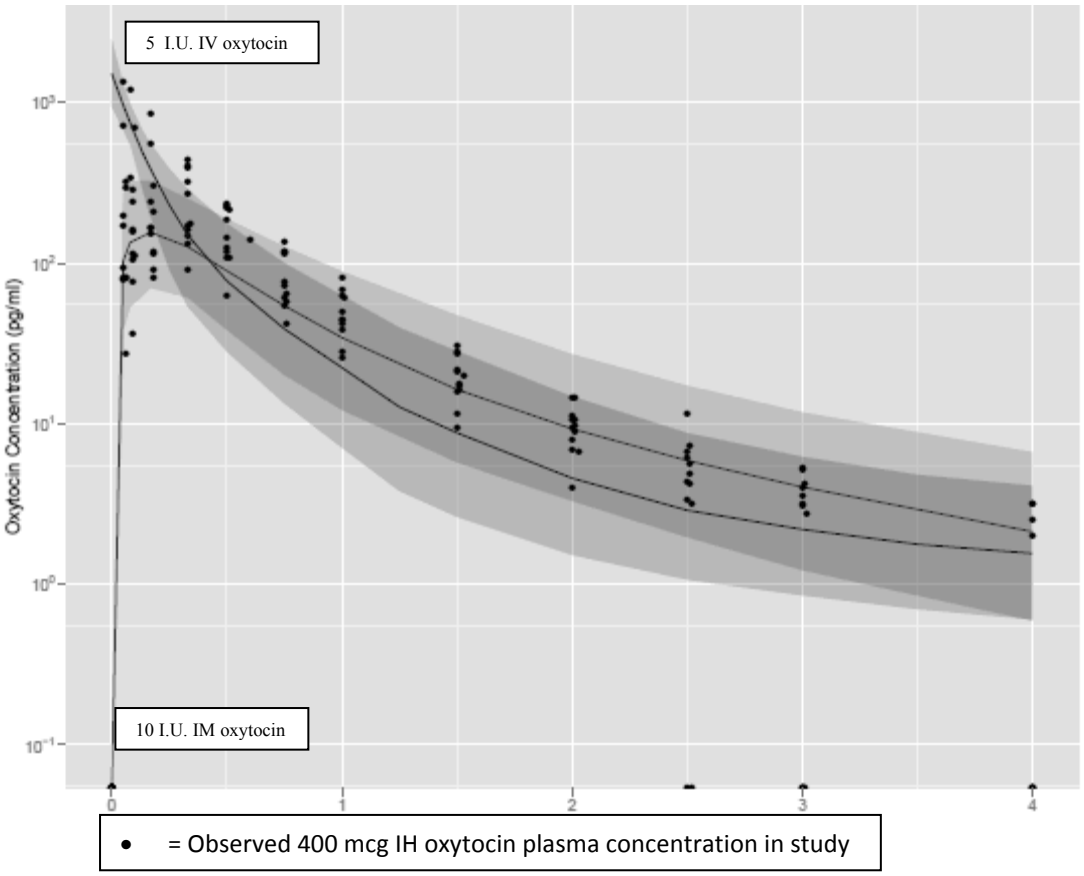
approximately proportional manner between 200 and 600 mcg. In general, the shape of the observed oxytocin concentration-time profile following inhaled administration was consistent with that following IM administration.

Based on the data from the FTIH study, and assuming that the PK characteristics of IH and IM oxytocin are similar in TSL compared with non-pregnant women, the 400 mcg inhaled dose is predicted to be an effective dose in women in TSL by ensuring that the systemic exposure (Cp10, Cp30 and AUC(0-3 h) following IH dosing is at least that following IM administration at the approved dose of 10 I.U. This would be based on the adjusted geometric mean ratio (90% Confidence Interval [CI]) treatment comparisons for Cp10, Cp30 and AUC (0-3 h) following 400 mcg IH compared with 10 I.U. IM, namely 1.10 (0.85,1.43), 1.65 (1.30, 2.09) and 1.27 (1.07, 1.50) respectively in study 201558. The PK parameters (Cp10, Cp30 and AUC(0-3 h)) have been selected to ensure onset and duration of action of the IH product is at least comparable to IM.

The clinical safety and reported AEs with oxytocin correlates to Cmax, with the Cmax of 10 I.U. IV representing the upper bounds of what could be considered safe in current clinical practice (AEs include flushing, which can cause a transient decrease in blood pressure and reflex tachycardia; see the Oxytocin Summary of Product Characteristics for more information). The recommendation in the United Kingdom (UK) in clinical practice has been to reduce the IV dose to 5 I.U. IV or administer by a controlled IV infusion [Bolton, 2003].

Minimising the risk of high Cmax levels of oxytocin following the IH administration is therefore important. Based on a comparison of model predicted systemic exposure following IV administration to non-pregnant, premenopausal female subjects with observed PK profiles following 400 mcg IH oxytocin, it is anticipated that Cmax following administration of the 400 mcg dose will not markedly exceed values following 5 I.U. IV bolus oxytocin (Figure 2). The inclusion of the 5 I.U. IV dose will allow an assessment of the potential safety and PK of the inhaled formulation compared to IV route of administration.

Figure 2 **Model predicted profiles (median (95%PI)) following IM (10 I.U. and IV bolus (5 I.U. administration of oxytocin overlaid with observed plasma concentrations of oxytocin following 400 mcg IH oxytocin to healthy non-pregnant females**



Whilst published literature on the PK of oxytocin in non-pregnant and pregnant women is limited there is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy. This may be related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy-related changes in hepatic and renal function [Syntocinon, 2014; Thornton, 1990]. In addition, there may be circulating levels of endogenous oxytocin in the plasma in women in TSL [Thornton, 1988] and increases in blood volume (40-50%) and total body water [Costantine, 2014]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in TSL for a given dose and route of administration of oxytocin. However, given that any pregnancy-related changes in systemic clearance, and/or distribution and baseline oxytocin levels, are considered to equally impact on each route of administration (IV, IM and IH), it is considered that the relative ratio of IV to IM and IH exposure observed in non-pregnant women is likely to be maintained in pregnancy. The only exception may be if pregnancy results in marked changes in absorption profiles. However, in a study of inhalation profiles of non-pregnant and women in the third stage of labour, the inhalation endpoints appeared to be broadly similar across the two cohorts and any small changes are not considered to markedly impact the delivery of an inhaled product in the third stage of labour [GlaxoSmithKline

Document Number 2015N239682_00]. In addition, in a pre-clinical sheep model the ratio IH:IV was generally similar in non-pregnant and post-partum ewes (Data on file Monash). In the event of enhanced pulmonary absorption in pregnancy, the selected 400 mcg inhaled dose is predicted to have an approximate 2-fold safe cover for Cmax compared with an 10 I.U. IV bolus oxytocin (assumes linearity from 5 -10 I.U. IV).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GR121619 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2015N240749_01] and oxytocin for parenteral administration [Syntocinon, 2014]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) – Inhaled Oxytocin – GR121619		
Bronchospasm, cough and dyspnoea, with increased *theoretical* risk in asthmatic subjects.	Oxytocin receptors are known to be expressed in human bronchial smooth muscle and up regulated by interleukin (IL)-13. Therefore, there is a hypothetical risk of bronchospasm, cough and dyspnoea.	See Section 5.2 for exclusion criteria. The oxytocin summary of product characteristics (SPC) does not list asthma as a contraindication to administration. Symptomatic wheezing may be treated with bronchodilator at the discretion of the investigator. Forced expiratory volume at 1 minute (FEV1) monitoring for both paradoxical and oxytocin induced bronchospasm Subjects with asthma or known pulmonary disease are excluded.
Hypotension, tachycardia and prolongation of QTc interval	Transient flushing, hypotension and tachycardia could be observed if the IH PK profile is comparable to an IM or IV oxytocin profile. Effects of oxytocin on the Cardiovascular system (CVS) is unclear and contradictory in	Ongoing assessments of study subjects' cardiovascular function including blood pressure (BP), heart rate (HR) and ECG. Only single-dose IH, IM, or 5 IU IV bolus injection routes of administration will be used

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the literature but IV administered oxytocin can have a vasodilatory and negative inotropic effect in humans. Hypotension is thought to arise as a result of vascular smooth muscle relaxation and oxytocin binding to cardiac atrial OTR which leads to atrial natriuetic peptide (ANP) being transiently released into the systemic circulation. Prolongation of the QTc interval has been reported at the time of caesarean delivery with 10 IU IV oxytocin administration, rather than IM injection, in susceptible individuals	as study treatment. Telemetry and frequent 12-lead ECGs will be used to monitor the healthy subject cohorts The 5 IU IV dose of oxytocin is the standard dose administered at the Rosie Maternity hospital post Caesarean Section. IV bolus will be given as a slow IV injection over 30 seconds with the option to change to a 5 minute infusion if frequent CV adverse effects are observed Exclusion of subjects with long QT syndrome, congenital cardiac abnormalities, and subjects taking anti-arrhythmic drugs. 12-lead ECG and telemetry covering Cmax in healthy subjects administered IH, IM and IV oxytocin
Insufficient uterotonic effect	The altered physiology and pharmacokinetics of women in the TSL my lead to a sub-optimal dose of inhaled oxytocin, resulting in a reduced or absent uterotonic effect.	In this setting, women in TSL and post-delivery are intensively observed. Therefore, any adverse events, including excessive blood loss due to unenhanced uterine contraction, will be managed in accordance with current local practice guidelines. This will usually include administration of additional uterotonic agents in the first instance. A follow-up within 24 h of discharge by the study team will be performed to specifically enquire if any late bleeding problems had occurred.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		An interim analysis of IH and IM PK in the TSL group will be performed to ensure that the PK is in the acceptable range for efficacy to be anticipated.
Reference Intervention - IM Oxytocin / IV Oxytocin		
Hypotension, tachycardia and prolongation of QTc interval	See above section.	See above section. Subjects receiving the IV Oxytocin are required to have a systolic BP ≥ 90 Millimeter of mercury (mmHg) prior to dosing.
Myocardial Ischaemia and ST change on ECG	ECG changes consistent with myocardial ischaemia have been observed with 10 IU oxytocin IV bolus in healthy women associated with hypotension and tachycardia.	Oxytocic cardiovascular effects appear to be transient and persistent myocardial damage very rare and associated with 10 IU IV. Study is only using 5 IU IV as a slow IV bolus which is associated with a short lived increase in heart rate and reduction in BP but not ST changes on ECG in women undergoing Caesarean Section. Telemetry and 12-lead ECG monitoring in healthy subjects.
Abdominal pain	There is a hypothetical risk that IM oxytocin may trigger abdominal pain through contractions of the non-pregnant uterus in healthy women. Given the short half-life of oxytocin (approximately 30 minutes), the duration of a single abdominal pain episode would be expected to be brief, not sustained and not	This is a theoretical possibility and not expected to occur. Ongoing assessments of study subjects' well-being along with vital signs and laboratory evaluations will be completed throughout the duration of the study. Abdominal pain which is clinically uncomfortable to the subject may be treated with paracetamol at the local investigator's discretion.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	recurrent in the absence of further oxytocin administration. Furthermore, no abdominal pain was observed in the FTiH study.	

4.6.2. Immunogenicity Risk

The oxytocin material used in the inhaled product is produced synthetically and so does not include any other protein/cell impuritites which might be intrinsically immunogenic. A review of the risk of immunogenicity of oxytocin and/or excipients was considered as part of the non-clinical safety studies but as the lymphoid tissues were not deemed to be pathologically affected and there were difficulties in generating a suitable assay, anti-drug antibodies (ADAs) were not measured. The FTIH study involved repeat dosing, and did not reveal any unexpected differences in PK which may have signalled the development of ADAs.

Oxytocin is an endogenous human peptide with a short systemic half-life and there are no reports of immunogenicity with oxytocin via parenteral administration. Thus it is considered unlikely that inhaled delivery of a small molecular weight (MW) peptide molecule like oxytocin would invoke an immunogenic response.

However, blood samples will be retained for anti-oxytocin antibody analysis if required in the event of an anaphylactic / allergic reaction (refer to Section 5.4.2) or other observation which would suggest an immunogenic effect.

4.6.3. Benefit Assessment and Overall Benefit:Risk Conclusion

Oxytocin has been administered to postpartum women for over 40 years via both the IM and IV routes, and has an established safety profile for each of these routes of administration. The FTIH study into IH oxytocin revealed no safety concerns for any of the subjects who received this new formulation. There are no direct clinical benefits to the volunteers within this study. The main contribution to their participation will be in the further development of a therapy (i.e. inhaled oxytocin) which may be ultimately used as a preventative therapy for postpartum haemorrhage in women during TSL in resource poor settings. It is fundamental to the project to clearly understand the PK of oxytocin following IH and IM administration to women in TSL in order to confirm the dose level that delivers a PK profile comparable to that of 10 I.U. IM (i.e. current standard of care in the developed world setting). Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with oxytocin (IH IM, and IV) are justified by the supporting data and overall benefit anticipated for women's health worldwide.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the investigator brochure for GR121619 [GlaxoSmithKline Document Number 2015N240749_01] and SPC for oxytocin administered IM or IV.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
All Groups: 1. Between 18 and 40 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
All Groups: 2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, and laboratory tests as required per protocol. Note: At time of randomisation, investigator or designee should confirm the subject feels fit and well, and is safely able to participate in the study. 3. Subject clinical chemistry and haematology values within an acceptable range for the population recruited and not of abnormal clinical significance. Note: Additional laboratory tests beyond those which are done as part of routine care (e.g. 28-week visit) are not required for subjects in Group 1. The investigator/designee may use his/her judgment in deciding whether to perform additional laboratory assessments to determine eligibility. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 4. Adequate peripheral venous access for cannulation.

Group 1 Only:

5. Currently pregnant, with an uncomplicated pregnancy as determined by the investigator or designee.
6. Estimated date of delivery within 24 weeks of screening.
7. Planned spontaneous vaginal birth and considered by investigator at low risk for PPH.
8. Planned birth in between the 37th and 42nd week of pregnancy.

   Note: Subjects can only receive study treatment if the onset of labour is between approximately 37 and 42 weeks estimated gestation. If a subject goes into labour before or after this timeframe, she should not receive study treatment.
9. Women who qualify for oxytocin as appropriate for active management of TSL and who agree to have active management.

Group 2 Only:

10. ECG normal, or abnormal and not clinically significant.
11. FEV1 >80% of predicted.
12. Systolic blood pressure ≥90 mmHg.

WEIGHT
Group 2 Only: 13. Body mass index (BMI) within the range 18 – 32 Kilogram (kg)/ meter $(m)^2$ (inclusive).

SEX
14. Female. Group 2, Cohort A Only: A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test), not lactating, and the following condition applies: a. Is of reproductive potential and agrees to use the same **combined estrogen and progestogen oral contraceptive** from 3 months prior to the first dose of study medication and until the follow-up contact. This method of contraception is only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method of contraception.

Group 2, Cohort B Only:

A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine hCG test), not lactating, and one of the following conditions applies:

a. Is of reproductive potential and has been using the same **non-hormonal contraceptive method** (see List of Acceptable Nonhormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential [see Appendix 5] from 3 months prior to the first dose of study medication and until the follow-up contact.

b. Would be of reproductive potential, but has undergone bilateral tubal ligation or occlusion or bilateral salpingectomy at least 12 months prior to first dose of study medication.

c. Is of reproductive potential with only same sex partners or who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

These methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method(s) of contraception.

Of Note: Group 2, Cohort B will enrol women of reproductive potential if they agree to use a nonhormonal contraceptive method from at least one month prior to receiving study drug and until the follow-up assessment. Although condoms with spermicide are not considered a highly effective method of contraception, the risk of receiving study drug during pregnancy is minimal for the following reasons:

- Pregnancy testing must be negative at screening and on the first day of dosing.
- Dosing is completed no greater than 14 days from the start of dosing.
- Oxytocin has a well established rapid half-life.

If a patient happened to conceive during the time of dosing, study drug would be eliminated before implantation would occur.

INFORMED CONSENT

All Groups:

15. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

All Groups:

1. Postmenopausal as defined by gynaecological history.
2. Chronic lung condition of any etiology including asthma, Chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease or active Tuberculosis (TB).
   Note: Childhood asthma (resolved) is not exclusionary.
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. Blood pressure >140 systolic or >90 diastolic.

Group 1 Only:

5. Females with planned Caesarean Section.
6. Females with significant medical complications as determined by investigator.

Group 2 Only:

7. Currently breastfeeding or lactating.
8. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 milliseconds (msec).
9. Alanine aminotransferase (ALT) and bilirubin >1.5 Upper Limit of Normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Subjects with highly-active or symptomatic gynaecological disorders (such as large symptomatic fibroids).

CONCOMITANT MEDICATIONS

All Groups:

11. Prescription or non-prescription drugs not approved by the investigator (refer to Section 6.12.1 for approved medications).
12. Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) prior to administration of study-related oxytocin.

RELEVANT HABITS
All Groups: 13. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >14 units. One unit is equivalent to 8 grams (g) of alcohol: a half-pint (~240 milliliter [ml]) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 14. Current smokers or subjects with a history of smoking within 6 months of screening, or with a total pack year history of >5 pack years. a. Confirmatory use via a Smokerlyzer is at the discretion of the local investigator, but is advised if the subject's recent smoking history is in doubt.

CONTRAINDICATIONS
All Groups: 15. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation (e.g. allergy to any previous inhaler use). 16. Participation in another clinical trial, which in the opinion of the investigator, jeopardizes the subject's safety or study outcomes.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
All Groups: 17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 18. The subject has participated in a clinical trial and has received an investigation product within the following time period prior to the first dosing day in the current study: 30 days or twice the duration of the biological effect of the investigational product (whichever is longer). 19. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. **Group 2 Only:** 20. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result. 21. A positive Human Immunodeficiency Virus (HIV) antibody test. 22. A positive pre-study drugs of abuse test (not explained by diet or approved concomitant medications). 23. A positive alcohol breath test.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.4).

5.3.1. Re-screening

If a subject fails screening, she may be rescreened one additional time.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Pregnancy Complication Stopping Criteria (Group 1 Only)

Any complication requiring clinical intervention which no longer allows for a vaginal delivery or safe completion of study procedures will be cause for immediate withdrawal from the study. Investigators should continue to manage any pregnancy complication per local guidelines, and record any associated AE/SAE or concomitant medication. This includes the need for additional uterotonic administration.

5.4.2. Anaphylaxis Stopping Criteria

Clinical signs or symptoms of anaphylaxis / allergic reaction to IH oxytocin will be an automatic stopping criterion. Stored serum samples will be analysed for anti-oxytocin antibody analysis for affected subjects as detailed in Section 7.5.2. The samples will be analysed for Immunoglobulin E (IgE)/ Immunoglobulin G (IgG) anti-oxytocin titres ± biochemical markers of mast cell degranulation (e.g. tryptase) in the event of an anaphylactic / allergic reaction occurring.

5.4.3. QTc Stopping Criteria (Group 2 Only)

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

QTcF is proposed to be used for this study. If a subject meets either of the following bulleted criterion below, she will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline: Increase in QTcF >60 msec.

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be withdrawn from the study.

5.4.4. Blood Pressure Stopping Criteria (Group 2 Only)

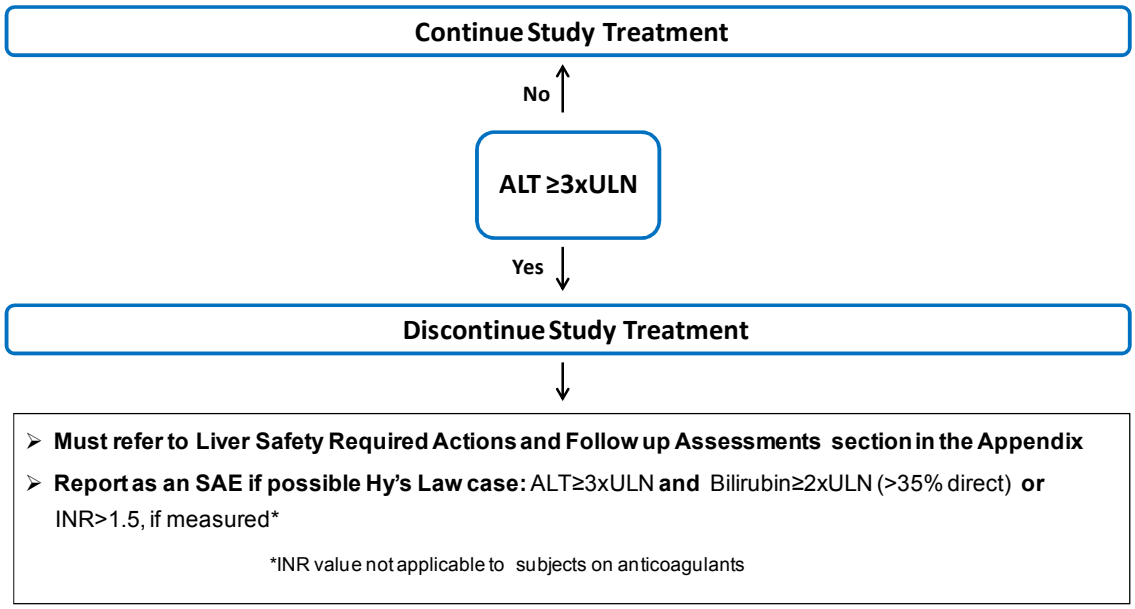
Subjects with a pre-dose systolic blood pressure of <90 mm Hg should not be dosed until systolic blood pressure is ≥90 mm Hg.

5.4.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.6. Plasma oxytocin concentration stopping criteria

Per Section 9.3.2.2, the plasma oxytocin concentrations in up to 5 subjects in Group 1 will be analysed in real time. If the plasma oxytocin concentration is BLQ or sufficiently low to prohibit interpretation in these 5 subjects irrespective of treatment, the study will be halted and reviewed.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit(s).

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Table 1 Study Treatment Information

	Study Treatment		
Product name:	Oxytocin (GR121619 capsule for inhalation)	Oxytocin	Oxytocin
Formulation description:	Powder Blend for Inhalation	Solution for Infusion	Solution for Infusion
Dosage form:	Inhalation powder, hard capsule	1ml ampoule	1ml ampoule
Unit dose strengths:	400 mcg 200 mcg	5 I.U./mL, or 10 I.U./mL	5 I.U./mL, or 10 I.U./mL
Route of Administration	For oral inhalation	Intramuscular (thigh)	Intravenous
Dosing instructions:	Capsule unit dose dispensed by ROTAHALER inhaler	Standard intramuscular injection	Adminster as a 30-second bolus
Physical description:	Colourless and clear HPMC capsules containing a white powder	Colourless and clear sterile solution	Colourless and clear sterile solution
Device:	ROTAHALER inhaler	Needle/Syringe	Intravenous Infusion Device

6.2. Medical Devices

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

6.3. Treatment Assignment

Subjects in Group 1 will be assigned to one of two treatments (IH oxytocin or IM oxytocin). Subjects in Group 2 will receive both IH and IV oxytocin in separate dosing sessions in a cross over design. Treatment assignment in Group 1, and order of dosing in Group 2, will be done in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in Table 2:

Table 2 Treatment Assignment

Group	Session	Treatment [1]	Number of Subjects[2]
Group 1	1	400 mcg IH oxytocin	10
		10 I.U. IM Oxytocin	10
Group 2, Cohort A	1	400 mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	
Group 2, Cohort B	1	400mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	

[1] See Section 6.4 for possible dose adjustment.

[2] See Section 9.2.2 for possible adjustment to subject numbers to Group 1

If deemed necessary or if there is a new site identified for conducting and/or continuing the clinical trial, then a new randomization schedule may be generated by Clinical Statistics, prior to the start of the study at the new site, using validated internal software.

6.4. Planned Dose Adjustments

There is no plan to adjust the dose of IH oxytocin in this study. However, if systemic exposure seen in 400 mcg IH oxytocin in TSL subjects is less than expected and not comparable to the 10 I.U. IM profile, a consideration to escalate the dose to 600 mcg may be made as detailed in Section 6.4.1.

For Group 2, if an exaggerated physiological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

6.4.1. Dose Adjustment

The decision to adjust the IH dose in women in TSL will be determined by the GSK study team based on Group 1 PK data in TSL and Group 2, Cohort A PK data. After a minimum of n=5 women in TSL have received 400 mcg IH and 10 I.U. IM and a minimum of n=5 non-pregnant women on the combined oral contraceptive (Group 2, Cohort A) have received 400 mcg IH oxytocin, PK samples will be analysed and PK parameters derived (including but not limited to Cp10, Cp30 and AUC(0-3h)).

The median Cp10 will be estimated for women in TSL for each dose group (IH or IM) and the median ratio (IH/IM; n=5) derived. Based on the estimated ratio, the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased per the criteria described in Table 3:

Table 3 Dose Adjustment Decision Criteria

Median Ratio IH/IM	Decision
< 0.5	Consider study halt and review data.
≥ 0.5 to <0.7	Consider dose adjust to 600 mcg IH in women in TSL.
≥ 0.7	Continue with 400 mcg IH dose.

If a decision to increase the dose is made, additional subjects will be enrolled into Group 1 such that 10 subjects receive the 600 mcg IH oxytocin dose.

6.5. Blinding

This will be an open-label study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

- The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner. The investigator/designee will always load and prime the ROTACAPS powder capsule in the device before the subject self-administers an IH oxytocin dose
- All subjects will be taught by the investigator/designee to use the device in the "full-tilt" position and to use a "fast and deep" inspiration technique per inhalation, to achieve two rapidly consecutive maximal inhalations for IH oxytocin administration. This will ensure optimal and consistent treatment delivery. For subjects, the training session will be at any time during the 28-day Screening Period, as deemed appropriate by the investigator/designee.
- ROTACAPS powder capsules should be kept in their sealed packaging at room temperature (15-25°Centigrade [C]). The packaging should only be opened immediately prior to use.
- ROTAHALER inhaler devices will be supplied in bulk and unlabelled to the site. After dosing all ROTAHALER inhaler devices will be uniquely labelled and retained after each dosing session. The devices (which should not be opened up at

the clinical study site) will be stored until further instruction from the sponsor is received.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.8. Compliance with Study Treatment Administration

Per ROTACAPS powder capsule dose, each subject will be asked to inhale twice from the ROTAHALER inhaler to reduce the possibility of inadequate administration due to a single poor inhalation manoeuvre. If failure of the ROTACAPS powder capsule actuation is suspected by the investigator (i.e. due to failure to open the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose using the same capsule.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Group 1 – Women in TSL

Following randomisation and any pre-dose procedures, subjects will receive a single study treatment as active management of TSL. The specific timing of this dose will be as per local standard of care.[2]

Administration will be documented in the source documents and reported in the Case report form (CRF).

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Following randomisation and all pre-dose procedures, subjects will receive two doses of oxytocin, separated by at least 48 hours. Randomisation will determine the order in which the IH and IV formulation is administered.

Administration will be documented in the source documents and reported in the Case report form (CRF).

6.9. Treatment of Study Treatment Overdose

For this study, any dose of the following compounds will be considered an overdose when administered as part of study procedures:

- IH oxytocin > 400 mcg
    - If study dose is increased to 600 mcg, then an overdose will be considered any dose > 600 mcg.
- Oxytocin > 10 I.U. IM
- Oxytocin > 5 I.U. IV

Note: Group 1 subjects may receive additional doses of oxytocin (IM or IV) when required as part of their general care and as clinically indicated. Additional doses of oxytocin will be recorded as concomitant medications, as will any related AEs.

General medical management consists of supportive care.

GSK does not recommend specific treatment for an overdose.

In the event of a study drug overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

[2] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until oxytocin can no longer be detected systemically (at least 4 hours).
3. Obtain an additional plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because either only healthy volunteers are eligible for study participation, or there are other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of postpartum subjects' medical conditions, whether or not GSK is providing specific post-study treatment.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Meals and Dietary Restrictions

There are no dietary restrictions for subjects in either cohort.

6.11.2. Caffeine and Alcohol

Group 1 – Women in TSL

- There are no restrictions for Group 1.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

6.11.3. Activity

Group 1 – Women in TSL

There are no activity restrictions.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses equal to or below the maximum recommended daily dose, is permitted for use during the screening period or at any time deemed necessary by the investigator or subject. All concomitant medication related to routine care during pregnancy and delivery is allowed (including pain relief [e.g. gas/air mixture] and epidural), and other medication may be considered on a case by case basis by the investigator or designee (in consultation with the Medical Monitor if required).

The start and stop time of any concomitant medications administered at any time during labour (including nitrous oxide gas/air mixtures) should be documented on the CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications will result in immediate withdrawal of subject:

- Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) before or after administration of study-related oxytocin.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table in Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic, immunogenic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

7.1.1. Time and Events Table – General Overview

Group 1

Procedure	Study Day			
	Screening[4]	Main Phase	Follow – Up 1 (approx. 24 hours post dose)	Follow – Up 2 (7-14 days post dose)
Informed Consent and Demography	X			
Brief Physical Examination	X			
Medical history (incl. substance abuse)	X			
Inhaler device training / education session	X			
Laboratory assessments[1]	X			
Vital signs[2]	X	X		
Pharmacokinetic blood sample		X		
Oxytocin Administration (IM/IH)		X		
Full blood count		X		
Labour Events Documentation		X		
Device acceptability questionnaire[3]		X		
Prior / concomitant medication review	X	X	X	X
AE review		---------- continuous review ----------		
SAE review	---------- continuous review ----------			

1. Only required if done as part of routine care. Additional study-specific laboratory assessments not required.
2. Includes blood pressure, heart rate, temperature, respiratory rate
3. Only to be used when randomized to IH oxytocin
4. To be completed after 18th week of pregnancy (based on estimated date of delivery).

Group 2

Procedure	Study Day		
	Screening[5]	**Main Phase**	**Follow - Up (7-21 days post dose)**
Informed Consent and Demography	X		
Brief Physical Examination	X	X	
Medical history	X		
Pregnancy test	X	X	
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X	X	
HIV, Hep B and Hep C screen[2]	X		
Inhaler device training / education session	X		
Laboratory assessments (including liver chemistries)	X	X	
Immunogenicity sample		X	X
12-lead ECG	X[4]	X	
CardiacTelemetry		X	
Vital signs[3]	X	X	
Spirometry (FEV-1)[4]	X	X	
Admission to unit		X	
Pharmacokinetic blood sample	X	X	
Oxytocin Administration (IH or IV)		X	
Prior / concomitant medication review	X	X	X
AE review		------ continuous review ----------	
SAE review	---------- continuous review ----------		
Discharge from unit		X	

1. Smokerlyzer at PI/designee discretion if smoking history in question.
2. If test otherwise performed within 3 months prior to first dose of study treatment, repeat testing at screening is not required.
3. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2.
4. Performed in triplicate.
5. To be completed within 28 days of randomization.

7.1.2. Time and Events – Main Phase Procedures

Group 1

		Time post dose										
Procedure	Pre-dose	3 min	5 min	10 min	15 min	20 min	30 min	1 hr	2 hr	2.5 hr	3 hr	4 hr
Vital signs[1]							X		X			
Pharmacokinetic blood sample	X[2]	X	X	X	X	X	X	X	X	X	X	X
Prior medication review	X											
Concomitant medication review		---------- continuous review ----------										
AE review		---------- continuous review ----------										
SAE Review	---------- continuous review ----------											
Device Acceptability Questionnaire[3]												X
Full Blood Count	X											X

1. Includes blood pressure, heart rate, temperature, respiratory rate
2. Predose PK sample to be taken immediately prior to administration of study treatment
3. Only to be administered when randomized to IH oxytocin

Group 2 – Sessions 1 and 2

		Time Post Dose														
Procedure	Pre-dose	2 min	3 min	5 min	8 min	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr
Brief Physical Exam	X															
Pregnancy Test	X															
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X															
Vital signs[2]	X			X			X		X		X					X
12-lead ECG	X	X				X		X	X		X					X
CardiacTelemetry	----------Continuous----------															
Spirometry[3]	X										X					
Pharmacokinetic blood sample	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sample	X															
Laboratory assessments (including liver chemistries)	X															X
Prior medication review	X															
Concomitant medication review		---------- continuous review ----------														
AE review		---------- continuous review ----------														
SAE Review	---------- continuous review ----------															
Discharge from unit[4]																X

1. Smokerlyzer at Principal Investigator (PI)/designee discretion if smoking history in question.
2. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2
3. FEV 1.0 will be performed in triplicate at each time point. Record all three values on source document, and record best effort in eCRF.
4. Discharge at PI discretion, no sooner than 4-hours post-dose.
5. 3 pre-dose samples: approximately 1 hr pre-dose, 30 minutes pre-dose, and 15 minutes pre-dose

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management [e.g. brief physical exam, laboratory assessments] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (see Section 12.3).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF or appropriate source document.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigators Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Adverse Events of Special Interest (AESI)

Any problem related to the delivery of the placenta or postpartum haemorrhage should be documented as an AESI using the appropriate case report form (CRF).

7.3.3. Pregnancy

Group 2 Only:

- Details of all pregnancies will be collected after the start of dosing and until follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.3.4. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Section 12.4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 12.3.6 and Appendix 3 of the Protocol.

7.3.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

  NOTE: The method of documenting Medical Device Incidents is provided in Appendix 4.

7.3.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). This applies to all subjects, including those withdrawn prematurely.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor or SAE coordinator.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.3.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.3.5. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen if palpable).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.6. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate (unless otherwise specified in T&E).

7.3.7. Documentation of Labour Events

The time that the following labour events occurred will be collected:

- Time of crowning
- Time of birth
- Time of delivery of placenta

7.3.8. Electrocardiogram (ECG) (Group 2 Only)

- Triplicate 12-lead ECGs will be obtained at screening as listed in Section 7.1.1.
- Single 12-lead ECGs will be obtained at each timepoint as listed in Section 7.1.2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At all single 12-lead ECG time-points if QTc >450, repeat twice and take average reading.

7.3.9. Continuous Cardiac Telemetry (Group 2 Only)

Continuous cardiac telemetry will be started at least 10 minutes pre-dose (to obtain a stable reading) and continue until at least the first hour after IV and IH placebo / oxytocin administration and then as deemed necessary by the investigator. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

7.3.10. Device Acceptability Questionnaire (Group 1 Only)

A device acceptability questionnaire will be administered to subjects in Group 1 following use of the ROTAHALER (Appendix 7).

7.3.11. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as required by Section 7.1 and defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Tests performed as part of routine care in Group 1.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Subjects in Group 1 are not required to undergo additional laboratory assessments beyond those done as part of their routine care. However, the investigator/designee may conduct any of the tests listed in Table 4 in order to confirm eligibility. Haematology, clinical chemistry, and additional parameters to be tested in all Group 2 subjects are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*White Blood Cell (WBC) count with Differential:*	
	Red Blood Cell (RBC) Count	Mean Corpuscular Volume (MCV)	Neutrophils	
	Hemoglobin	Mean Corpuscular Hemoglobin (MCH)	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST) (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT) (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Other Screening Tests	HIV Hepatitis B (HBsAg) Hepatitis C (Hep C antibody) Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of suspected non-child bearing potential only)			

Laboratory Assessments	Parameters
	Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) Serum or urine hCG Pregnancy test (Group 2 only) [2]
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2 and Appendix 2 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.	

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of oxytocin will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

At each time point, 4 mL of blood will be collected into study-specific tubes formulated to further inhibit peptidase activity. Additional details regarding collection/shipping procedures are provided in the SRM.

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of oxytocin will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM). Once the plasma has been analyzed for oxytocin any remaining plasma may be analysed for metabolites of oxytocin and the results reported separately.

7.5. Biomarkers

7.5.1. Pharmacodynamic Markers

Pre and post-delivery full blood counts will be collected from Group 1 subjects to assess for a change in haemoglobin levels.

7.5.2. Immunogenicity

Blood samples will be taken at the time points specified in the Time and Events Table (Section 7.1) to assess the immunogenicity of oxytocin.

Pre- and post-dose samples will be retained in the event that further immunologic tests are deemed necessary to support observations of unexpected anaphylaxis/ hypersensitivity, and / or a PK profile for IH oxytocin in any Dosing Session which is regarded by the GSK Study Team to be reasonably attributable to circulating anti-oxytocin antibodies.

Details of the collection / shipping procedures are provided in the SRM.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to characterize the pharmacokinetics of 400 mcg IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

No formal hypotheses will be tested, however, the following comparisons are of interest, within Group 1, (IH vs. IM) and between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on oral contraception) and between Cohorts A and B in

Group 2 (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive). For each PK endpoint of interest, point estimates and corresponding two-sided 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference) to provide the range of plausible values for the comparisons of interest.

9.2. Sample Size Considerations

A sufficient number of subjects will be enrolled to ensure approximately 20 evaluable subjects (10 in each of the IM and IH groups) complete all dosing and critical assessments in Group 1, as well as 5 subjects in each cohort in Group 2. Whilst sample size is based on feasibility, precision calculation was also done to approximate the estimate of the expected half width of 90% CI around point estimate for the main comparison of interest (IH oxytocin to 10 I.U. IM oxytocin in women in TSL) using a t-test.

Table 5 illustrates the associated 90% CIs for the mean treatment ratios, assuming between subject SDs of 0.424 and 0.601 (SDs are based on log transformed data) for AUC (0-3h) and CP10 respectively, for the comparisons of interest detailed in Section 9.1. Calculations are based on a symmetric two-tailed procedure on the loge scale and a type I error rate of 10%. These values represent estimates of the between-subject variability observed in the FTIH study 201558 [GlaxoSmithKline Document Number 2016N277949_00].

Table 5 Estimated 90% Confidence Intervals for Treatment Ratios

N	Parameter	Between Subject Standard Deviation (SD)	Estimated Treatment Ratio	Precision	Expected 90% CI
10	AUC(0-3h)	0.424 (CVb=44.35%)	1	38.30%	(0.72, 1.38)
10	Cp10	0.601 (Cvb=65.96%)	1	58.20%	(0.63,1.58)

The precision estimates are deemed acceptable to assess the study objectives at this stage of development.

9.2.1. Sample Size Sensitivity

Considering the variability of AUC(0-3h) and Cp10, Table 6 shows the scenarios for different sample size and the precision estimates for IH vs. IM in Group 1.

Table 6 Estimated 90% Confidence Intervals for Treatment Ratios for Sample Size Sensitivity

%CVb	N	Precision	Assuming ratio 1, the confidence interval
44.35%	5	61.90%	(0.61, 1.61)
	15	29.80%	(0.77,1.29)
65.96%	5	98.00%	(0.50, 1.98)
	15	44.80%	(0.69, 1.44)
	20	37.40%	(0.72,1.37)
85.35%*	5	131.90%	(0.43, 2.31)
	10	75.90%	(0.56, 1.75)
	15	57.60%	(0.63, 1.57)
	20	48.00%	(0.67, 1.48)

* 85.35% was the largest between subject CV for AUC(0-10) observed for FTIH study 201558 [GlaxoSmithKline Document Number:2016N277949_00]

9.2.2. Sample Size Re-estimation or Adjustment

No formal sample size re-estimation is planned for this study. However, if the variability is high (for example approaching 85%) then the sample size for Group 1 may be increased to a maximum of 10 additional subjects per treatment arm (IH and IM only).

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exist on the study database. This population will be used for summarizing screening failure reasons.
All Subjects Population	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays.
Pharmacokinetic Population	• Subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.

9.3.2. Interim Analyses

No formal interim analyses are planned. PK data will be reviewed per Section 9.3.2.1, Section 9.3.2.2 and Section 9.3.2.3, and may be shared with any relevant third party to allow for discussion around future partnering opportunities for IH oxytocin.

9.3.2.1. Informal Interim Reviews

PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

This will be repeated after restart from the temporary halt for Group 1.

9.3.2.2. In-Stream Analysis of Group 1

Following restart from temporary halt, PK specimens from each of up to 5 subjects in Group 1 will be analysed as soon as possible after collection. This will allow for confirmation that the revised specimen collection procedures allow for detection of adequate oxytocin PK profile.

9.3.2.3. Analysis of Group 2

An analysis of Group 2 (non-pregnant volunteers) will be performed once Group 2 has completed to allow for full reporting of non-pregnant volunteer data prior to completion of Group 1.

There will be no changes to the study design or Group 1 of the study as a result of this analysis. The Reporting and Analysis Plan (RAP) will describe the planned analysis in greater detail.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

9.4.1.1. Safety Analysis

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.1.2. Pharmacokinetic Analysis

Pharmacokinetics analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline. Plasma oxytocin concentration-time data will be analyzed by non-compartmental methods with WinNonlin V6.3 or greater. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-3h) and AUC(0-∞)], the last observed quantifiable concentration (Clast), time of the last quantifiable

concentration (tlast), Cp10, Cp20, Cp30 (observed plasma concentrations at 10, 20 and 30minutes post-dose, respectively), plasma clearance (CL; IV only), volume of distribution (V; IV only) and apparent terminal phase half-life (t1/2). Other PK parameters may also be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

If appropriate, a population PK analysis may also be conducted, in addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis.

9.4.2. Secondary Analyses

Statistical analyses of the PK parameter data will be performed by, or under direct auspices of Clinical Statistics, QSci.

9.4.2.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons within Group 1 IH vs. IM, point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the RAP.

9.4.3. Exploratory Analyses

9.4.3.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on the combined oral contraceptive), and within Group 2 between Cohorts A and B (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive), point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the RAP.

9.4.3.2. Device Acceptability Questionnaire

In Group 1, subject satisfaction with device, including instructions and ease of use, will be assessed. The questionnaire is located in Section 12.7

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRFs <or> entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where

applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Frontiers in Pharmacology*. 2014. Volume 5. Article 65: 1-5.

GlaxoSmithKline Document Number 2015N234711_01. Study ID 201558. Clinical Pharmacology Study Protocol. A single centre, single blind study to investigate the safety, tolerability and pharmacokinetics of single doses of oxytocin (GR121619) administered via an inhaled route in healthy female volunteers. 16-NOV-2015.

GlaxoSmithKline Document Number 2015N239682_00. Study ID 201248 – Clinical Pharmacology Study Report. An enabling study to compare the inhalation profiles of women in the third stage of labour to those of non-pregnant female volunteers and to explore whether there are any differences which could impact the delivery of an inhaled medicinal product, 16-OCT-2016.

GlaxoSmithKline Document Number 2015N240749_01. GR121619 Investigator's Brochure, AUG-2015.

GlaxoSmithKline Document Number 2016N277949_00. Study ID 201558 – Clinical Pharmacology Study Report. A single centre, single blind study to investigate the safety, tolerability and pharmacokinetics of single doses of oxytocin (GR121619) administered via an inhaled route in healthy female volunteers. 30-JUN-2016.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.

Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2014, *Issue* 2. *Art. No.: CD003249. DOI:* 10.1002/14651858.CD003249.pub3.

Prankerd RJ, Nguyen T, Ibrahim JP, et al. Pulmonary Delivery of an Ultra-Fine Oxytocin Dry Powder Formulation: Potential for Treatment of Postpartum Haemorrhage in Developing Countries. 2013; *PLoS One*. Vol 8: 12: Article e82965

Syntocinon Summary of Product Characteristics, Novartis, 2014

Thornton S, Davison JM, Baylis PH. Effect of human pregnancy on metabolic clearance rate of oxytocin. *American Physiological Society*. 1990. 0363-6119: R21-R24.

Thornton S, Davison JM, Baylis PH. Plasma oxytocin during third stage of labour: comparison of natural and active management.*BMJ.* 1988. Volume 297:167-169.

WHO Model List of Essential Medicines 18th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO Model List of Essential Medicines for Children 4th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO, UNICEF, UNFPA. The World Bank World Health Organization (WHO) Press. Trends in Maternal Mortality: 1990 to 2008: Estimates Developed by WHO, UNICEF, UNFPA and The World Bank. Geneva*: WHO,* 2010.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADAs	Anti drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANP	Atrial natriuretic peptide
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-3)	Area under the concentration-time curve from time zero (pre-dose) to three hours
AUC(0-∞)	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
Ca2+	Intracellular calcium
CI	Confidence Interval
CL	Plasma clearance
Clast	last observed quantifiable concentration
Cmax	Maximum observed plasma concentration
COC	Combined oral contraceptive
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
Cp10	Observed plasma concentrations at 10 minutes post-dose
Cp20	Observed plasma concentrations at 20 minutes post-dose
Cp30	Observed plasma concentrations at 30 minutes post-dose
CPK	Creatinine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry powder inhaler
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1.0	Forced expiratory volume at 1 minute
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram
GCP	Good Clinical Practice

GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care professional
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
I.U.	International units
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IH	Inhaled
IL	Interleukin
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
Kg	kilogram
LDH	Lactate dehydrogenase
m	Meter
mcg	Micrograms
MCH	Mean Corpuscular Hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
mmHg	Millimeter of mercury
MSDS	Material Safety Data Sheet
Msec	Milliseconds
MW	Molecular weight
OTR	Oxytocin receptor
PGF	Prostaglandin F
PI	Principal Investigator
PK	Pharmacokinetics
PPH	Post-partum haemorrhage
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis plan
RBC	Red blood cells
SAE	Serious Adverse Event

SD	Standard deviation
SMC	Smooth muscle cells
SPC	Summary of product characteristics
SpO2	Peripheral capillary oxygen saturation
SRM	Study reference manual
T&E	Time and event
t1/2	Terminal phase half-life
TB	Tuberculosis
tmax	Time to Cmax
TSL	Third stage of labour
UK	United Kingdom
ULN	Upper Limit of Normal
V	Vassopresin
VOD	Volume of distribution
WBC	White blood cells
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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ROTAHALER

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Syntocinon
Uniject
WinNonlin

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 4h of the last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or</td></tr>
</table>

recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; International normalized ratio (INR) measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism

- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4: Definition of and Procedures for Documenting Medical Device Incidents

12.4.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.4.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.5. Appendix 5: List of Acceptable Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Group 2, Cohort B Only: List of Acceptable Non-hormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Nonhormonal Intrauterine device or
2. Male condom combined with vaginal spermicide
3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

Group 2 Only

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication or be withdrawn from the study.

12.5.3. References

Bolton TJ, Randall K, Yentis SM. Effect of the Confidential Enquiries into Maternal Deaths on the use of Syntocinon at Caesarean section in the UK. Anaesthesia 2003(58-3):277-9.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.6. Appendix 6: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Device Acceptability Questionnaire

Device Acceptability Questionnaire

Please answer the following questions regarding your use of the ROTAHALER inhaler for oxytocin.

1. Did you feel confident you had received the medicine?

   Yes No Neutral Decline to answer

2. Did you find the inhaler easy to use?

   Yes No Neutral Decline to answer

3. Did you prefer to have your medicine from an inhaler instead of an injection?

   Yes No Neutral Decline to answer

4. Do you feel using this inhaler is an acceptable way to administer the medicine?

   Yes No Neutral Decline to answer

Thank you for answering these questions.

12.8. Appendix 8: Protocol Changes

12.8.1. Protocol Amendment 01

As part of the Medical Device Notification assessment process, the Medicines and Healthcare products Regulatory Agency (MHRA) requested that the protocol prominently reflect that although the investigational device (the ROTAHALER) bears a CE mark, it has not been CE marked in accordance with the Medical Device Directive 93/42/EEC as updated. This change applies to all sites.

Section 6.2 Medical Devices

Change From:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device).

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

Change to:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

12.8.2. Protocol Amendment 02

This amendment has been implemented to update the PK sample collection procedures in order to enhance ex-vivo PK stability, and to implement in-stream PK data analysis following the informal interim analysis of the first 10 subjects to complete Group 1. Location of name and contact information for Secondary Medical Monitor has also been updated.

Medical Monitor/Sponsor Information Page

Medical Monitor/SAE Contact Information

Change from:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK

Change to

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	Name and contact details available in Study Reference Manual				

Section 1 Type and number of subjects

Change of typographical error from 45 to 50 subjects.

Change from:

In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

Change to:

In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

Section 2.2.2 PK Specimen Stability as Observed in 205920

Addition of this section to describe results from first informal interim analysis:

Prior to the initiation of the current trial, a sample-handling process was developed using blood from pregnant subjects of at least 37 weeks gestation to ensure ex-vivo oxytocin stability in specimens collected from Group 1 TSL subjects.

Per protocol, after 10 subjects had completed all procedures in Group 1, an informal interim PK analysis was conducted. It was observed that in the majority of the plasma samples collected from TSL subjects, oxytocin concentrations were below the limit of quantification (BLQ) or at very low concentrations (approximately 3pg/mL) approaching the lower limit of quantification (LLQ) of the assay (2pg/mL). This was seen across both IM and IH routes of administration. This was an unexpected finding which has been confirmed by re-analysis of selected samples. As such, it is considered that it may be due to ex-vivo oxytocin instability related to uninhibited oxytocinase and peptidases, which are believed to be at increased concentrations in the plasma of postpartum women compared with non-pregnant women, and women at 37 weeks gestation. This finding resulted in a temporary halt to the trial.

Section 3.1 Group 1: Women in TSL

Typographical error correction.

Change from:

To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocinin women in TSL.

Change to:

To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

Section 4.3 Type and Number of Subjects

Change of typographical error from 45 to 50 subjects.

Change from:

In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

Change to:

In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

Section 5.4.6 Plasma oxytocin concentration stopping criteria

Addition of this section and following text:

Per Section 9.3.2.1, the plasma oxytocin concentrations in up to 5 subjects in Group 1 will be analysed in real time. If the plasma oxytocin concentration is BLQ or sufficiently low to prohibit interpretation in these 5 subjects irrespective of treatment, the study will be halted and reviewed.

Section 6.3 Treatment Assignment

Addition of following text:

If deemed necessary or if there is a new site identified for conducting and/or continuing the clinical trial, then a new randomization schedule may be generated by Clinical Statistics, prior to the start of the study at the new site, using validated internal software.

Section 6.4 Planned Dose Adjustments

Typographical error correction

Change from:

For Group 2, if an exaggerated physicological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

Change to:

For Group 2, if an exaggerated <u>physiological</u> response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

Section 7.4.1 Blood Sample Collection

Change from:

At each time point, 4 mL of blood will be collected into K2 or K3 Ethylenediaminetetraacetic acid (EDTA) tubes and stored on ice for up to 2 hours prior to centrifugation in a refrigerated centrifuge. Further details regarding collection/shipping procedures are provided in the SRM.

Change to:

At each time point, 4 mL of blood will be collected into study-specific tubes formulated to further inhibit peptidase activity. Additional details regarding collection/shipping procedures are provided in the SRM.

Section 7.4.2 Sample Analysis

Addition of the following text:

Once the plasma has been analyzed for oxytocin any remaining plasma may be analysed for metabolites of oxytocin and the results reported separately.

Section 9.3.2 Interim Analyses

Change from:

No formal interim analysis is planned. However, PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

Change to:

No formal interim analyses are planned. PK data will be reviewed per Section 9.3.2.1 and Section 9.3.2.2.

9.3.2.1 Informal Interim Reviews

PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

This will be repeated after restart from the temporary halt for Group 1.

9.3.2.2 In-Stream Analysis of Group 1

Following restart from temporary halt, PK specimens from each of up to 5 subjects in Group 1 will be analysed as soon as possible after collection. This will allow for confirmation that the revised specimen collection procedures allow for detection of adequate oxytocin PK profile.

12.8.3. Protocol Amendment 03

This protocol amendment updates the analysis plans to permit sharing of informal interim data with key partners, and to complete the analysis of Group 2 before Group 1 is complete.

Section 1 Protocol Synopsis (Objectives/Endpoints), Section 3.2, Section 3.3

Correction of typographical error: "AUC(0-3h)" listed twice in various endpoints.

Section 9.3.2

Addition of the following italic text:

No formal interim analyses are planned. PK data will be reviewed per Section 9.3.2.1, Section 9.3.2.2, *and Section 9.3.2.3, and may be shared with any relevant third party to allow for discussion around future partnering opportunities for IH oxytocin.*

Addition of the following section:

Section 9.3.2.3 Analysis of Group 2

An analysis of Group 2 (non-pregnant volunteers) will be performed once Group 2 has completed to allow for full reporting of non-pregnant volunteer data prior to completion of Group 1.

There will be no changes to the study design or Group 1 of the study as a result of this analysis. The RAP will describe the planned analysis in greater detail.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomized, open-label study to characterize the pharmacokinetics of inhaled oxytocin (GR121619) compared with IM oxytocin in women in the third stage of labour, and with IV oxytocin in non-pregnant, non-lactating women of childbearing potential.

Compound Number: GR121619

Development Phase I

Effective Date: 04-JAN-2018

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N281575_00	2016-AUG-22	Original
2016N281575_01	2016-OCT-10	Amendment No. 1
Section 6.2: Inclusion of information on CE marking.		
2016N281575_02	2018-JAN-04	Amendment No. 2
Update to PK collection procedures and implementation of in-stream PK data analysis. Update to location of Secondary Medical Monitor contact information.		

SPONSOR SIGNATORY

PPD

4th Jan 2018

Pauline Williams
Head of Global Health
Head Physician

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK
Secondary Medical Monitor	Name and contact details available in Study Reference Manual				
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline (GSK) Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **EudraCT 2016-002672-27**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 205920

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 205920

Rationale

Post-partum hemorrhage is one of the main causes of maternal mortality in the developing world. The World Health Organization (WHO) lists oxytocin on its list of 'Essential Medicines' for Humanity as a preventative treatment for post-partum hemorrhage; however, because of its cold-chain storage requirement and parenteral administration route, high-quality oxytocin is not always available in resource-poor settings. GlaxoSmithKline (GSK) has developed a stable, dry-powder formulation of oxytocin to address this unmet need, with the goal of reducing post-partum hemorrhage morbidity and mortality in these settings.

This study is being conducted to further assess safety and tolerability of inhaled oxytocin, and to characterize the pharmacokinetic (PK) profile of inhaled oxytocin compared to oxytocin administered as standard of care. Two groups of subjects will be enrolled. Group 1 will enroll pregnant women, who will be randomized to receive either inhaled (IH) or intramuscular (IM) oxytocin as active management of the third stage of labour. Group 2 will enroll non-pregnant women of childbearing potential, who will receive IH oxytocin and intravenous (IV) oxytocin in a cross over design over two dosing sessions.

Objectives/Endpoints

Group 1 – Women in Third Stage of Labour (TSL)

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 International Units (I.U.) IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events (AE); absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax, Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h])

Objectives	Endpoints
	will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

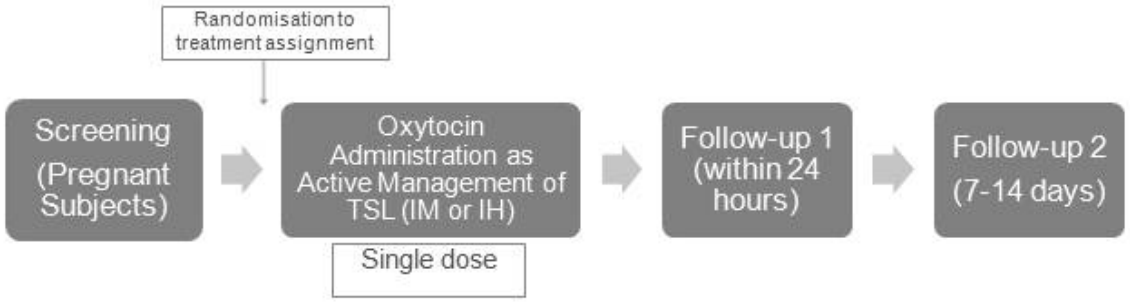
Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

Groups 1 and 2 – Women in TSL and Non-pregnant, non-lactating females of child bearing potential

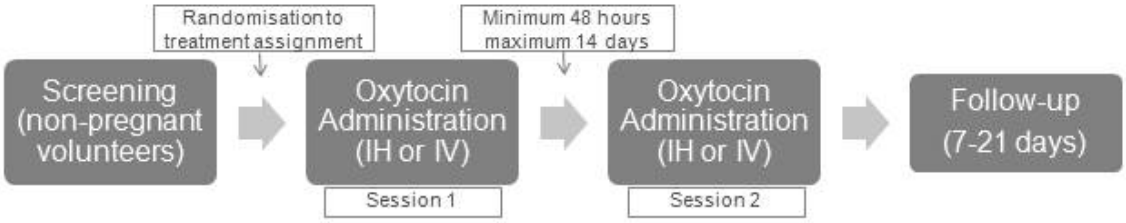
Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

Overall Design

Group 1 – Women in TSL



Group 2 – Non-pregnant, non-lactating females of child bearing potential



Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery). Group 2: All screening assessments to be completed within 28 days prior to the first dose.
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions.
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 micrograms (mcg) IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 h post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2).

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor. Replacement subjects will complete all study procedures.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for inhaled and intramuscular oxytocin. In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose.

Analysis

The primary objective of this study is to characterize pharmacokinetics of IH oxytocin and IM oxytocin in women in the third stage of labour.

No formal hypotheses will be tested, however, comparisons of interest, within Group 1, and between Group 1 and Group 2 and between Cohorts A and B in Group 2 will be made and the point estimates and corresponding two-sided 90% confidence intervals (CI) will be presented to provide the range of plausible values for the comparisons.

2. INTRODUCTION

Maternal mortality associated with postpartum hemorrhage (PPH) is one of the major public health problems in the developing world. Approximately half a million women worldwide die annually from causes directly related to pregnancy and childbirth, and up to one third of these deaths in Africa and Asia are caused by complications as a result of PPH [Khan, 2006;WHO, 2010]. A Cochrane Review meta-analysis of the data from multiple preventative trials with oxytocin at 10 international units (I.U.) given via the intramuscular (IM) route has confirmed this specific uterotonic, and this particular route of administration, to be the gold standard prophylactic therapy for PPH [Mousa, 2014]. For this reason, the World Health Organization (WHO) has designated oxytocin as one of its 'Essential Medicines' for humanity [WHO Model List of Essential Medicines 18th list, April 2013; WHO Model List of Essential Medicines for Children 4th list, April 2013].

However, in resource-poor settings within the developing world, the effectiveness of prophylactic IM oxytocin is diminished by a lack of appropriate refrigeration facilities and availability of trained health care professionals (HCPs) to administer IM injections [Mousa, 2014]. Although single-use, oxytocin prefilled, syringes for IM injection are available in many developing countries (e.g. UNIJECT device), the development of a needle-free and self-administered inhaled (IH) oxytocin product, which delivers comparable systemic exposure to 10 I.U. IM, would be a major step-change in the

administration of this life-saving medicine to pregnant women in resource-poor regions of the developing world. This would be particularly relevant in rural areas where the mother has no routine access to a trained HCP and/or where there is no reliable electricity supply to permit refrigerated storage of oxytocin injection vials.

We have developed a stable, dry-powder formulation of oxytocin to be administered via the oral inhaled pulmonary route (compared to 10 I.U. of IM oxytocin) using a GlaxoSmithKline (GSK)-manufactured medical device (or device manufactured for GSK by a third party) which is a capsule-based inhaler (Modified Air Inlet ROTAHALER™ Dry Powder Inhaler (DPI) device, hereafter referred to as ROTAHALER). This formulation and delivery method has the potential to be used in settings where effective oxytocin is currently unavailable to women in the third stage of labour (TSL).

2.1. Study Rationale

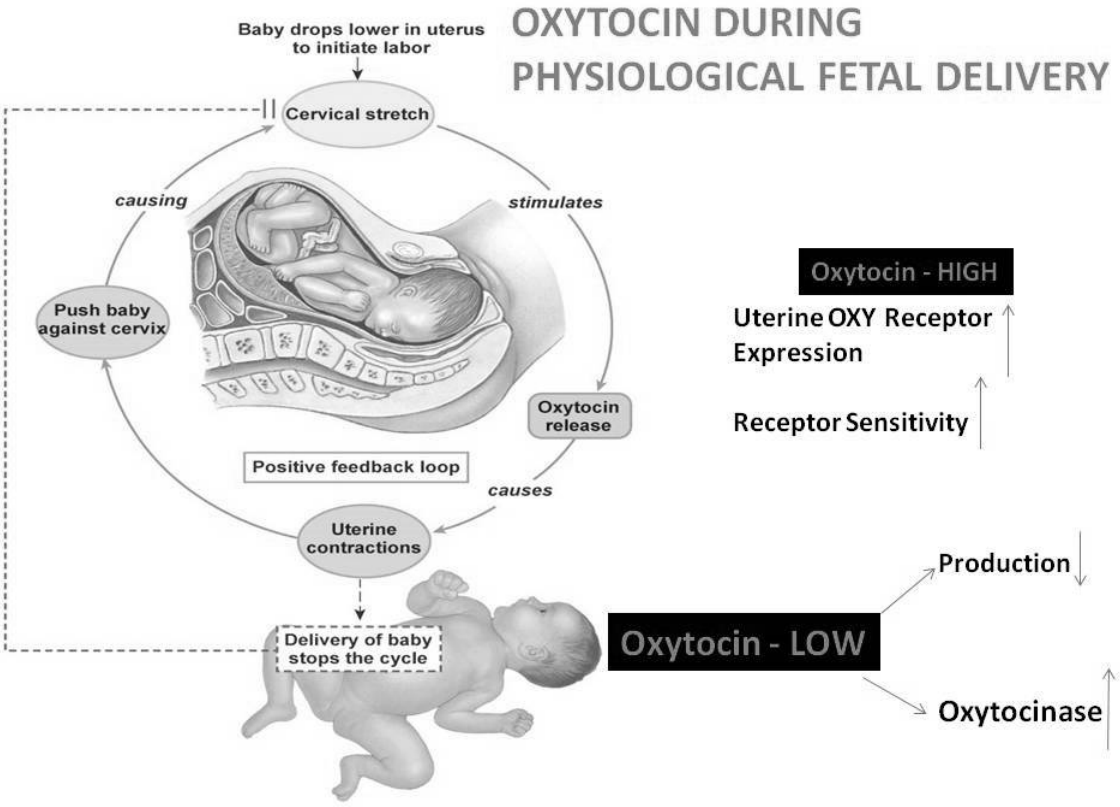
This study will be the second investigation of oxytocin in humans via the IH route, which follows the first time in human (FTIH) study, 201558 [GlaxoSmithKline Document Number 2015N234711_01, 2015; see Section 2.2.1 for more information on the FTIH trial)]. Published literature on the pharmacokinetics (PK) of oxytocin in non-pregnant and pregnant women is limited. There is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy; potentially related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy related changes in hepatic and renal function [Syntocinon Summary of Product Characteristics, Novartis, 2014; Thornton, 1990]. In addition, endogenous oxytocin plasma concentrations have been reported to either increase or remain constant after the delivery of the fetal anterior shoulder [Thornton, 1988]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in the TSL for a given dose and route of administration of oxytocin. To further understand the effect of pregnancy on the PK of oxytocin, this study will investigate the PK of oxytocin in pregnant women in TSL following either IH (400 micrograms [mcg]) or 10 I.U. IM (17 mcg) administration. A greater understanding of the PK of oxytocin in TSL will help facilitate extrapolation of data obtained in healthy non-pregnant women to women in TSL. An additional group of non-pregnant non-lactating female volunteers will also be included as a control group and will receive 400 mcg IH oxytocin and 5 I.U. intravenous (IV) oxytocin. This second group will enrol one cohort of subjects taking the combined oral contraceptive (COC), and another cohort using a non-hormonal form of contraception. This will assess if women need to be on an oral contraceptive vs. other methods of birth control in future clinical studies, since although the COC is believed to suppress endogenous oxytocin levels the literature is not consistent about this observation. As the requirement to be taking the COC makes recruitment more of a challenge it will be helpful to know if this inclusion is essential, or if women using non-hormonal forms of birth control might also have sufficiently low systemic oxytocin levels suitable for PK studies.

2.2. Brief Background

Oxytocin is a nonapeptide which is produced by the hypothalamus and released into the systemic circulation by the posterior pituitary gland. Within the brain, oxytocin, like most

hypothalamic synthesized hormones, acts as a neurotransmitter. In human pregnancy, during the later phases of the third trimester, increasing circulating levels of oxytocin act as a potent endogenous uterotonic which facilitates the initiation of labour. Furthermore, a neurohormonal positive feedback loop exists between dilatation of the cervico-vaginal canal by fetal passage and the hypothalamus (i.e. Fergusson reflex) which augments oxytocin production, thus increasing uterine contraction intensity and frequency which facilitates vaginal delivery. However, once the fetus is delivered, plasma oxytocin levels rapidly diminish probably due to a combination of increased circulating levels of oxytocinase (the principal oxytocin deactivating enzyme), in the plasma, an overall reduction in hypothalamic oxytocin synthesis (Figure 1), and a reduction in uterine oxytocin receptor (OTR) density. This oxytocin-depleted, relatively auterotonic, physiological environment puts the mother at risk of PPH during the subsequent placental delivery phase (i.e. TSL).

Figure 1 Oxytocin During Physiological Fetal Delivery



Oxytocin receptors are constitutively expressed in smooth muscle cells (SMCs) in the uterine myometrium, muscular walls of the bronchi and upper digestive tract, myoepithelial cells of the breast duct which are essential for the oxytocin-dependent postpartum breast milk let-down reflex, and in different regions of the brain. Although uterine OTR expression increases during the later stages of pregnancy, it is not known whether pregnancy increases OTR expression at non-uterine sites, such as the maternal brain, where neuronal oxytocin signalling has been implicated in postpartum bonding behaviour with the baby. Within the kidney, oxytocin is known to bind to vasopressin

(V2) receptors, rather than OTR, in the medullary renal collecting duct which triggers an antidiuretic effect.

Binding of oxytocin to OTR triggers an increase in intracellular calcium (Ca2+), which is partly mediated through oxytocin-dependent up-regulation of prostaglandin F (PGF)2α synthesis, which in the uterine myometrium leads to physiological uterine contractions during 3rd-stage labour.

More recent research has shown oxytocin to be present in broncho-alveloar lavage fluid collected from the respiratory tract of adult humans of both sexes, but oxytocinase expression was not assessed. In an in vivo pharmacology study [Prankerd , 2013] in pregnant ewes intratracheal insufflation of a dry-powder formulation of oxytocin was associated with poor absolute bioavailability (ca 5%), but despite low systemic exposure, this still caused a pharmacodynamic response that was manifested by increased electrical uterine activity measured by electromyography, probably as a result of increased OTR stimulation in the pregnant uterus.

2.2.1. IH Oxytocin FTIH Study 201558

Study 201558 [GlaxoSmithKline Document Number 2016N277949_00] was the FTIH study to evaluate safety, tolerability, and characterize the PK profile of 4 dose strengths of IH oxytocin compared to oxytocin 10 I.U. IM. The study enrolled 16 healthy, non-pregnant, premenopausal female subjects. One subject was withdrawn prior to IH oxytocin dosing due to inability to cannulate. Subjects were administered 10 I.U. IM oxytocin, IH placebo containing (only) the excipients found in the IH oxytocin formulation, and IH oxytocin. A minimum washout period of 48 hours (h) was required between each dose of active drug. This dose escalation study evaluated 4 doses of IH oxytocin: 50 mcg, 200 mcg, 400 mcg, and 600 mcg. The most frequently reported Adverse Event (AE) was headache, and occurred in at least one subject in each treatment arm. In general, IH oxytocin was well-tolerated, no safety concerns with IH dosing were identified, no clinically significant effect on respiratory parameters were observed, and no Serious Adverse Events (SAEs) were reported. The PK profile of the 400 mcg IH oxytocin dose was similar to that of 10 I.U. IM, and has been selected for further evaluation. See Section 4.5 for further information on PK characteristics.

2.2.2. PK Specimen Stability as Observed in 205920

Prior to the initiation of the current trial, a sample-handling process was developed using blood from pregnant subjects of at least 37 weeks gestation to ensure ex-vivo oxytocin stability in specimens collected from Group 1 TSL subjects.

Per protocol, after 10 subjects had completed all procedures in Group 1, an informal interim PK analysis was conducted. It was observed that in the majority of the plasma samples collected from TSL subjects, oxytocin concentrations were below the limit of quantification (BLQ) or at very low concentrations (approximately 3pg/mL) approaching the lower limit of quantification (LLQ) of the assay (2pg/mL). This was seen across both IM and IH routes of administration. This was an unexpected finding which has been confirmed by re-analysis of selected samples. As such, it is considered that it may be due to ex-vivo oxytocin instability related to uninhibited oxytocinase and peptidases, which

are believed to be at increased concentrations in the plasma of postpartum women compared with non-pregnant women, and women at 37 weeks gestation. This finding resulted in a temporary halt to the trial.

3. OBJECTIVES AND ENDPOINTS

3.1. Group 1: Women in TSL

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h]) will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

3.2. Group 2: Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

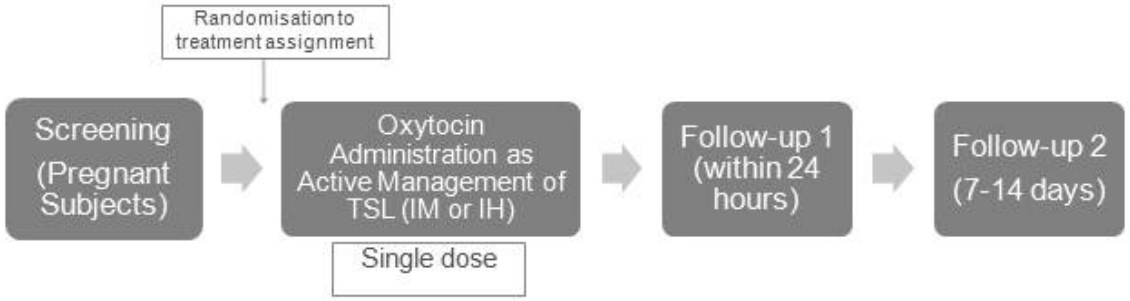
3.3. Groups 1 and 2: Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2.	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Study Schematic Group 1: Women in TSL



4.1.2. Study Schematic Group 2: Non-pregnant, non-lactating females of child bearing potential

4.1.3. Study Design Detail

This study will enrol two groups.

Group 1 - Women in TSL

Group 1 will enrol women with an uncomplicated pregnancy, and main phase procedures will occur during TSL. Subjects will be randomized to receive either IH or IM oxytocin

as active management of TSL. The specific timing of this dose will be as per local standard of care.[1]

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Group 2 will enrol healthy, non-pregnant, non-lactating female subjects of childbearing potential, and each subject will participate in 2 dosing sessions. Group 2 will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive, and Cohort B will enrol women who are not using a hormonal form of contraceptive. Group 2 subjects will receive IH oxytocin at one dosing session, and IV oxytocin at the other dosing session; the order of IH versus IV oxytocin administration will be randomly assigned.

PK samples will be analysed periodically throughout the study duration to enable development of the population PK model and derivation of PK parameters via non-compartmental methods, as data permits.

No formal interim analysis is planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: IH, IM in Group 1 and IH in Group 2 Cohort A in order to assess if dose escalation is required.

4.1.3.1. Pregnant Females (Group 1)

Subjects will review the study information and if they agree to participate, sign the informed consent form. For most subjects this is expected to take place at an outpatient antenatal visit, or additional study-specific screening visit. If a subject meets all inclusion/exclusion criteria for the study, she will be eligible for enrolment in the study.

To facilitate recruitment, and provide subjects ample time to consider participation, screening may occur any time after 18 weeks gestation (based on estimated date of delivery). See time and events (T&E) table in Section 7.1 for details.

4.1.3.2. Non-pregnant Females (Group 2)

Subjects will review the study information and if they agree to participate, sign the informed consent form. If a subject meets all inclusion/exclusion criteria for the study, she will be enrolled in the study.

Screening may occur within 28 days prior to randomization for non-pregnant volunteers. If a subject falls outside this window prior to randomization and enrolment, she must be re-screened. Certain screening procedures may not be required to be repeated; see T&E (Section 7.1) for details.

[1] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

Group 2 subjects will take part in 2 dosing sessions, which must be conducted a minimum of 48 hours apart. It is recommended that subjects complete Session 2 within 14 days of Session 1. Subjects will be randomized to receive either IH or IV oxytocin during Session 1, and to receive the other treatment during Session 2, such that all subjects in Group 2 receive both treatments over the course of the 2 sessions.

4.1.4. ROTAHALER Inhaler Training

The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner (refer to Section 6.7). Subjects will be instructed by the investigator/designee to use an inspiration technique (2 inhalations) that enables maximal inhalation of the ROTACAPS powder capsule contents (refer to Section 6.7 for full details). This will ensure optimal and consistent drug delivery (full instructions available in the Study Reference Manual [SRM]).

4.1.5. Length of Stay for All Subjects

Group 1 - Women in TSL

Subjects in Group 1 will be admitted to hospital during labour as part of their routine care, and will be required to remain inpatient for a minimum of 4 hours after receiving any study-related dose of oxytocin. After final PK collection, subjects will be finished with study procedures and the main phase of the study will be considered complete. Discharge from hospital will be determined by the subject's medical provider.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Subjects in Group 2 will be admitted to the clinical unit prior to dosing on Day 1 and are to remain inpatient until at least 4 hours after dosing. Discharge will occur at the discretion of the investigator.

4.2. Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery) Group 2: All screening assessments to be completed within 28 days prior to the first dose
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 mcg IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 hours post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

[1] See Section 6.4 for possible dose adjustment to IH oxytocin.

4.3. Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2). Refer to Section 6.3 for treatment assignment information.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment at the discretion of the Sponsor. Replacement subjects will complete all study procedures as outlined in Section 7.1.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for IH and IM. In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose. See Section 6.4.1 for more details.

4.4. Design Justification

Group 1 - Women in TSL

This trial uses a randomized, single-dose approach to assign women in TSL to receive oxytocin by one of two routes: IM or IH. No placebo is being used, as the current standard of care is to administer oxytocin as active management of TSL to prevent PPH.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

A group of non-pregnant, non-lactating women of childbearing potential will receive IH and IV oxytocin. This group will be divided into two cohorts: Cohort A will enrol women on the combined oral contraceptive. This cohort will serve as a control group, as they most closely resemble the population enrolled in the FTIH study. Cohort B will enrol women using a non-hormonal form of contraception. This comparison group will help characterize the effect of oral contraceptives on endogenous oxytocin production and the PK profile of oxytocin.

Blinding

This study uses an open-label design.

4.5. Dose Justification

Single inhaled doses of oxytocin (50-600 mcg) have been generally well tolerated in the FTIH study, with no emerging safety signals, in healthy, non-pregnant, premenopausal female subjects (Study 201558) [GlaxoSmithKline Document Number 2016N277949_00; see also Section 2.2.1]. Following inhaled administration oxytocin was rapidly absorbed into the systemic circulation (tmax ranging from 0.05 to 0.50 h) with systemic exposure (Cmax and AUC) increasing with inhaled dose in an

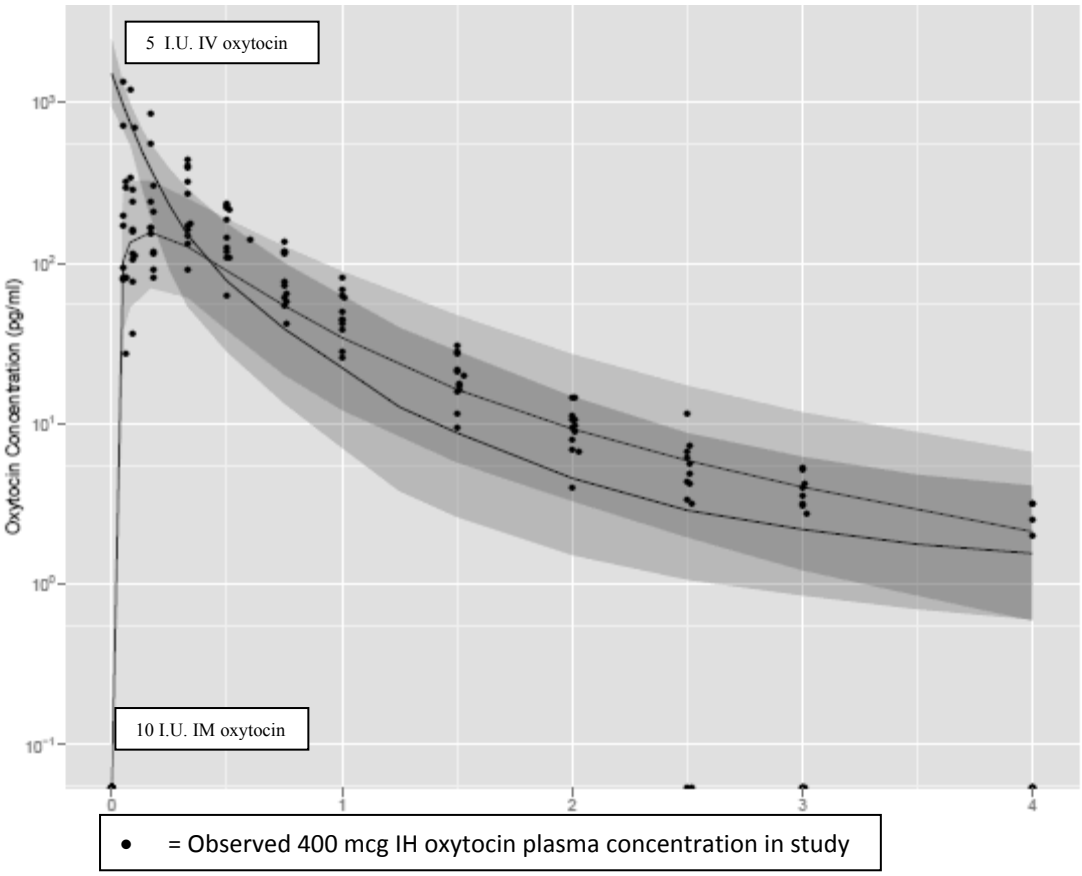
approximately proportional manner between 200 and 600 mcg. In general, the shape of the observed oxytocin concentration-time profile following inhaled administration was consistent with that following IM administration.

Based on the data from the FTIH study, and assuming that the PK characteristics of IH and IM oxytocin are similar in TSL compared with non-pregnant women, the 400 mcg inhaled dose is predicted to be an effective dose in women in TSL by ensuring that the systemic exposure (Cp10, Cp30 and AUC(0-3 h) following IH dosing is at least that following IM administration at the approved dose of 10 I.U. This would be based on the adjusted geometric mean ratio (90% Confidence Interval [CI]) treatment comparisons for Cp10, Cp30 and AUC (0-3 h) following 400 mcg IH compared with 10 I.U. IM, namely 1.10 (0.85,1.43), 1.65 (1.30, 2.09) and 1.27 (1.07, 1.50) respectively in study 201558. The PK parameters (Cp10, Cp30 and AUC(0-3 h)) have been selected to ensure onset and duration of action of the IH product is at least comparable to IM.

The clinical safety and reported AEs with oxytocin correlates to Cmax, with the Cmax of 10 I.U. IV representing the upper bounds of what could be considered safe in current clinical practice (AEs include flushing, which can cause a transient decrease in blood pressure and reflex tachycardia; see the Oxytocin Summary of Product Characteristics for more information). The recommendation in the United Kingdom (UK) in clinical practice has been to reduce the IV dose to 5 I.U. IV or administer by a controlled IV infusion [Bolton, 2003].

Minimising the risk of high Cmax levels of oxytocin following the IH administration is therefore important. Based on a comparison of model predicted systemic exposure following IV administration to non-pregnant, premenopausal female subjects with observed PK profiles following 400 mcg IH oxytocin, it is anticipated that Cmax following administration of the 400 mcg dose will not markedly exceed values following 5 I.U. IV bolus oxytocin (Figure 2). The inclusion of the 5 I.U. IV dose will allow an assessment of the potential safety and PK of the inhaled formulation compared to IV route of administration.

Figure 2 **Model predicted profiles (median (95%PI)) following IM (10 I.U. and IV bolus (5 I.U. administration of oxytocin overlaid with observed plasma concentrations of oxytocin following 400 mcg IH oxytocin to healthy non-pregnant females**



Whilst published literature on the PK of oxytocin in non-pregnant and pregnant women is limited there is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy. This may be related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy-related changes in hepatic and renal function [Syntocinon, 2014;Thornton, 1990]. In addition, there may be circulating levels of endogenous oxytocin in the plasma in women in TSL [Thornton, 1988] and increases in blood volume (40-50%) and total body water [Costantine, 2014]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in TSL for a given dose and route of administration of oxytocin. However, given that any pregnancy-related changes in systemic clearance, and/or distribution and baseline oxytocin levels, are considered to equally impact on each route of administration (IV, IM and IH), it is considered that the relative ratio of IV to IM and IH exposure observed in non-pregnant women is likely to be maintained in pregnancy. The only exception may be if pregnancy results in marked changes in absorption profiles. However, in a study of inhalation profiles of non-pregnant and women in the third stage of labour, the inhalation endpoints appeared to be broadly similar across the two cohorts and any small changes are not considered to markedly impact the delivery of an inhaled product in the third stage of labour [GlaxoSmithKline

Document Number 2015N239682_00]. In addition, in a pre-clinical sheep model the ratio IH:IV was generally similar in non-pregnant and post-partum ewes (Data on file Monash). In the event of enhanced pulmonary absorption in pregnancy, the selected 400 mcg inhaled dose is predicted to have an approximate 2-fold safe cover for Cmax compared with an 10 I.U. IV bolus oxytocin (assumes linearity from 5 -10 I.U. IV).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GR121619 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2015N240749_01] and oxytocin for parenteral administration [Syntocinon, 2014]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) – Inhaled Oxytocin – GR121619		
Bronchospasm, cough and dyspnoea, with increased *theoretical* risk in asthmatic subjects.	Oxytocin receptors are known to be expressed in human bronchial smooth muscle and up regulated by interleukin (IL)-13. Therefore, there is a hypothetical risk of bronchospasm, cough and dyspnoea.	See Section 5.2 for exclusion criteria. The oxytocin summary of product characteristics (SPC) does not list asthma as a contraindication to administration. Symptomatic wheezing may be treated with bronchodilator at the discretion of the investigator. Forced expiratory volume at 1 minute (FEV1) monitoring for both paradoxical and oxytocin induced bronchospasm Subjects with asthma or known pulmonary disease are excluded.
Hypotension, tachycardia and prolongation of QTc interval	Transient flushing, hypotension and tachycardia could be observed if the IH PK profile is comparable to an IM or IV oxytocin profile. Effects of oxytocin on the	Ongoing assessments of study subjects' cardiovascular function including blood pressure (BP), heart rate (HR) and ECG. Only single-dose IH, IM, or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Cardiovascular system (CVS) is unclear and contradictory in the literature but IV administered oxytocin can have a vasodilatory and negative inotropic effect in humans. Hypotension is thought to arise as a result of vascular smooth muscle relaxation and oxytocin binding to cardiac atrial OTR which leads to atrial natriuetic peptide (ANP) being transiently released into the systemic circulation. Prolongation of the QTc interval has been reported at the time of caesarean delivery with 10 IU IV oxytocin administration, rather than IM injection, in susceptible individuals	5 IU IV bolus injection routes of administration will be used as study treatment. Telemetry and frequent 12-lead ECGs will be used to monitor the healthy subject cohorts The 5 IU IV dose of oxytocin is the standard dose administered at the Rosie Maternity hospital post Caesarean Section. IV bolus will be given as a slow IV injection over 30 seconds with the option to change to a 5 minute infusion if frequent CV adverse effects are observed Exclusion of subjects with long QT syndrome, congenital cardiac abnormalities, and subjects taking anti-arrhythmic drugs. 12-lead ECG and telemetry covering Cmax in healthy subjects administered IH, IM and IV oxytocin
Insufficient uterotonic effect	The altered physiology and pharmacokinetics of women in the TSL my lead to a sub-optimal dose of inhaled oxytocin, resulting in a reduced or absent uterotonic effect.	In this setting, women in TSL and post-delivery are intensively observed. Therefore, any adverse events, including excessive blood loss due to unenhanced uterine contraction, will be managed in accordance with current local practice guidelines. This will usually include administration of additional uterotonic agents in the first instance. A follow-up within 24 h of discharge by the study team will be performed to specifically enquire if any late bleeding problems had

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		occurred. An interim analysis of IH and IM PK in the TSL group will be performed to ensure that the PK is in the acceptable range for efficacy to be anticipated.
Reference Intervention - IM Oxytocin / IV Oxytocin		
Hypotension, tachycardia and prolongation of QTc interval	See above section.	See above section. Subjects receiving the IV Oxytocin are required to have a systolic BP ≥ 90 Millimeter of mercury (mmHg) prior to dosing.
Myocardial Ischaemia and ST change on ECG	ECG changes consistent with myocardial ischaemia have been observed with 10 IU oxytocin IV bolus in healthy women associated with hypotension and tachycardia.	Oxytocic cardiovascular effects appear to be transient and persistent myocardial damage very rare and associated with 10 IU IV. Study is only using 5 IU IV as a slow IV bolus which is associated with a short lived increase in heart rate and reduction in BP but not ST changes on ECG in women undergoing Caesarean Section. Telemetry and 12-lead ECG monitoring in healthy subjects.
Abdominal pain	There is a hypothetical risk that IM oxytocin may trigger abdominal pain through contractions of the non-pregnant uterus in healthy women. Given the short half-life of oxytocin (approximately 30 minutes), the duration of a single abdominal pain episode	This is a theoretical possibility and not expected to occur. Ongoing assessments of study subjects' well-being along with vital signs and laboratory evaluations will be completed throughout the duration of the study. Abdominal pain which is clinically uncomfortable to the subject may be treated with paracetamol at the local

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	would be expected to be brief, not sustained and not recurrent in the absence of further oxytocin administration. Furthermore, no abdominal pain was observed in the FTiH study.	investigator's discretion.

4.6.2. Immunogenicity Risk

The oxytocin material used in the inhaled product is produced synthetically and so does not include any other protein/cell impuritites which might be intrinsically immunogenic. A review of the risk of immunogenicity of oxytocin and/or excipients was considered as part of the non-clinical safety studies but as the lymphoid tissues were not deemed to be pathologically affected and there were difficulties in generating a suitable assay, anti-drug antibodies (ADAs) were not measured. The FTIH study involved repeat dosing, and did not reveal any unexpected differences in PK which may have signalled the development of ADAs.

Oxytocin is an endogenous human peptide with a short systemic half-life and there are no reports of immunogenicity with oxytocin via parenteral administration. Thus it is considered unlikely that inhaled delivery of a small molecular weight (MW) peptide molecule like oxytocin would invoke an immunogenic response.

However, blood samples will be retained for anti-oxytocin antibody analysis if required in the event of an anaphylactic / allergic reaction (refer to Section 5.4.2) or other observation which would suggest an immunogenic effect.

4.6.3. Benefit Assessment and Overall Benefit:Risk Conclusion

Oxytocin has been administered to postpartum women for over 40 years via both the IM and IV routes, and has an established safety profile for each of these routes of administration. The FTIH study into IH oxytocin revealed no safety concerns for any of the subjects who received this new formulation. There are no direct clinical benefits to the volunteers within this study. The main contribution to their participation will be in the further development of a therapy (i.e. inhaled oxytocin) which may be ultimately used as a preventative therapy for postpartum haemorrhage in women during TSL in resource poor settings. It is fundamental to the project to clearly understand the PK of oxytocin following IH and IM administration to women in TSL in order to confirm the dose level that delivers a PK profile comparable to that of 10 I.U. IM (i.e. current standard of care in the developed world setting). Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with oxytocin (IH IM, and IV) are justified by the supporting data and overall benefit anticipated for women's health worldwide.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the investigator brochure for GR121619 [GlaxoSmithKline Document Number 2015N240749_01] and SPC for oxytocin administered IM or IV.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
All Groups: 1. Between 18 and 40 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
All Groups: 2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, and laboratory tests as required per protocol. Note: At time of randomisation, investigator or designee should confirm the subject feels fit and well, and is safely able to participate in the study. 3. Subject clinical chemistry and haematology values within an acceptable range for the population recruited and not of abnormal clinical significance. Note: Additional laboratory tests beyond those which are done as part of routine care (e.g. 28-week visit) are not required for subjects in Group 1. The investigator/designee may use his/her judgment in deciding whether to perform additional laboratory assessments to determine eligibility. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 4. Adequate peripheral venous access for cannulation.

Group 1 Only:

5. Currently pregnant, with an uncomplicated pregnancy as determined by the investigator or designee.
6. Estimated date of delivery within 24 weeks of screening.
7. Planned spontaneous vaginal birth and considered by investigator at low risk for PPH.
8. Planned birth in between the 37th and 42nd week of pregnancy.

   Note: Subjects can only receive study treatment if the onset of labour is between approximately 37 and 42 weeks estimated gestation. If a subject goes into labour before or after this timeframe, she should not receive study treatment.
9. Women who qualify for oxytocin as appropriate for active management of TSL and who agree to have active management.

Group 2 Only:

10. ECG normal, or abnormal and not clinically significant.
11. FEV1 >80% of predicted.
12. Systolic blood pressure ≥90 mmHg.

WEIGHT

Group 2 Only:

13. Body mass index (BMI) within the range 18 – 32 Kilogram (kg)/ meter $(m)^2$ (inclusive).

SEX

14. Female.

Group 2, Cohort A Only:

A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test), not lactating, and the following condition applies:

a. Is of reproductive potential and agrees to use the same **combined estrogen and progestogen oral contraceptive** from 3 months prior to the first dose of study medication and until the follow-up contact.

This method of contraception is only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method of contraception.

Group 2, Cohort B Only:

A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine hCG test), not lactating, and one of the following conditions applies:

a. Is of reproductive potential and has been using the same **non-hormonal contraceptive method** (see List of Acceptable Nonhormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential [see Appendix 5] from 3 months prior to the first dose of study medication and until the follow-up contact.

b. Would be of reproductive potential, but has undergone bilateral tubal ligation or occlusion or bilateral salpingectomy at least 12 months prior to first dose of study medication.

c. Is of reproductive potential with only same sex partners or who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

These methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method(s) of contraception.

Of Note: Group 2, Cohort B will enrol women of reproductive potential if they agree to use a nonhormonal contraceptive method from at least one month prior to receiving study drug and until the follow-up assessment. Although condoms with spermicide are not considered a highly effective method of contraception, the risk of receiving study drug during pregnancy is minimal for the following reasons:

- Pregnancy testing must be negative at screening and on the first day of dosing.
- Dosing is completed no greater than 14 days from the start of dosing.
- Oxytocin has a well established rapid half-life.

If a patient happened to conceive during the time of dosing, study drug would be eliminated before implantation would occur.

INFORMED CONSENT

All Groups:

15. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

All Groups:

1. Postmenopausal as defined by gynaecological history.
2. Chronic lung condition of any etiology including asthma, Chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease or active Tuberculosis (TB).
   Note: Childhood asthma (resolved) is not exclusionary.
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. Blood pressure >140 systolic or >90 diastolic.

Group 1 Only:

5. Females with planned Caesarean Section.
6. Females with significant medical complications as determined by investigator.

Group 2 Only:

7. Currently breastfeeding or lactating.
8. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 milliseconds (msec).
9. Alanine aminotransferase (ALT) and bilirubin >1.5 Upper Limit of Normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Subjects with highly-active or symptomatic gynaecological disorders (such as large symptomatic fibroids).

CONCOMITANT MEDICATIONS

All Groups:

11. Prescription or non-prescription drugs not approved by the investigator (refer to Section 6.12.1 for approved medications).
12. Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) prior to administration of study-related oxytocin.

RELEVANT HABITS
All Groups: 13. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >14 units. One unit is equivalent to 8 grams (g) of alcohol: a half-pint (~240 milliliter [ml]) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 14. Current smokers or subjects with a history of smoking within 6 months of screening, or with a total pack year history of >5 pack years. a. Confirmatory use via a Smokerlyzer is at the discretion of the local investigator, but is advised if the subject's recent smoking history is in doubt.

CONTRAINDICATIONS
All Groups: 15. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation (e.g. allergy to any previous inhaler use). 16. Participation in another clinical trial, which in the opinion of the investigator, jeopardizes the subject's safety or study outcomes.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
All Groups: 17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 18. The subject has participated in a clinical trial and has received an investigation product within the following time period prior to the first dosing day in the current study: 30 days or twice the duration of the biological effect of the investigational product (whichever is longer). 19. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. **Group 2 Only:** 20. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result. 21. A positive Human Immunodeficiency Virus (HIV) antibody test. 22. A positive pre-study drugs of abuse test (not explained by diet or approved concomitant medications). 23. A positive alcohol breath test.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.4).

5.3.1. Re-screening

If a subject fails screening, she may be rescreened one additional time.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Pregnancy Complication Stopping Criteria (Group 1 Only)

Any complication requiring clinical intervention which no longer allows for a vaginal delivery or safe completion of study procedures will be cause for immediate withdrawal from the study. Investigators should continue to manage any pregnancy complication per local guidelines, and record any associated AE/SAE or concomitant medication. This includes the need for additional uterotonic administration.

5.4.2. Anaphylaxis Stopping Criteria

Clinical signs or symptoms of anaphylaxis / allergic reaction to IH oxytocin will be an automatic stopping criterion. Stored serum samples will be analysed for anti-oxytocin antibody analysis for affected subjects as detailed in Section 7.5.2. The samples will be analysed for Immunoglobulin E (IgE)/ Immunoglobulin G (IgG) anti-oxytocin titres ± biochemical markers of mast cell degranulation (e.g. tryptase) in the event of an anaphylactic / allergic reaction occurring.

5.4.3. QTc Stopping Criteria (Group 2 Only)

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

QTcF is proposed to be used for this study. If a subject meets either of the following bulleted criterion below, she will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline: Increase in QTcF >60 msec.

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be withdrawn from the study.

5.4.4. Blood Pressure Stopping Criteria (Group 2 Only)

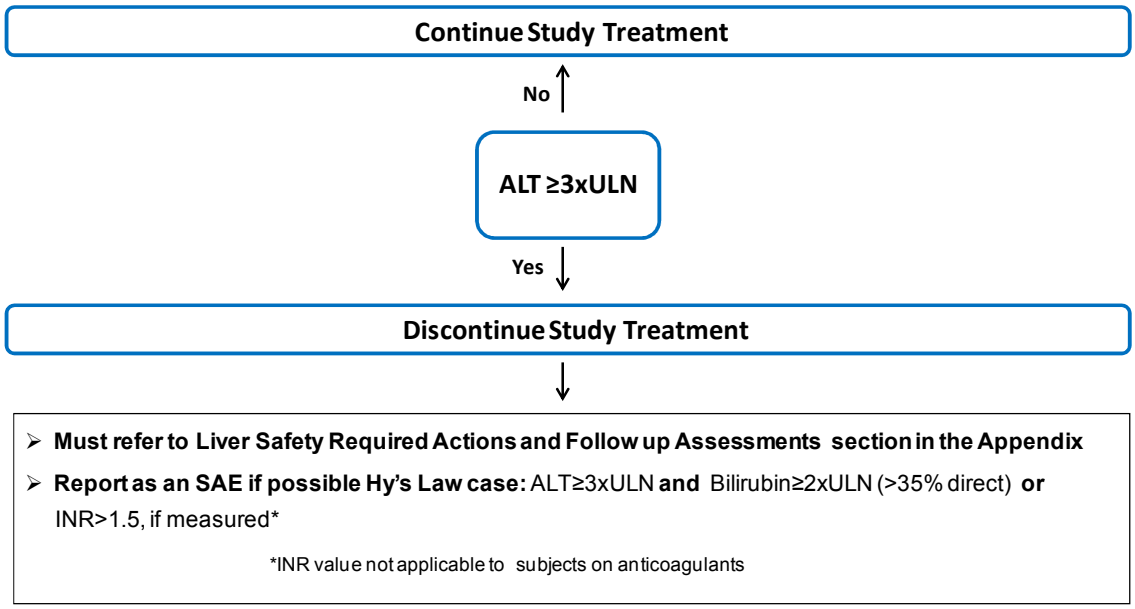
Subjects with a pre-dose systolic blood pressure of <90 mm Hg should not be dosed until systolic blood pressure is ≥90 mm Hg.

5.4.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.6. Plasma oxytocin concentration stopping criteria

Per Section 9.3.2.2, the plasma oxytocin concentrations in up to 5 subjects in Group 1 will be analysed in real time. If the plasma oxytocin concentration is BLQ or sufficiently low to prohibit interpretation in these 5 subjects irrespective of treatment, the study will be halted and reviewed.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit(s).

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Table 1 Study Treatment Information

	Study Treatment		
Product name:	Oxytocin (GR121619 capsule for inhalation)	Oxytocin	Oxytocin
Formulation description:	Powder Blend for Inhalation	Solution for Infusion	Solution for Infusion
Dosage form:	Inhalation powder, hard capsule	1ml ampoule	1ml ampoule
Unit dose strengths:	400 mcg 200 mcg	5 I.U./mL, or 10 I.U./mL	5 I.U./mL, or 10 I.U./mL
Route of Administration	For oral inhalation	Intramuscular (thigh)	Intravenous
Dosing instructions:	Capsule unit dose dispensed by ROTAHALER inhaler	Standard intramuscular injection	Adminster as a 30-second bolus
Physical description:	Colourless and clear HPMC capsules containing a white powder	Colourless and clear sterile solution	Colourless and clear sterile solution
Device:	ROTAHALER inhaler	Needle/Syringe	Intravenous Infusion Device

6.2. Medical Devices

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

6.3. Treatment Assignment

Subjects in Group 1 will be assigned to one of two treatments (IH oxytocin or IM oxytocin). Subjects in Group 2 will receive both IH and IV oxytocin in separate dosing sessions in a cross over design. Treatment assignment in Group 1, and order of dosing in Group 2, will be done in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in Table 2:

Table 2 Treatment Assignment

Group	Session	Treatment [1]	Number of Subjects[2]
Group 1	1	400 mcg IH oxytocin	10
		10 I.U. IM Oxytocin	10
Group 2, Cohort A	1	400 mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	
Group 2, Cohort B	1	400mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	

[1] See Section 6.4 for possible dose adjustment.

[2] See Section 9.2.2 for possible adjustment to subject numbers to Group 1

If deemed necessary or if there is a new site identified for conducting and/or continuing the clinical trial, then a new randomization schedule may be generated by Clinical Statistics, prior to the start of the study at the new site, using validated internal software.

6.4. Planned Dose Adjustments

There is no plan to adjust the dose of IH oxytocin in this study. However, if systemic exposure seen in 400 mcg IH oxytocin in TSL subjects is less than expected and not comparable to the 10 I.U. IM profile, a consideration to escalate the dose to 600 mcg may be made as detailed in Section 6.4.1.

For Group 2, if an exaggerated physiological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

6.4.1. Dose Adjustment

The decision to adjust the IH dose in women in TSL will be determined by the GSK study team based on Group 1 PK data in TSL and Group 2, Cohort A PK data. After a minimum of n=5 women in TSL have received 400 mcg IH and 10 I.U. IM and a minimum of n=5 non-pregnant women on the combined oral contraceptive (Group 2, Cohort A) have received 400 mcg IH oxytocin, PK samples will be analysed and PK parameters derived (including but not limited to Cp10, Cp30 and AUC(0-3h)).

The median Cp10 will be estimated for women in TSL for each dose group (IH or IM) and the median ratio (IH/IM; n=5) derived. Based on the estimated ratio, the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased per the criteria described in Table 3:

Table 3 Dose Adjustment Decision Criteria

Median Ratio IH/IM	Decision
< 0.5	Consider study halt and review data.
≥ 0.5 to <0.7	Consider dose adjust to 600 mcg IH in women in TSL.
≥ 0.7	Continue with 400 mcg IH dose.

If a decision to increase the dose is made, additional subjects will be enrolled into Group 1 such that 10 subjects receive the 600 mcg IH oxytocin dose.

6.5. Blinding

This will be an open-label study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

- The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner. The investigator/designee will always load and prime the ROTACAPS powder capsule in the device before the subject self-administers an IH oxytocin dose
- All subjects will be taught by the investigator/designee to use the device in the "full-tilt" position and to use a "fast and deep" inspiration technique per inhalation, to achieve two rapidly consecutive maximal inhalations for IH oxytocin administration. This will ensure optimal and consistent treatment delivery. For subjects, the training session will be at any time during the 28-day Screening Period, as deemed appropriate by the investigator/designee.
- ROTACAPS powder capsules should be kept in their sealed packaging at room temperature (15-25°Centigrade [C]). The packaging should only be opened immediately prior to use.
- ROTAHALER inhaler devices will be supplied in bulk and unlabelled to the site. After dosing all ROTAHALER inhaler devices will be uniquely labelled and retained after each dosing session. The devices (which should not be opened up at

the clinical study site) will be stored until further instruction from the sponsor is received.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.8. Compliance with Study Treatment Administration

Per ROTACAPS powder capsule dose, each subject will be asked to inhale twice from the ROTAHALER inhaler to reduce the possibility of inadequate administration due to a single poor inhalation manoeuvre. If failure of the ROTACAPS powder capsule actuation is suspected by the investigator (i.e. due to failure to open the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose using the same capsule.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Group 1 – Women in TSL

Following randomisation and any pre-dose procedures, subjects will receive a single study treatment as active management of TSL. The specific timing of this dose will be as per local standard of care.[2]

Administration will be documented in the source documents and reported in the Case report form (CRF).

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Following randomisation and all pre-dose procedures, subjects will receive two doses of oxytocin, separated by at least 48 hours. Randomisation will determine the order in which the IH and IV formulation is administered.

Administration will be documented in the source documents and reported in the Case report form (CRF).

6.9. Treatment of Study Treatment Overdose

For this study, any dose of the following compounds will be considered an overdose when administered as part of study procedures:

- IH oxytocin > 400 mcg
    - If study dose is increased to 600 mcg, then an overdose will be considered any dose > 600 mcg.
- Oxytocin > 10 I.U. IM
- Oxytocin > 5 I.U. IV

Note: Group 1 subjects may receive additional doses of oxytocin (IM or IV) when required as part of their general care and as clinically indicated. Additional doses of oxytocin will be recorded as concomitant medications, as will any related AEs.

General medical management consists of supportive care.

GSK does not recommend specific treatment for an overdose.

In the event of a study drug overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

[2] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until oxytocin can no longer be detected systemically (at least 4 hours).
3. Obtain an additional plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because either only healthy volunteers are eligible for study participation, or there are other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of postpartum subjects' medical conditions, whether or not GSK is providing specific post-study treatment.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Meals and Dietary Restrictions

There are no dietary restrictions for subjects in either cohort.

6.11.2. Caffeine and Alcohol

Group 1 – Women in TSL

- There are no restrictions for Group 1.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

6.11.3. Activity

Group 1 – Women in TSL

There are no activity restrictions.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses equal to or below the maximum recommended daily dose, is permitted for use during the screening period or at any time deemed necessary by the investigator or subject. All concomitant medication related to routine care during pregnancy and delivery is allowed (including pain relief [e.g. gas/air mixture] and epidural), and other medication may be considered on a case by case basis by the investigator or designee (in consultation with the Medical Monitor if required).

The start and stop time of any concomitant medications administered at any time during labour (including nitrous oxide gas/air mixtures) should be documented on the CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications will result in immediate withdrawal of subject:

- Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) before or after administration of study-related oxytocin.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table in Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
    1. 12-lead ECG
    2. vital signs

3. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic, immunogenic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

7.1.1. Time and Events Table – General Overview

Group 1

Procedure	Study Day			
	Screening[4]	**Main Phase**	**Follow – Up 1 (approx. 24 hours post dose)**	**Follow – Up 2 (7-14 days post dose)**
Informed Consent and Demography	X			
Brief Physical Examination	X			
Medical history (incl. substance abuse)	X			
Inhaler device training / education session	X			
Laboratory assessments[1]	X			
Vital signs[2]	X	X		
Pharmacokinetic blood sample		X		
Oxytocin Administration (IM/IH)		X		
Full blood count		X		
Labour Events Documentation		X		
Device acceptability questionnaire[3]		X		
Prior / concomitant medication review	X	X	X	X
AE review		---------- continuous review ----------		
SAE review	---------- continuous review ----------			

1. Only required if done as part of routine care. Additional study-specific laboratory assessments not required.
2. Includes blood pressure, heart rate, temperature, respiratory rate
3. Only to be used when randomized to IH oxytocin
4. To be completed after 18th week of pregnancy (based on estimated date of delivery).

Group 2

Procedure	Study Day		
	Screening[5]	**Main Phase**	**Follow - Up (7-21 days post dose)**
Informed Consent and Demography	X		
Brief Physical Examination	X	X	
Medical history	X		
Pregnancy test	X	X	
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X	X	
HIV, Hep B and Hep C screen[2]	X		
Inhaler device training / education session	X		
Laboratory assessments (including liver chemistries)	X	X	
Immunogenicity sample		X	X
12-lead ECG	X[4]	X	
CardiacTelemetry		X	
Vital signs[3]	X	X	
Spirometry (FEV-1)[4]	X	X	
Admission to unit		X	
Pharmacokinetic blood sample	X	X	
Oxytocin Administration (IH or IV)		X	
Prior / concomitant medication review	X	X	X
AE review		------ continuous review ----------	
SAE review	---------- continuous review ----------		
Discharge from unit		X	

1. Smokerlyzer at PI/designee discretion if smoking history in question.
2. If test otherwise performed within 3 months prior to first dose of study treatment, repeat testing at screening is not required.
3. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2.
4. Performed in triplicate.
5. To be completed within 28 days of randomization.

7.1.2. Time and Events – Main Phase Procedures

Group 1

		Time post dose										
Procedure	Pre-dose	3 min	5 min	10 min	15 min	20 min	30 min	1 hr	2 hr	2.5 hr	3 hr	4 hr
Vital signs[1]							X		X			
Pharmacokinetic blood sample	X[2]	X	X	X	X	X	X	X	X	X	X	X
Prior medication review	X											
Concomitant medication review		---------- continuous review ----------										
AE review		---------- continuous review ----------										
SAE Review	---------- continuous review ----------											
Device Acceptability Questionnaire[3]												X
Full Blood Count	X											X

1. Includes blood pressure, heart rate, temperature, respiratory rate
2. Predose PK sample to be taken immediately prior to administration of study treatment
3. Only to be administered when randomized to IH oxytocin

Group 2 – Sessions 1 and 2

		Time Post Dose														
Procedure	Pre-dose	2 min	3 min	5 min	8 min	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr
Brief Physical Exam	X															
Pregnancy Test	X															
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X															
Vital signs[2]	X			X			X		X		X					X
12-lead ECG	X	X				X		X	X		X					X
CardiacTelemetry	----------Continuous----------															
Spirometry[3]	X										X					
Pharmacokinetic blood sample	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sample	X															
Laboratory assessments (including liver chemistries)	X															X
Prior medication review	X															
Concomitant medication review		---------- continuous review ----------														
AE review		---------- continuous review ----------														
SAE Review	---------- continuous review ----------															
Discharge from unit[4]																X

1. Smokerlyzer at Principal Investigator (PI)/designee discretion if smoking history in question.
2. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2
3. FEV 1.0 will be performed in triplicate at each time point. Record all three values on source document, and record best effort in eCRF.
4. Discharge at PI discretion, no sooner than 4-hours post-dose.
5. 3 pre-dose samples: approximately 1 hr pre-dose, 30 minutes pre-dose, and 15 minutes pre-dose

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management [e.g. brief physical exam, laboratory assessments] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (see Section 12.3).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF or appropriate source document.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigators Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Adverse Events of Special Interest (AESI)

Any problem related to the delivery of the placenta or postpartum haemorrhage should be documented as an AESI using the appropriate case report form (CRF).

7.3.3. Pregnancy

Group 2 Only:

- Details of all pregnancies will be collected after the start of dosing and until follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.3.4. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Section 12.4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 12.3.6 and Appendix 3 of the Protocol.

7.3.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

  NOTE: The method of documenting Medical Device Incidents is provided in Appendix 4.

7.3.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.

- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor or SAE coordinator.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.3.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.3.5. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen if palpable).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.6. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate (unless otherwise specified in T&E).

7.3.7. Documentation of Labour Events

The time that the following labour events occurred will be collected:

- Time of crowning
- Time of birth
- Time of delivery of placenta

7.3.8. Electrocardiogram (ECG) (Group 2 Only)

- Triplicate 12-lead ECGs will be obtained at screening as listed in Section 7.1.1.
- Single 12-lead ECGs will be obtained at each timepoint as listed in Section 7.1.2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At all single 12-lead ECG time-points if QTc >450, repeat twice and take average reading.

7.3.9. Continuous Cardiac Telemetry (Group 2 Only)

Continuous cardiac telemetry will be started at least 10 minutes pre-dose (to obtain a stable reading) and continue until at least the first hour after IV and IH placebo / oxytocin administration and then as deemed necessary by the investigator. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

7.3.10. Device Acceptability Questionnaire (Group 1 Only)

A device acceptability questionnaire will be administered to subjects in Group 1 following use of the ROTAHALER (Appendix 7).

7.3.11. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as required by Section 7.1 and defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Tests performed as part of routine care in Group 1.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Subjects in Group 1 are not required to undergo additional laboratory assessments beyond those done as part of their routine care. However, the investigator/designee may conduct any of the tests listed in Table 4 in order to confirm eligibility. Haematology, clinical chemistry, and additional parameters to be tested in all Group 2 subjects are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>White Blood Cell (WBC) count with Differential</u>:</td></tr>
<tr><td>Red Blood Cell (RBC) Count</td><td>Mean Corpuscular Volume (MCV)</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>Mean Corpuscular Hemoglobin (MCH)</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate aminotransferase (AST) (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine aminotransferase (ALT) (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>HIV

Hepatitis B (HBsAg)

Hepatitis C (Hep C antibody)

Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of suspected non-child bearing potential only)

Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)

Serum or urine hCG Pregnancy test (Group 2 only) [2]</td></tr>
<tr><td colspan="2">NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2 and</td></tr>
</table>

Appendix 2 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of oxytocin will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

At each time point, 4 mL of blood will be collected into study-specific tubes formulated to further inhibit peptidase activity. Additional details regarding collection/shipping procedures are provided in the SRM.

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of oxytocin will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM). Once the plasma has been analyzed for oxytocin any remaining plasma may be analysed for metabolites of oxytocin and the results reported separately.

7.5. Biomarkers

7.5.1. Pharmacodynamic Markers

Pre and post-delivery full blood counts will be collected from Group 1 subjects to assess for a change in haemoglobin levels.

7.5.2. Immunogenicity

Blood samples will be taken at the time points specified in the Time and Events Table (Section 7.1) to assess the immunogenicity of oxytocin.

Pre- and post-dose samples will be retained in the event that further immunologic tests are deemed necessary to support observations of unexpected anaphylaxis/ hypersensitivity, and / or a PK profile for IH oxytocin in any Dosing Session which is regarded by the GSK Study Team to be reasonably attributable to circulating anti-oxytocin antibodies.

Details of the collection / shipping procedures are provided in the SRM.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to characterize the pharmacokinetics of 400 mcg IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

No formal hypotheses will be tested, however, the following comparisons are of interest, within Group 1, (IH vs. IM) and between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on oral contraception) and between Cohorts A and B in Group 2 (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive). For each PK endpoint of interest, point estimates and corresponding two-sided 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, $\mu(test)/\mu(reference)$ to provide the range of plausible values for the comparisons of interest.

9.2. Sample Size Considerations

A sufficient number of subjects will be enrolled to ensure approximately 20 evaluable subjects (10 in each of the IM and IH groups) complete all dosing and critical assessments in Group 1, as well as 5 subjects in each cohort in Group 2. Whilst sample size is based on feasibility, precision calculation was also done to approximate the estimate of the expected half width of 90% CI around point estimate for the main comparison of interest (IH oxytocin to 10 I.U. IM oxytocin in women in TSL) using a t-test.

Table 5 illustrates the associated 90% CIs for the mean treatment ratios, assuming between subject SDs of 0.424 and 0.601 (SDs are based on log transformed data) for AUC (0-3h) and CP10 respectively, for the comparisons of interest detailed in Section 9.1. Calculations are based on a symmetric two-tailed procedure on the loge scale and a type I error rate of 10%. These values represent estimates of the between-subject variability observed in the FTIH study 201558 [GlaxoSmithKline Document Number 2016N277949_00].

Table 5 Estimated 90% Confidence Intervals for Treatment Ratios

N	Parameter	Between Subject Standard Deviation (SD)	Estimated Treatment Ratio	Precision	Expected 90% CI
10	AUC(0-3h)	0.424 (CVb=44.35%)	1	38.30%	(0.72, 1.38)
10	Cp10	0.601 (Cvb=65.96%)	1	58.20%	(0.63,1.58)

The precision estimates are deemed acceptable to assess the study objectives at this stage of development.

9.2.1. Sample Size Sensitivity

Considering the variability of AUC(0-3h) and Cp10, Table 6 shows the scenarios for different sample size and the precision estimates for IH vs. IM in Group 1.

Table 6 Estimated 90% Confidence Intervals for Treatment Ratios for Sample Size Sensitivity

%CVb	N	Precision	Assuming ratio 1, the confidence interval
44.35%	5	61.90%	(0.61, 1.61)
	15	29.80%	(0.77,1.29)
65.96%	5	98.00%	(0.50, 1.98)
	15	44.80%	(0.69, 1.44)
	20	37.40%	(0.72,1.37)
85.35%*	5	131.90%	(0.43, 2.31)
	10	75.90%	(0.56, 1.75)
	15	57.60%	(0.63, 1.57)
	20	48.00%	(0.67, 1.48)

* 85.35% was the largest between subject CV for AUC(0-10) observed for FTIH study 201558 [GlaxoSmithKline Document Number:2016N277949_00]

9.2.2. Sample Size Re-estimation or Adjustment

No formal sample size re-estimation is planned for this study. However, if the variability is high (for example approaching 85%) then the sample size for Group 1 may be increased to a maximum of 10 additional subjects per treatment arm (IH and IM only).

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exist on the study database. This population will be used for summarizing screening failure reasons.
All Subjects Population	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays.
Pharmacokinetic Population	• Subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.

9.3.2. Interim Analyses

No formal interim analyses are planned. PK data will be reviewed per Section 9.3.2.1 and Section 9.3.2.2

9.3.2.1. Informal Interim Reviews

PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

This will be repeated after restart from the temporary halt for Group 1.

9.3.2.2. In-Stream Analysis of Group 1

Following restart from temporary halt, PK specimens from each of up to 5 subjects in Group 1 will be analysed as soon as possible after collection. This will allow for confirmation that the revised specimen collection procedures allow for detection of adequate oxytocin PK profile.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

9.4.1.1. Safety Analysis

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.1.2. Pharmacokinetic Analysis

Pharmacokinetics analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline. Plasma oxytocin concentration-time data will be analyzed by non-compartmental methods with WinNonlin V6.3 or greater. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-3h) and AUC(0-∞)], the last observed quantifiable concentration (Clast), time of the last quantifiable concentration (tlast), Cp10, Cp20, Cp30 (observed plasma concentrations at 10, 20 and 30minutes post-dose, respectively), plasma clearance (CL; IV only), volume of distribution (V; IV only) and apparent terminal phase half-life (t1/2). Other PK parameters may also be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

If appropriate, a population PK analysis may also be conducted, in addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis.

9.4.2. Secondary Analyses

Statistical analyses of the PK parameter data will be performed by, or under direct auspices of Clinical Statistics, QSci.

9.4.2.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons within Group 1 IH vs. IM, point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3. Exploratory Analyses

9.4.3.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on the combined oral contraceptive), and within Group 2 between Cohorts A and B (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive), point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3.2. Device Acceptability Questionnaire

In Group 1, subject satisfaction with device, including instructions and ease of use, will be assessed. The questionnaire is located in Section 12.7

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRFs <or> entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the

discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Frontiers in Pharmacology*. 2014. Volume 5. Article 65: 1-5.

GlaxoSmithKline Document Number 2015N234711_01. Study ID 201558. Clinical Pharmacology Study Protocol. A single centre, single blind study to investigate the safety, tolerability and pharmacokinetics of single doses of oxytocin (GR121619) administered via an inhaled route in healthy female volunteers. 16-NOV-2015.

GlaxoSmithKline Document Number 2015N239682_00. Study ID 201248 – Clinical Pharmacology Study Report. An enabling study to compare the inhalation profiles of women in the third stage of labour to those of non-pregnant female volunteers and to explore whether there are any differences which could impact the delivery of an inhaled medicinal product, 16-OCT-2016.

GlaxoSmithKline Document Number 2015N240749_01. GR121619 Investigator's Brochure, AUG-2015.

GlaxoSmithKline Document Number 2016N277949_00. Study ID 201558 – Clinical Study Report.. 30-JUN-2016.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.

Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2014, *Issue* 2. *Art. No.: CD003249. DOI:* 10.1002/14651858.CD003249.pub3.

Prankerd RJ, Nguyen T, Ibrahim JP, et al. Pulmonary Delivery of an Ultra-Fine Oxytocin Dry Powder Formulation: Potential for Treatment of Postpartum Haemorrhage in Developing Countries. 2013; *PLoS One*. Vol 8: 12: Article e82965

Syntocinon Summary of Product Characteristics, Novartis, 2014

Thornton S, Davison JM, Baylis PH. Effect of human pregnancy on metabolic clearance rate of oxytocin. *American Physiological Society*. 1990. 0363-6119: R21-R24.

Thornton S, Davison JM, Baylis PH. Plasma oxytocin during third stage of labour: comparison of natural and active management.*BMJ.* 1988. Volume 297:167-169.

WHO Model List of Essential Medicines 18th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO Model List of Essential Medicines for Children 4th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO, UNICEF, UNFPA. The World Bank World Health Organization (WHO) Press. Trends in Maternal Mortality: 1990 to 2008: Estimates Developed by WHO, UNICEF, UNFPA and The World Bank. Geneva*: WHO,* 2010.

12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

Abbreviations

ADAs	Anti drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANP	Atrial natriuretic peptide
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-3)	Area under the concentration-time curve from time zero (pre-dose) to three hours
AUC(0-∞)	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
Ca2+	Intracellular calcium
CI	Confidence Interval
CL	Plasma clearance
Clast	last observed quantifiable concentration
Cmax	Maximum observed plasma concentration
COC	Combined oral contraceptive
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
Cp10	Observed plasma concentrations at 10 minutes post-dose
Cp20	Observed plasma concentrations at 20 minutes post-dose
Cp30	Observed plasma concentrations at 30 minutes post-dose
CPK	Creatinine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry powder inhaler
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1.0	Forced expiratory volume at 1 minute
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram
GCP	Good Clinical Practice

GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care professional
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
I.U.	International units
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IH	Inhaled
IL	Interleukin
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
Kg	kilogram
LDH	Lactate dehydrogenase
m	Meter
mcg	Micrograms
MCH	Mean Corpuscular Hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
mmHg	Millimeter of mercury
MSDS	Material Safety Data Sheet
Msec	Milliseconds
MW	Molecular weight
OTR	Oxytocin receptor
PGF	Prostaglandin F
PI	Principal Investigator
PK	Pharmacokinetics
PPH	Post-partum haemorrhage
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis plan
RBC	Red blood cells
SAE	Serious Adverse Event

SD	Standard deviation
SMC	Smooth muscle cells
SPC	Summary of product characteristics
SpO2	Peripheral capillary oxygen saturation
SRM	Study reference manual
T&E	Time and event
t1/2	Terminal phase half-life
TB	Tuberculosis
tmax	Time to Cmax
TSL	Third stage of labour
UK	United Kingdom
ULN	Upper Limit of Normal
V	Vassopresin
VOD	Volume of distribution
WBC	White blood cells
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ROTACAPS
ROTAHALER

Trademarks not owned by the GlaxoSmithKline group of companies
Syntocinon
Uniject
WinNonlin

12.2. Appendix 2 Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 4h of the last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or</td></tr>
</table>

recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; International normalized ratio (INR) measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism

- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4 Definition of and Procedures for Documenting Medical Device Incidents

12.4.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.4.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.5. Appendix 5 List of Acceptable Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Group 2, Cohort B Only: List of Acceptable Non-hormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Nonhormonal Intrauterine device or
2. Male condom combined with vaginal spermicide
3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

Group 2 Only

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication or be withdrawn from the study.

12.5.3. References

Bolton TJ, Randall K, Yentis SM. Effect of the Confidential Enquiries into Maternal Deaths on the use of Syntocinon at Caesarean section in the UK. Anaesthesia 2003(58-3):277-9.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.6. Appendix 6 Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7 Device Acceptability Questionnaire

Device Acceptability Questionnaire

Please answer the following questions regarding your use of the ROTAHALER inhaler for oxytocin.

1. Did you feel confident you had received the medicine?

   Yes No Neutral Decline to answer

2. Did you find the inhaler easy to use?

   Yes No Neutral Decline to answer

3. Did you prefer to have your medicine from an inhaler instead of an injection?

   Yes No Neutral Decline to answer

4. Do you feel using this inhaler is an acceptable way to administer the medicine?

   Yes No Neutral Decline to answer

Thank you for answering these questions.

12.8. Appendix 8 Protocol Changes

12.8.1. Protocol Amendment 01

As part of the Medical Device Notification assessment process, the Medicines and Healthcare products Regulatory Agency (MHRA) requested that the protocol prominently reflect that although the investigational device (the ROTAHALER) bears a CE mark, it has not been CE marked in accordance with the Medical Device Directive 93/42/EEC as updated. This change applies to all sites.

Section 6.2 Medical Devices

Change From:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device).

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

Change to:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

12.8.2. Protocol Amendment 02

This amendment has been implemented to update the PK sample collection procedures in order to enhance ex-vivo PK stability, and to implement in-stream PK data analysis following the informal interim analysis of the first 10 subjects to complete Group 1. Location of name and contact information for Secondary Medical Monitor has also been updated.

Medical Monitor/Sponsor Information Page

Medical Monitor/SAE Contact Information

Change from:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK

Change to

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	Name and contact details available in Study Reference Manual				

Section 1 Type and number of subjects

Change of typographical error from 45 to 50 subjects.

Change from:

In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

Change to:

In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

Section 2.2.2 PK Specimen Stability as Observed in 205920

Addition of this section to describe results from first informal interim analysis:

Prior to the initiation of the current trial, a sample-handling process was developed using blood from pregnant subjects of at least 37 weeks gestation to ensure ex-vivo oxytocin stability in specimens collected from Group 1 TSL subjects.

Per protocol, after 10 subjects had completed all procedures in Group 1, an informal interim PK analysis was conducted. It was observed that in the majority of the plasma samples collected from TSL subjects, oxytocin concentrations were below the limit of quantification (BLQ) or at very low concentrations (approximately 3pg/mL) approaching the lower limit of quantification (LLQ) of the assay (2pg/mL). This was seen across both IM and IH routes of administration. This was an unexpected finding which has been confirmed by re-analysis of selected samples. As such, it is considered that it may be due to ex-vivo oxytocin instability related to uninhibited oxytocinase and peptidases, which are believed to be at increased concentrations in the plasma of postpartum women compared with non-pregnant women, and women at 37 weeks gestation. This finding resulted in a temporary halt to the trial.

Section 3.1 Group 1: Women in TSL

Typographical error correction.

Change from:

To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocinin women in TSL.

Change to:

To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

Section 4.3 Type and Number of Subjects

Change of typographical error from 45 to 50 subjects.

Change from:

In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

Change to:

In the event of this, sufficient subjects will be screened such that a maximum of 50 subjects complete Group 1.

Section 5.4.6 Plasma oxytocin concentration stopping criteria

Addition of this section and following text:

Per Section 9.3.2.1, the plasma oxytocin concentrations in up to 5 subjects in Group 1 will be analysed in real time. If the plasma oxytocin concentration is BLQ or sufficiently low to prohibit interpretation in these 5 subjects irrespective of treatment, the study will be halted and reviewed.

Section 6.3 Treatment Assignment

Addition of following text:

If deemed necessary or if there is a new site identified for conducting and/or continuing the clinical trial, then a new randomization schedule may be generated by Clinical Statistics, prior to the start of the study at the new site, using validated internal software.

Section 6.4 Planned Dose Adjustments

Typographical error correction

Change from:

For Group 2, if an exaggerated physicological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

Change to:

For Group 2, if an exaggerated physiological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

Section 7.4.1 Blood Sample Collection

Change from:

At each time point, 4 mL of blood will be collected into K2 or K3 Ethylenediaminetetraacetic acid (EDTA) tubes and stored on ice for up to 2 hours prior to centrifugation in a refrigerated centrifuge. Further details regarding collection/shipping procedures are provided in the SRM.

Change to:

At each time point, 4 mL of blood will be collected into study-specific tubes formulated to further inhibit peptidase activity. Additional details regarding collection/shipping procedures are provided in the SRM.

Section 7.4.2 Sample Analysis

Addition of the following text:

Once the plasma has been analyzed for oxytocin any remaining plasma may be analysed for metabolites of oxytocin and the results reported separately.

Section 9.3.2 Interim Analyses

Change from:

No formal interim analysis is planned. However, PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the

following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

Change to:

No formal interim analyses are planned. PK data will be reviewed per Sections 9.3.2.1 and 9.3.2.2.

9.3.2.1 Informal Interim Reviews

PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

This will be repeated after restart from the temporary halt for Group 1.

9.3.2.2 In-Stream Analysis of Group 1

Following restart from temporary halt, PK specimens from each of up to 5 subjects in Group 1 will be analysed as soon as possible after collection. This will allow for confirmation that the revised specimen collection procedures allow for detection of adequate oxytocin PK profile.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomized, open-label study to characterize the pharmacokinetics of inhaled oxytocin (GR121619) compared with IM oxytocin in women in the third stage of labour, and with IV oxytocin in non-pregnant, non-lactating women of childbearing potential.

Compound Number: GR121619

Development Phase: I

Effective Date: 10-OCT-2016

Protocol Amendment Number: 01

Author (s): PPD **(Respiratory TAU);** PPD **(GCSP);** PPD PPD **(MNHU),** PPD **(Clinical Statistics);** PPD **(GCSP);** PPD **(QSci CPMS);** PPD **(CPSSO)**

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2016N281575_00	2016-AUG-22	Original
2016N281575_01	2016-OCT-10	Amendment No. 1
Section 6.2: Inclusion of information on CE marking.		

SPONSOR SIGNATORY

PPD

10th October 2016

Pauline Williams Date

Head of Global Health R&D

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK
Secondary Medical Monitor					GSK Gunnels Wood Road Stevenage SG1 2NY UK
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline (GSK) Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **EudraCT 2016-002672-27**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205920

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 205920

Rationale

Post-partum hemorrhage is one of the main causes of maternal mortality in the developing world. The World Health Organization (WHO) lists oxytocin on its list of 'Essential Medicines' for Humanity as a preventative treatment for post-partum hemorrhage; however, because of its cold-chain storage requirement and parenteral administration route, high-quality oxytocin is not always available in resource-poor settings. GlaxoSmithKline (GSK) has developed a stable, dry-powder formulation of oxytocin to address this unmet need, with the goal of reducing post-partum hemorrhage morbidity and mortality in these settings.

This study is being conducted to further assess safety and tolerability of inhaled oxytocin, and to characterize the pharmacokinetic (PK) profile of inhaled oxytocin compared to oxytocin administered as standard of care. Two groups of subjects will be enrolled. Group 1 will enroll pregnant women, who will be randomized to receive either inhaled (IH) or intramuscular (IM) oxytocin as active management of the third stage of labour. Group 2 will enroll non-pregnant women of childbearing potential, who will receive IH oxytocin and intravenous (IV) oxytocin in a cross over design over two dosing sessions.

Objectives/Endpoints

Group 1 – Women in Third Stage of Labour (TSL)

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 International Units (I.U.) IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events (AE); absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h])

Objectives	Endpoints
	will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

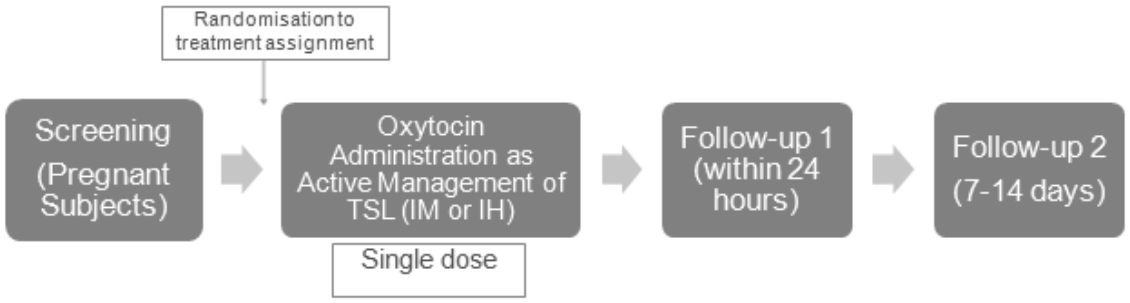
Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

Groups 1 and 2 – Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

Overall Design

Group 1 – Women in TSL



Group 2 – Non-pregnant, non-lactating females of child bearing potential

Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery). Group 2: All screening assessments to be completed within 28 days prior to the first dose.
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions.

Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 micrograms (mcg) IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 h post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2).

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor. Replacement subjects will complete all study procedures.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per

treatment group for inhaled and intramuscular oxytocin. In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose.

Analysis

The primary objective of this study is to characterize pharmacokinetics of IH oxytocin and IM oxytocin in women in the third stage of labour.

No formal hypotheses will be tested, however, comparisons of interest, within Group 1, and between Group 1 and Group 2 and between Cohorts A and B in Group 2 will be made and the point estimates and corresponding two-sided 90% confidence intervals (CI) will be presented to provide the range of plausible values for the comparisons.

2. INTRODUCTION

Maternal mortality associated with postpartum hemorrhage (PPH) is one of the major public health problems in the developing world. Approximately half a million women worldwide die annually from causes directly related to pregnancy and childbirth, and up to one third of these deaths in Africa and Asia are caused by complications as a result of PPH [Khan, 2006;WHO, 2010]. A Cochrane Review meta-analysis of the data from multiple preventative trials with oxytocin at 10 international units (I.U.) given via the intramuscular (IM) route has confirmed this specific uterotonic, and this particular route of administration, to be the gold standard prophylactic therapy for PPH [Mousa, 2014]. For this reason, the World Health Organization (WHO) has designated oxytocin as one of its 'Essential Medicines' for humanity [WHO Model List of Essential Medicines 18th list, April 2013; WHO Model List of Essential Medicines for Children 4th list, April 2013].

However, in resource-poor settings within the developing world, the effectiveness of prophylactic IM oxytocin is diminished by a lack of appropriate refrigeration facilities and availability of trained health care professionals (HCPs) to administer IM injections [Mousa, 2014]. Although single-use, oxytocin prefilled, syringes for IM injection are available in many developing countries (e.g. UNIJECT device), the development of a needle-free and self-administered inhaled (IH) oxytocin product, which delivers comparable systemic exposure to 10 I.U. IM, would be a major step-change in the administration of this life-saving medicine to pregnant women in resource-poor regions of the developing world. This would be particularly relevant in rural areas where the mother has no routine access to a trained HCP and/or where there is no reliable electricity supply to permit refrigerated storage of oxytocin injection vials.

We have developed a stable, dry-powder formulation of oxytocin to be administered via the oral inhaled pulmonary route (compared to 10 I.U. of IM oxytocin) using a GlaxoSmithKline (GSK)-manufactured medical device (or device manufactured for GSK by a third party) which is a capsule-based inhaler (Modified Air Inlet ROTAHALER^{TM} Dry Powder Inhaler (DPI) device, hereafter referred to as ROTAHALER). This formulation and delivery method has the potential to be used in settings where effective oxytocin is currently unavailable to women in the third stage of labour (TSL).

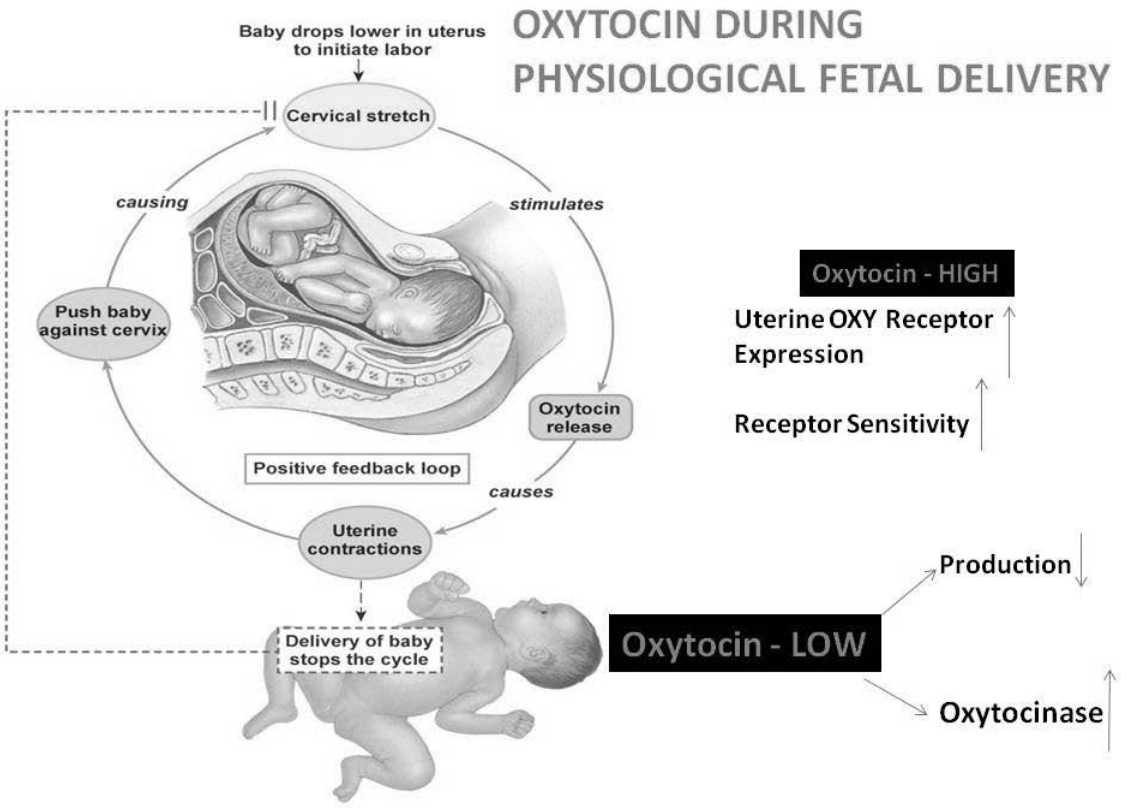
2.1. Study Rationale

This study will be the second investigation of oxytocin in humans via the IH route, which follows the first time in human (FTIH) study, 201558 [GlaxoSmithKline Document Number 2015N234711_01, 2015; see Section 2.2.1 for more information on the FTIH trial)]. Published literature on the pharmacokinetics (PK) of oxytocin in non-pregnant and pregnant women is limited. There is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy; potentially related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy related changes in hepatic and renal function [Syntocinon Summary of Product Characteristics, Novartis, 2014; Thornton, 1990]. In addition, endogenous oxytocin plasma concentrations have been reported to either increase or remain constant after the delivery of the fetal anterior shoulder [Thornton, 1988]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in the TSL for a given dose and route of administration of oxytocin. To further understand the effect of pregnancy on the PK of oxytocin, this study will investigate the PK of oxytocin in pregnant women in TSL following either IH (400 micrograms [mcg]) or 10 I.U. IM (17 mcg) administration. A greater understanding of the PK of oxytocin in TSL will help facilitate extrapolation of data obtained in healthy non-pregnant women to women in TSL. An additional group of non-pregnant non-lactating female volunteers will also be included as a control group and will receive 400 mcg IH oxytocin and 5 I.U. intravenous (IV) oxytocin. This second group will enrol one cohort of subjects taking the combined oral contraceptive (COC), and another cohort using a non-hormonal form of contraception. This will assess if women need to be on an oral contraceptive vs. other methods of birth control in future clinical studies, since although the COC is believed to suppress endogenous oxytocin levels the literature is not consistent about this observation. As the requirement to be taking the COC makes recruitment more of a challenge it will be helpful to know if this inclusion is essential, or if women using non-hormonal forms of birth control might also have sufficiently low systemic oxytocin levels suitable for PK studies.

2.2. Brief Background

Oxytocin is a nonapeptide which is produced by the hypothalamus and released into the systemic circulation by the posterior pituitary gland. Within the brain, oxytocin, like most hypothalamic synthesized hormones, acts as a neurotransmitter. In human pregnancy, during the later phases of the third trimester, increasing circulating levels of oxytocin act as a potent endogenous uterotonic which facilitates the initiation of labour. Furthermore, a neurohormonal positive feedback loop exists between dilatation of the cervico-vaginal canal by fetal passage and the hypothalamus (i.e. Fergusson reflex) which augments oxytocin production, thus increasing uterine contraction intensity and frequency which facilitates vaginal delivery. However, once the fetus is delivered, plasma oxytocin levels rapidly diminish probably due to a combination of increased circulating levels of oxytocinase (the principal oxytocin deactivating enzyme), in the plasma, an overall reduction in hypothalamic oxytocin synthesis (Figure 1), and a reduction in uterine oxytocin receptor (OTR) density. This oxytocin-depleted, relatively auterotonic, physiological environment puts the mother at risk of PPH during the subsequent placental delivery phase (i.e. TSL).

Figure 1 Oxytocin During Physiological Fetal Delivery



Oxytocin receptors are constitutively expressed in smooth muscle cells (SMCs) in the uterine myometrium, muscular walls of the bronchi and upper digestive tract, myoepithelial cells of the breast duct which are essential for the oxytocin-dependent postpartum breast milk let-down reflex, and in different regions of the brain. Although uterine OTR expression increases during the later stages of pregnancy, it is not known whether pregnancy increases OTR expression at non-uterine sites, such as the maternal brain, where neuronal oxytocin signalling has been implicated in postpartum bonding behaviour with the baby. Within the kidney, oxytocin is known to bind to vasopressin (V2) receptors, rather than OTR, in the medullary renal collecting duct which triggers an antidiuretic effect.

Binding of oxytocin to OTR triggers an increase in intracellular calcium (Ca2+), which is partly mediated through oxytocin-dependent up-regulation of prostaglandin F (PGF)2α synthesis, which in the uterine myometrium leads to physiological uterine contractions during 3rd-stage labour.

More recent research has shown oxytocin to be present in broncho-alveloar lavage fluid collected from the respiratory tract of adult humans of both sexes, but oxytocinase expression was not assessed. In an in vivo pharmacology study [Prankerd , 2013] in pregnant ewes intratracheal insufflation of a dry-powder formulation of oxytocin was associated with poor absolute bioavailability (ca 5%), but despite low systemic exposure, this still caused a pharmacodynamic response that was manifested by increased electrical

uterine activity measured by electromyography, probably as a result of increased OTR stimulation in the pregnant uterus.

2.2.1. IH Oxytocin FTIH Study 201558

Study 201558 [GlaxoSmithKline Document Number 2016N277949_00] was the FTIH study to evaluate safety, tolerability, and characterize the PK profile of 4 dose strengths of IH oxytocin compared to oxytocin 10 I.U. IM. The study enrolled 16 healthy, non-pregnant, premenopausal female subjects. One subject was withdrawn prior to IH oxytocin dosing due to inability to cannulate. Subjects were administered 10 I.U. IM oxytocin, IH placebo containing (only) the excipients found in the IH oxytocin formulation, and IH oxytocin. A minimum washout period of 48 hours (h) was required between each dose of active drug. This dose escalation study evaluated 4 doses of IH oxytocin: 50 mcg, 200 mcg, 400 mcg, and 600 mcg. The most frequently reported Adverse Event (AE) was headache, and occurred in at least one subject in each treatment arm. In general, IH oxytocin was well-tolerated, no safety concerns with IH dosing were identified, no clinically significant effect on respiratory parameters were observed, and no Serious Adverse Events (SAEs) were reported. The PK profile of the 400 mcg IH oxytocin dose was similar to that of 10 I.U. IM, and has been selected for further evaluation. See Section 4.5 for further information on PK characteristics.

3. OBJECTIVES AND ENDPOINTS

3.1. Group 1: Women in TSL

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocinin women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h]) will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

3.2. Group 2: Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in	• Pre-dose plasma concentrations of oxytocin.

Objectives	Endpoints
the presence and absence of the combined oral contraceptive.	
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

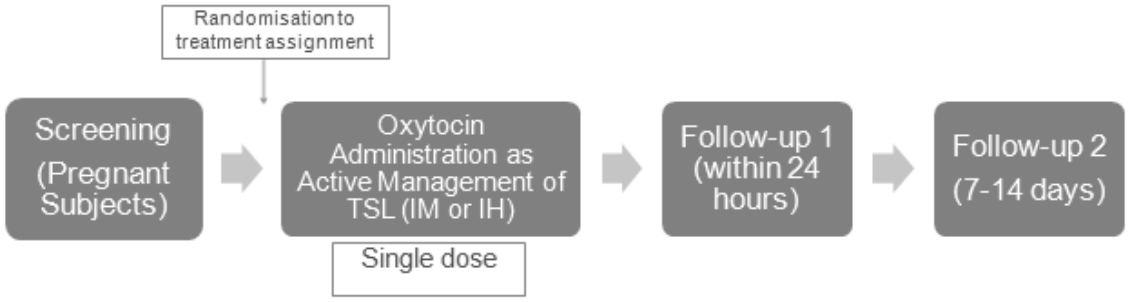
3.3. Groups 1 and 2: Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2.	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

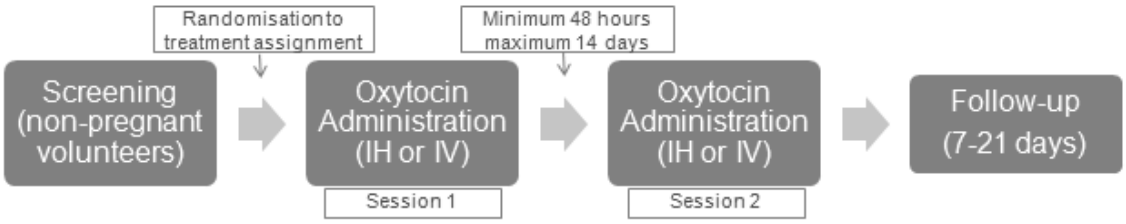
4. STUDY DESIGN

4.1. Overall Design

4.1.1. Study Schematic Group 1: Women in TSL



4.1.2. Study Schematic Group 2: Non-pregnant, non-lactating females of child bearing potential



4.1.3. Study Design Detail

This study will enrol two groups.

Group 1 - Women in TSL

Group 1 will enrol women with an uncomplicated pregnancy, and main phase procedures will occur during TSL. Subjects will be randomized to receive either IH or IM oxytocin as active management of TSL. The specific timing of this dose will be as per local standard of care.[1]

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Group 2 will enrol healthy, non-pregnant, non-lactating female subjects of childbearing potential, and each subject will participate in 2 dosing sessions. Group 2 will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive, and Cohort B will enrol women who are not using a hormonal form of contraceptive. Group 2 subjects will receive IH oxytocin at one dosing session, and IV oxytocin at the other dosing session; the order of IH versus IV oxytocin administration will be randomly assigned.

PK samples will be analysed periodically throughout the study duration to enable development of the population PK model and derivation of PK parameters via non-compartmental methods, as data permits.

No formal interim analysis is planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: IH, IM in Group 1 and IH in Group 2 Cohort A in order to assess if dose escalation is required.

[1] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

4.1.3.1. Pregnant Females (Group 1)

Subjects will review the study information and if they agree to participate, sign the informed consent form. For most subjects this is expected to take place at an outpatient antenatal visit, or additional study-specific screening visit. If a subject meets all inclusion/exclusion criteria for the study, she will be eligible for enrolment in the study.

To facilitate recruitment, and provide subjects ample time to consider participation, screening may occur any time after 18 weeks gestation (based on estimated date of delivery). See time and events (T&E) table in Section 7.1 for details.

4.1.3.2. Non-pregnant Females (Group 2)

Subjects will review the study information and if they agree to participate, sign the informed consent form. If a subject meets all inclusion/exclusion criteria for the study, she will be enrolled in the study.

Screening may occur within 28 days prior to randomization for non-pregnant volunteers. If a subject falls outside this window prior to randomization and enrolment, she must be re-screened. Certain screening procedures may not be required to be repeated; see T&E (Section 7.1) for details.

Group 2 subjects will take part in 2 dosing sessions, which must be conducted a minimum of 48 hours apart. It is recommended that subjects complete Session 2 within 14 days of Session 1. Subjects will be randomized to receive either IH or IV oxytocin during Session 1, and to receive the other treatment during Session 2, such that all subjects in Group 2 receive both treatments over the course of the 2 sessions.

4.1.4. ROTAHALER Inhaler Training

The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner (refer to Section 6.7). Subjects will be instructed by the investigator/designee to use an inspiration technique (2 inhalations) that enables maximal inhalation of the ROTACAPS powder capsule contents (refer to Section 6.7 for full details). This will ensure optimal and consistent drug delivery (full instructions available in the Study Reference Manual [SRM]).

4.1.5. Length of Stay for All Subjects

Group 1 - Women in TSL

Subjects in Group 1 will be admitted to hospital during labour as part of their routine care, and will be required to remain inpatient for a minimum of 4 hours after receiving any study-related dose of oxytocin. After final PK collection, subjects will be finished with study procedures and the main phase of the study will be considered complete. Discharge from hospital will be determined by the subject's medical provider.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Subjects in Group 2 will be admitted to the clinical unit prior to dosing on Day 1 and are to remain inpatient until at least 4 hours after dosing. Discharge will occur at the discretion of the investigator.

4.2. Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery) Group 2: All screening assessments to be completed within 28 days prior to the first dose
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 mcg IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 hours post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

[1] See Section 6.4 for possible dose adjustment to IH oxytocin.

4.3. Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2). Refer to Section 6.3 for treatment assignment information.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment at the discretion of the Sponsor. Replacement subjects will complete all study procedures as outlined in Section 7.1.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for IH and IM. In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose. See Section 6.4.1 for more details.

4.4. Design Justification

Group 1 - Women in TSL

This trial uses a randomized, single-dose approach to assign women in TSL to receive oxytocin by one of two routes: IM or IH. No placebo is being used, as the current standard of care is to administer oxytocin as active management of TSL to prevent PPH.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

A group of non-pregnant, non-lactating women of childbearing potential will receive IH and IV oxytocin. This group will be divided into two cohorts: Cohort A will enrol women on the combined oral contraceptive. This cohort will serve as a control group, as they most closely resemble the population enrolled in the FTIH study. Cohort B will enrol women using a non-hormonal form of contraception. This comparison group will help characterize the effect of oral contraceptives on endogenous oxytocin production and the PK profile of oxytocin.

Blinding

This study uses an open-label design.

4.5. Dose Justification

Single inhaled doses of oxytocin (50-600 mcg) have been generally well tolerated in the FTIH study, with no emerging safety signals, in healthy, non-pregnant, premenopausal female subjects (Study 201558) [GlaxoSmithKline Document Number 2016N277949_00; see also Section 2.2.1]. Following inhaled administration oxytocin was rapidly absorbed into the systemic circulation (tmax ranging from 0.05 to 0.50 h) with systemic exposure (Cmax and AUC) increasing with inhaled dose in an

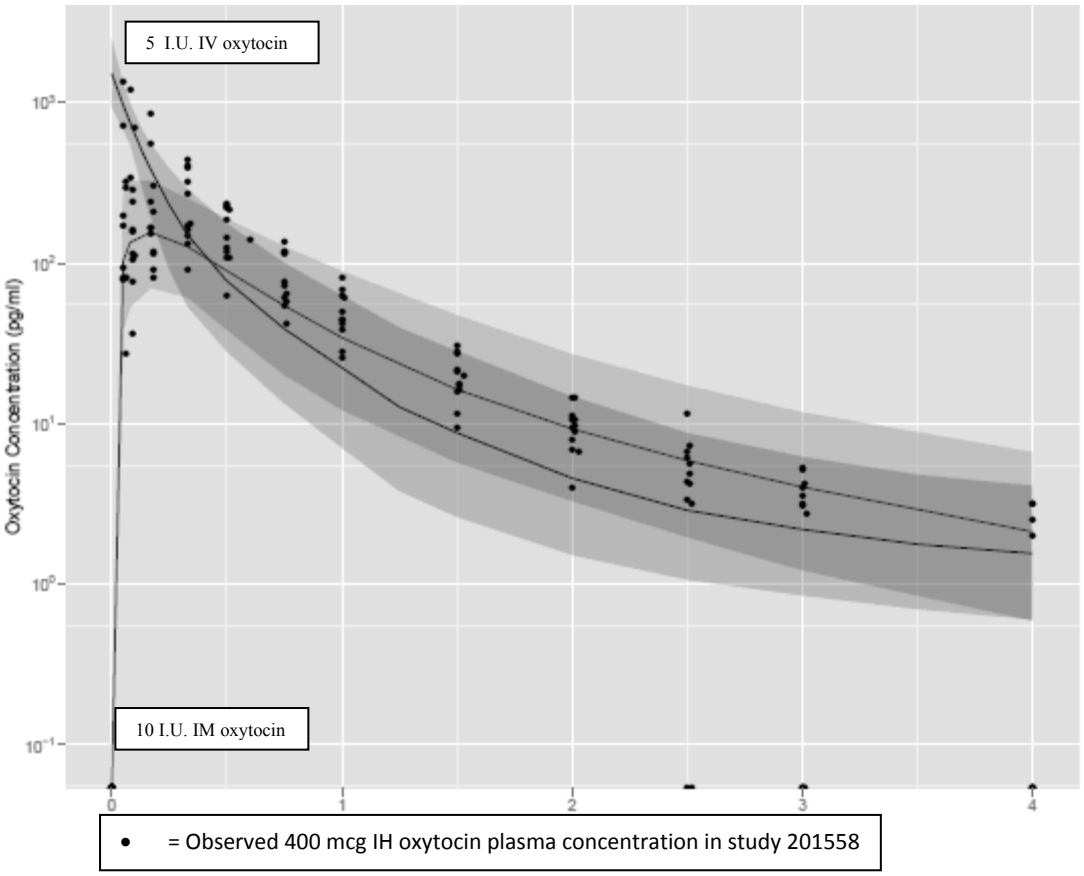
approximately proportional manner between 200 and 600 mcg. In general, the shape of the observed oxytocin concentration-time profile following inhaled administration was consistent with that following IM administration.

Based on the data from the FTIH study, and assuming that the PK characteristics of IH and IM oxytocin are similar in TSL compared with non-pregnant women, the 400 mcg inhaled dose is predicted to be an effective dose in women in TSL by ensuring that the systemic exposure (Cp10, Cp30 and AUC(0-3 h) following IH dosing is at least that following IM administration at the approved dose of 10 I.U. This would be based on the adjusted geometric mean ratio (90% Confidence Interval [CI]) treatment comparisons for Cp10, Cp30 and AUC (0-3 h) following 400 mcg IH compared with 10 I.U. IM, namely 1.10 (0.85,1.43), 1.65 (1.30, 2.09) and 1.27 (1.07, 1.50) respectively in study 201558. The PK parameters (Cp10, Cp30 and AUC(0-3 h)) have been selected to ensure onset and duration of action of the IH product is at least comparable to IM.

The clinical safety and reported AEs with oxytocin correlates to Cmax, with the Cmax of 10 I.U. IV representing the upper bounds of what could be considered safe in current clinical practice (AEs include flushing, which can cause a transient decrease in blood pressure and reflex tachycardia; see the Oxytocin Summary of Product Characteristics for more information). The recommendation in the United Kingdom (UK) in clinical practice has been to reduce the IV dose to 5 I.U. IV or administer by a controlled IV infusion [Bolton, 2003].

Minimising the risk of high Cmax levels of oxytocin following the IH administration is therefore important. Based on a comparison of model predicted systemic exposure following IV administration to non-pregnant, premenopausal female subjects with observed PK profiles following 400 mcg IH oxytocin, it is anticipated that Cmax following administration of the 400 mcg dose will not markedly exceed values following 5 I.U. IV bolus oxytocin (Figure 2). The inclusion of the 5 I.U. IV dose will allow an assessment of the potential safety and PK of the inhaled formulation compared to IV route of administration.

Figure 2 **Model predicted profiles (median (95%PI)) following IM (10 I.U. and IV bolus (5 I.U. administration of oxytocin overlaid with observed plasma concentrations of oxytocin following 400 mcg IH oxytocin to healthy non-pregnant females**



Whilst published literature on the PK of oxytocin in non-pregnant and pregnant women is limited there is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy. This may be related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy-related changes in hepatic and renal function [Syntocinon, 2014;Thornton, 1990]. In addition, there may be circulating levels of endogenous oxytocin in the plasma in women in TSL [Thornton, 1988] and increases in blood volume (40-50%) and total body water [Costantine, 2014]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in TSL for a given dose and route of administration of oxytocin. However, given that any pregnancy-related changes in systemic clearance, and/or distribution and baseline oxytocin levels, are considered to equally impact on each route of administration (IV, IM and IH), it is considered that the relative ratio of IV to IM and IH exposure observed in non-pregnant women is likely to be maintained in pregnancy. The only exception may be if pregnancy results in marked changes in absorption profiles. However, in a study of inhalation profiles of non-pregnant and women in the third stage of labour, the inhalation endpoints appeared to be broadly similar across the two cohorts and any small changes are not considered to markedly impact the delivery of an inhaled product in the third stage of labour [GlaxoSmithKline

Document Number 2015N239682_00]. In addition, in a pre-clinical sheep model the ratio IH:IV was generally similar in non-pregnant and post-partum ewes (Data on file Monash). In the event of enhanced pulmonary absorption in pregnancy, the selected 400 mcg inhaled dose is predicted to have an approximate 2-fold safe cover for Cmax compared with an 10 I.U. IV bolus oxytocin (assumes linearity from 5 -10 I.U. IV).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GR121619 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2015N240749_01] and oxytocin for parenteral administration [Syntocinon, 2014]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) – Inhaled Oxytocin – GR121619		
Bronchospasm, cough and dyspnoea, with increased *theoretical* risk in asthmatic subjects.	Oxytocin receptors are known to be expressed in human bronchial smooth muscle and up regulated by interleukin (IL)-13. Therefore, there is a hypothetical risk of bronchospasm, cough and dyspnoea.	See Section 5.2 for exclusion criteria. The oxytocin summary of product characteristics (SPC) does not list asthma as a contraindication to administration. Symptomatic wheezing may be treated with bronchodilator at the discretion of the investigator. Forced expiratory volume at 1 minute (FEV1) monitoring for both paradoxical and oxytocin induced bronchospasm Subjects with asthma or known pulmonary disease are excluded.
Hypotension, tachycardia and prolongation of QTc interval	Transient flushing, hypotension and tachycardia could be observed if the IH PK profile is comparable to an IM or IV oxytocin profile. Effects of oxytocin on the	Ongoing assessments of study subjects' cardiovascular function including blood pressure (BP), heart rate (HR) and ECG. Only single-dose IH, IM, or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Cardiovascular system (CVS) is unclear and contradictory in the literature but IV administered oxytocin can have a vasodilatory and negative inotropic effect in humans. Hypotension is thought to arise as a result of vascular smooth muscle relaxation and oxytocin binding to cardiac atrial OTR which leads to atrial natriuetic peptide (ANP) being transiently released into the systemic circulation. Prolongation of the QTc interval has been reported at the time of caesarean delivery with 10 IU IV oxytocin administration, rather than IM injection, in susceptible individuals	5 IU IV bolus injection routes of administration will be used as study treatment. Telemetry and frequent 12-lead ECGs will be used to monitor the healthy subject cohorts The 5 IU IV dose of oxytocin is the standard dose administered at the Rosie Maternity hospital post Caesarean Section. IV bolus will be given as a slow IV injection over 30 seconds with the option to change to a 5 minute infusion if frequent CV adverse effects are observed Exclusion of subjects with long QT syndrome, congenital cardiac abnormalities, and subjects taking anti-arrhythmic drugs. 12-lead ECG and telemetry covering Cmax in healthy subjects administered IH, IM and IV oxytocin
Insufficient uterotonic effect	The altered physiology and pharmacokinetics of women in the TSL my lead to a sub-optimal dose of inhaled oxytocin, resulting in a reduced or absent uterotonic effect.	In this setting, women in TSL and post-delivery are intensively observed. Therefore, any adverse events, including excessive blood loss due to unenhanced uterine contraction, will be managed in accordance with current local practice guidelines. This will usually include administration of additional uterotonic agents in the first instance. A follow-up within 24 h of discharge by the study team will be performed to specifically enquire if any late bleeding problems had

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		occurred. An interim analysis of IH and IM PK in the TSL group will be performed to ensure that the PK is in the acceptable range for efficacy to be anticipated.
Reference Intervention - IM Oxytocin / IV Oxytocin		
Hypotension, tachycardia and prolongation of QTc interval	See above section.	See above section. Subjects receiving the IV Oxytocin are required to have a systolic BP ≥ 90 Millimeter of mercury (mmHg) prior to dosing.
Myocardial Ischaemia and ST change on ECG	ECG changes consistent with myocardial ischaemia have been observed with 10 IU oxytocin IV bolus in healthy women associated with hypotension and tachycardia.	Oxytocic cardiovascular effects appear to be transient and persistent myocardial damage very rare and associated with 10 IU IV. Study is only using 5 IU IV as a slow IV bolus which is associated with a short lived increase in heart rate and reduction in BP but not ST changes on ECG in women undergoing Caesarean Section. Telemetry and 12-lead ECG monitoring in healthy subjects.
Abdominal pain	There is a hypothetical risk that IM oxytocin may trigger abdominal pain through contractions of the non-pregnant uterus in healthy women. Given the short half-life of oxytocin (approximately 30 minutes), the duration of a single abdominal pain episode	This is a theoretical possibility and not expected to occur. Ongoing assessments of study subjects' well-being along with vital signs and laboratory evaluations will be completed throughout the duration of the study. Abdominal pain which is clinically uncomfortable to the subject may be treated with paracetamol at the local

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	would be expected to be brief, not sustained and not recurrent in the absence of further oxytocin administration. Furthermore, no abdominal pain was observed in the FTiH study.	investigator's discretion.

4.6.2. Immunogenicity Risk

The oxytocin material used in the inhaled product is produced synthetically and so does not include any other protein/cell impuritites which might be intrinsically immunogenic. A review of the risk of immunogenicity of oxytocin and/or excipients was considered as part of the non-clinical safety studies but as the lymphoid tissues were not deemed to be pathologically affected and there were difficulties in generating a suitable assay, anti-drug antibodies (ADAs) were not measured. The FTIH study involved repeat dosing, and did not reveal any unexpected differences in PK which may have signalled the development of ADAs.

Oxytocin is an endogenous human peptide with a short systemic half-life and there are no reports of immunogenicity with oxytocin via parenteral administration. Thus it is considered unlikely that inhaled delivery of a small molecular weight (MW) peptide molecule like oxytocin would invoke an immunogenic response.

However, blood samples will be retained for anti-oxytocin antibody analysis if required in the event of an anaphylactic / allergic reaction (refer to Section 5.4.2) or other observation which would suggest an immunogenic effect.

4.6.3. Benefit Assessment and Overall Benefit:Risk Conclusion

Oxytocin has been administered to postpartum women for over 40 years via both the IM and IV routes, and has an established safety profile for each of these routes of administration. The FTIH study into IH oxytocin revealed no safety concerns for any of the subjects who received this new formulation. There are no direct clinical benefits to the volunteers within this study. The main contribution to their participation will be in the further development of a therapy (i.e. inhaled oxytocin) which may be ultimately used as a preventative therapy for postpartum haemorrhage in women during TSL in resource poor settings. It is fundamental to the project to clearly understand the PK of oxytocin following IH and IM administration to women in TSL in order to confirm the dose level that delivers a PK profile comparable to that of 10 I.U. IM (i.e. current standard of care in the developed world setting). Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with oxytocin (IH IM, and IV) are justified by the supporting data and overall benefit anticipated for women's health worldwide.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the investigator brochure for GR121619 [GlaxoSmithKline Document Number 2015N240749_01] and SPC for oxytocin administered IM or IV.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
All Groups: 1. Between 18 and 40 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
All Groups: 2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, and laboratory tests as required per protocol. Note: At time of randomisation, investigator or designee should confirm the subject feels fit and well, and is safely able to participate in the study. 3. Subject clinical chemistry and haematology values within an acceptable range for the population recruited and not of abnormal clinical significance. Note: Additional laboratory tests beyond those which are done as part of routine care (e.g. 28-week visit) are not required for subjects in Group 1. The investigator/designee may use his/her judgment in deciding whether to perform additional laboratory assessments to determine eligibility. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 4. Adequate peripheral venous access for cannulation.

Group 1 Only:

5. Currently pregnant, with an uncomplicated pregnancy as determined by the investigator or designee.
6. Estimated date of delivery within 24 weeks of screening.
7. Planned spontaneous vaginal birth and considered by investigator at low risk for PPH.
8. Planned birth in between the 37th and 42nd week of pregnancy.

   Note: Subjects can only receive study treatment if the onset of labour is between approximately 37 and 42 weeks estimated gestation. If a subject goes into labour before or after this timeframe, she should not receive study treatment.
9. Women who qualify for oxytocin as appropriate for active management of TSL and who agree to have active management.

Group 2 Only:

10. ECG normal, or abnormal and not clinically significant.
11. FEV1 >80% of predicted.
12. Systolic blood pressure ≥90 mmHg.

WEIGHT
Group 2 Only: 13. Body mass index (BMI) within the range 18 – 32 Kilogram (kg)/ meter $(m)^2$ (inclusive).

SEX
14. Female. Group 2, Cohort A Only: A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test), not lactating, and the following condition applies: a. Is of reproductive potential and agrees to use the same **combined estrogen and progestogen oral contraceptive** from 3 months prior to the first dose of study medication and until the follow-up contact. This method of contraception is only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method of contraception.

Group 2, Cohort B Only:

A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine hCG test), not lactating, and one of the following conditions applies:

a. Is of reproductive potential and has been using the same **non-hormonal contraceptive method** (see List of Acceptable Nonhormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential [see Appendix 5] from 3 months prior to the first dose of study medication and until the follow-up contact.

b. Would be of reproductive potential, but has undergone bilateral tubal ligation or occlusion or bilateral salpingectomy at least 12 months prior to first dose of study medication.

c. Is of reproductive potential with only same sex partners or who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

These methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method(s) of contraception.

Of Note: Group 2, Cohort B will enrol women of reproductive potential if they agree to use a nonhormonal contraceptive method from at least one month prior to receiving study drug and until the follow-up assessment. Although condoms with spermicide are not considered a highly effective method of contraception, the risk of receiving study drug during pregnancy is minimal for the following reasons:

- Pregnancy testing must be negative at screening and on the first day of dosing.
- Dosing is completed no greater than 14 days from the start of dosing.
- Oxytocin has a well established rapid half-life.

If a patient happened to conceive during the time of dosing, study drug would be eliminated before implantation would occur.

INFORMED CONSENT
All Groups: 15. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
All Groups: 1. Postmenopausal as defined by gynaecological history. 2. Chronic lung condition of any etiology including asthma, Chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease or active Tuberculosis (TB). Note: Childhood asthma (resolved) is not exclusionary. 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 4. Blood pressure >140 systolic or >90 diastolic. **Group 1 Only:** 5. Females with planned Caesarean Section. 6. Females with significant medical complications as determined by investigator. **Group 2 Only:** 7. Currently breastfeeding or lactating. 8. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 milliseconds (msec). 9. Alanine aminotransferase (ALT) and bilirubin >1.5 Upper Limit of Normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 10. Subjects with highly-active or symptomatic gynaecological disorders (such as large symptomatic fibroids).

CONCOMITANT MEDICATIONS
All Groups: 11. Prescription or non-prescription drugs not approved by the investigator (refer to Section 6.12.1 for approved medications). 12. Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) prior to administration of study-related oxytocin.

RELEVANT HABITS
All Groups: 13. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >14 units. One unit is equivalent to 8 grams (g) of alcohol: a half-pint (~240 milliliter [ml]) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 14. Current smokers or subjects with a history of smoking within 6 months of screening, or with a total pack year history of >5 pack years. a. Confirmatory use via a Smokerlyzer is at the discretion of the local investigator, but is advised if the subject's recent smoking history is in doubt.

CONTRAINDICATIONS
All Groups: 15. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation (e.g. allergy to any previous inhaler use). 16. Participation in another clinical trial, which in the opinion of the investigator, jeopardizes the subject's safety or study outcomes.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
All Groups: 17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 18. The subject has participated in a clinical trial and has received an investigation product within the following time period prior to the first dosing day in the current study: 30 days or twice the duration of the biological effect of the investigational product (whichever is longer). 19. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. **Group 2 Only:** 20. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result. 21. A positive Human Immunodeficiency Virus (HIV) antibody test. 22. A positive pre-study drugs of abuse test (not explained by diet or approved concomitant medications). 23. A positive alcohol breath test.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.4).

5.3.1. Re-screening

If a subject fails screening, she may be rescreened one additional time.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Pregnancy Complication Stopping Criteria (Group 1 Only)

Any complication requiring clinical intervention which no longer allows for a vaginal delivery or safe completion of study procedures will be cause for immediate withdrawal from the study. Investigators should continue to manage any pregnancy complication per local guidelines, and record any associated AE/SAE or concomitant medication. This includes the need for additional uterotonic administration.

5.4.2. Anaphylaxis Stopping Criteria

Clinical signs or symptoms of anaphylaxis / allergic reaction to IH oxytocin will be an automatic stopping criterion. Stored serum samples will be analysed for anti-oxytocin antibody analysis for affected subjects as detailed in Section 7.5.2. The samples will be analysed for Immunoglobulin E (IgE)/ Immunoglobulin G (IgG) anti-oxytocin titres ± biochemical markers of mast cell degranulation (e.g. tryptase) in the event of an anaphylactic / allergic reaction occurring.

5.4.3. QTc Stopping Criteria (Group 2 Only)

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

QTcF is proposed to be used for this study. If a subject meets either of the following bulleted criterion below, she will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline: Increase in QTcF >60 msec.

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be withdrawn from the study.

5.4.4. Blood Pressure Stopping Criteria (Group 2 Only)

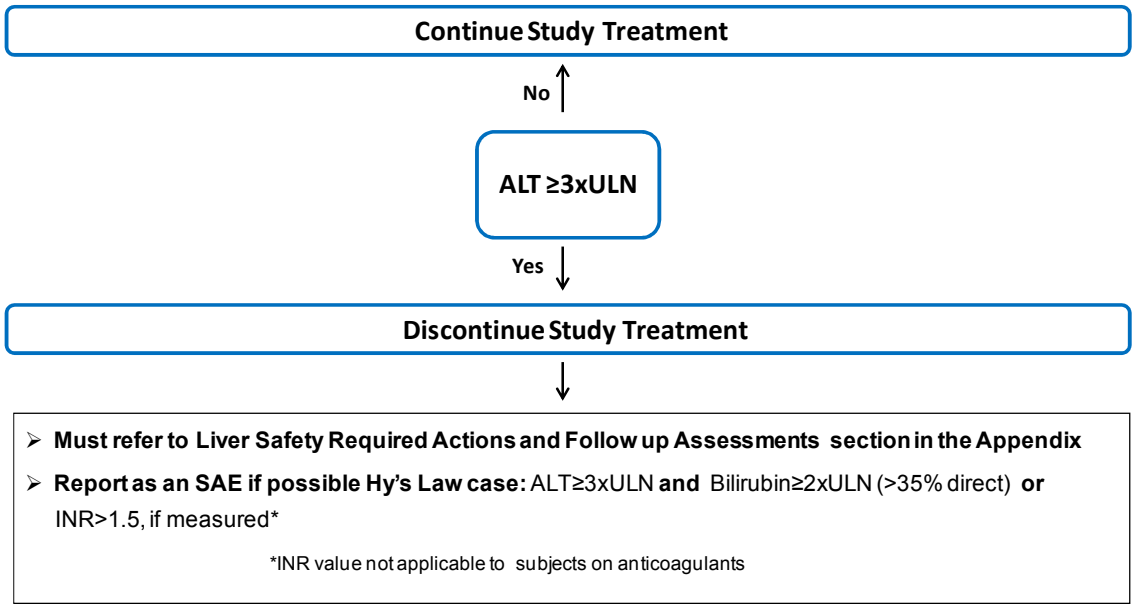
Subjects with a pre-dose systolic blood pressure of <90 mm Hg should not be dosed until systolic blood pressure is ≥90 mm Hg.

5.4.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit(s).

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Table 1 Study Treatment Information

	Study Treatment		
Product name:	Oxytocin (GR121619 capsule for inhalation)	Oxytocin	Oxytocin
Formulation description:	Powder Blend for Inhalation	Solution for Infusion	Solution for Infusion
Dosage form:	Inhalation powder, hard capsule	1ml ampoule	1ml ampoule
Unit dose strengths:	400 mcg 200 mcg	5 I.U./mL, or 10 I.U./mL	5 I.U./mL, or 10 I.U./mL
Route of Administration	For oral inhalation	Intramuscular (thigh)	Intravenous
Dosing instructions:	Capsule unit dose dispensed by ROTAHALER inhaler	Standard intramuscular injection	Adminster as a 30-second bolus
Physical description:	Colourless and clear HPMC capsules containing a white powder	Colourless and clear sterile solution	Colourless and clear sterile solution
Device:	ROTAHALER inhaler	Needle/Syringe	Intravenous Infusion Device

6.2. Medical Devices

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

6.3. Treatment Assignment

Subjects in Group 1 will be assigned to one of two treatments (IH oxytocin or IM oxytocin). Subjects in Group 2 will receive both IH and IV oxytocin in separate dosing sessions in a cross over design. Treatment assignment in Group 1, and order of dosing in Group 2, will be done in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in Table 2:

Table 2 Treatment Assignment

Group	Session	Treatment [1]	Number of Subjects[2]
Group 1	1	400 mcg IH oxytocin	10
		10 I.U. IM Oxytocin	10
Group 2, Cohort A	1	400 mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	
Group 2, Cohort B	1	400mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	

[1] See Section 6.4 for possible dose adjustment.

[2] See Section 9.2.2 for possible adjustment to subject numbers to Group 1

6.4. Planned Dose Adjustments

There is no plan to adjust the dose of IH oxytocin in this study. However, if systemic exposure seen in 400 mcg IH oxytocin in TSL subjects is less than expected and not comparable to the 10 I.U. IM profile, a consideration to escalate the dose to 600 mcg may be made as detailed in Section 6.4.1.

For Group 2, if an exaggerated physicological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

6.4.1. Dose Adjustment

The decision to adjust the IH dose in women in TSL will be determined by the GSK study team based on Group 1 PK data in TSL and Group 2, Cohort A PK data. After a minimum of n=5 women in TSL have received 400 mcg IH and 10 I.U. IM and a minimum of n=5 non-pregnant women on the combined oral contraceptive (Group 2, Cohort A) have received 400 mcg IH oxytocin, PK samples will be analysed and PK parameters derived (including but not limited to Cp10, Cp30 and AUC(0-3h)).

The median Cp10 will be estimated for women in TSL for each dose group (IH or IM) and the median ratio (IH/IM; n=5) derived. Based on the estimated ratio, the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased per the criteria described in Table 3:

Table 3 Dose Adjustment Decision Criteria

Median Ratio IH/IM	Decision
< 0.5	Consider study halt and review data.
≥ 0.5 to <0.7	Consider dose adjust to 600 mcg IH in women in TSL.
≥ 0.7	Continue with 400 mcg IH dose.

If a decision to increase the dose is made, additional subjects will be enrolled into Group 1 such that 10 subjects receive the 600 mcg IH oxytocin dose.

6.5. Blinding

This will be an open-label study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

- The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner. The investigator/designee will always load and prime the ROTACAPS powder capsule in the device before the subject self-administers an IH oxytocin dose
- All subjects will be taught by the investigator/designee to use the device in the "full-tilt" position and to use a "fast and deep" inspiration technique per inhalation, to achieve two rapidly consecutive maximal inhalations for IH oxytocin administration. This will ensure optimal and consistent treatment delivery. For subjects, the training session will be at any time during the 28-day Screening Period, as deemed appropriate by the investigator/designee.
- ROTACAPS powder capsules should be kept in their sealed packaging at room temperature (15-25°Centigrade [C]). The packaging should only be opened immediately prior to use.
- ROTAHALER inhaler devices will be supplied in bulk and unlabelled to the site. After dosing all ROTAHALER inhaler devices will be uniquely labelled and retained after each dosing session. The devices (which should not be opened up at the clinical study site) will be stored until further instruction from the sponsor is received.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.8. Compliance with Study Treatment Administration

Per ROTACAPS powder capsule dose, each subject will be asked to inhale twice from the ROTAHALER inhaler to reduce the possibility of inadequate administration due to a single poor inhalation manoeuvre. If failure of the ROTACAPS powder capsule actuation is suspected by the investigator (i.e. due to failure to open the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose using the same capsule.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Group 1 – Women in TSL

Following randomisation and any pre-dose procedures, subjects will receive a single study treatment as active management of TSL. The specific timing of this dose will be as per local standard of care.[2]

Administration will be documented in the source documents and reported in the Case report form (CRF).

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Following randomisation and all pre-dose procedures, subjects will receive two doses of oxytocin, separated by at least 48 hours. Randomisation will determine the order in which the IH and IV formulation is administered.

Administration will be documented in the source documents and reported in the Case report form (CRF).

6.9. Treatment of Study Treatment Overdose

For this study, any dose of the following compounds will be considered an overdose when administered as part of study procedures:

- IH oxytocin > 400 mcg
    - If study dose is increased to 600 mcg, then an overdose will be considered any dose > 600 mcg.
- Oxytocin > 10 I.U. IM
- Oxytocin > 5 I.U. IV

Note: Group 1 subjects may receive additional doses of oxytocin (IM or IV) when required as part of their general care and as clinically indicated. Additional doses of oxytocin will be recorded as concomitant medications, as will any related AEs.

General medical management consists of supportive care.

GSK does not recommend specific treatment for an overdose.

In the event of a study drug overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

[2] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until oxytocin can no longer be detected systemically (at least 4 hours).
3. Obtain an additional plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because either only healthy volunteers are eligible for study participation, or there are other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of postpartum subjects' medical conditions, whether or not GSK is providing specific post-study treatment.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Meals and Dietary Restrictions

There are no dietary restrictions for subjects in either cohort.

6.11.2. Caffeine and Alcohol

Group 1 – Women in TSL

- There are no restrictions for Group 1.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

6.11.3. Activity

Group 1 – Women in TSL

There are no activity restrictions.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses equal to or below the maximum recommended daily dose, is permitted for use during the screening period or at any time deemed necessary by the investigator or subject. All concomitant medication related to routine care during pregnancy and delivery is allowed (including pain relief [e.g. gas/air mixture] and epidural), and other medication may be considered on a case by case basis by the investigator or designee (in consultation with the Medical Monitor if required).

The start and stop time of any concomitant medications administered at any time during labour (including nitrous oxide gas/air mixtures) should be documented on the CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications will result in immediate withdrawal of subject:

- Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) before or after administration of study-related oxytocin.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table in Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
    1. 12-lead ECG
    2. vital signs

3. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic, immunogenic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

7.1.1. Time and Events Table – General Overview

Group 1

Procedure	Study Day			
	Screening[4]	Main Phase	Follow – Up 1 (approx. 24 hours post dose)	Follow – Up 2 (7-14 days post dose)
Informed Consent and Demography	X			
Brief Physical Examination	X			
Medical history (incl. substance abuse)	X			
Inhaler device training / education session	X			
Laboratory assessments[1]	X			
Vital signs[2]	X	X		
Pharmacokinetic blood sample		X		
Oxytocin Administration (IM/IH)		X		
Full blood count		X		
Labour Events Documentation		X		
Device acceptability questionnaire[3]		X		
Prior / concomitant medication review	X	X	X	X
AE review		---------- continuous review ----------		
SAE review	---------- continuous review ----------			

1. Only required if done as part of routine care. Additional study-specific laboratory assessments not required.
2. Includes blood pressure, heart rate, temperature, respiratory rate
3. Only to be used when randomized to IH oxytocin
4. To be completed after 18th week of pregnancy (based on estimated date of delivery).

Group 2

Procedure	Study Day		
	Screening[5]	**Main Phase**	**Follow - Up (7-21 days post dose)**
Informed Consent and Demography	X		
Brief Physical Examination	X	X	
Medical history	X		
Pregnancy test	X	X	
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X	X	
HIV, Hep B and Hep C screen[2]	X		
Inhaler device training / education session	X		
Laboratory assessments (including liver chemistries)	X	X	
Immunogenicity sample		X	X
12-lead ECG	X[4]	X	
CardiacTelemetry		X	
Vital signs[3]	X	X	
Spirometry (FEV-1)[4]	X	X	
Admission to unit		X	
Pharmacokinetic blood sample	X	X	
Oxytocin Administration (IH or IV)		X	
Prior / concomitant medication review	X	X	X
AE review		------ continuous review ----------	
SAE review	---------- continuous review ----------		
Discharge from unit		X	

1. Smokerlyzer at PI/designee discretion if smoking history in question.
2. If test otherwise performed within 3 months prior to first dose of study treatment, repeat testing at screening is not required.
3. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2.
4. Performed in triplicate.
5. To be completed within 28 days of randomization.

7.1.2. Time and Events – Main Phase Procedures

Group 1

		Time post dose										
Procedure	Pre-dose	3 min	5 min	10 min	15 min	20 min	30 min	1 hr	2 hr	2.5 hr	3 hr	4 hr
Vital signs[1]							X		X			
Pharmacokinetic blood sample	X[2]	X	X	X	X	X	X	X	X	X	X	X
Prior medication review	X											
Concomitant medication review		---------- continuous review ----------										
AE review		---------- continuous review ----------										
SAE Review	---------- continuous review ----------											
Device Acceptability Questionnaire[3]												X
Full Blood Count	X											X

1. Includes blood pressure, heart rate, temperature, respiratory rate
2. Predose PK sample to be taken immediately prior to administration of study treatment
3. Only to be administered when randomized to IH oxytocin

Group 2 – Sessions 1 and 2

		Time Post Dose														
Procedure	Pre-dose	2 min	3 min	5 min	8 min	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr
Brief Physical Exam	X															
Pregnancy Test	X															
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X															
Vital signs[2]	X			X			X		X		X					X
12-lead ECG	X	X				X		X	X		X					X
CardiacTelemetry	----------Continuous----------															
Spirometry[3]	X										X					
Pharmacokinetic blood sample	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sample	X															
Laboratory assessments (including liver chemistries)	X															X
Prior medication review	X															
Concomitant medication review		---------- continuous review ----------														
AE review		---------- continuous review ----------														
SAE Review	---------- continuous review ----------															
Discharge from unit[4]																X

1. Smokerlyzer at Principal Investigator (PI)/designee discretion if smoking history in question.
2. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2
3. FEV 1.0 will be performed in triplicate at each time point. Record all three values on source document, and record best effort in eCRF.
4. Discharge at PI discretion, no sooner than 4-hours post-dose.
5. 3 pre-dose samples: approximately 1 hr pre-dose, 30 minutes pre-dose, and 15 minutes pre-dose

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management [e.g. brief physical exam, laboratory assessments] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (see Section 12.3).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF or appropriate source document.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigators Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Adverse Events of Special Interest (AESI)

Any problem related to the delivery of the placenta or postpartum haemorrhage should be documented as an AESI using the appropriate case report form (CRF).

7.3.3. Pregnancy

Group 2 Only:

- Details of all pregnancies will be collected after the start of dosing and until follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.3.4. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Section 12.4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 12.3.6 and Appendix 3 of the Protocol.

7.3.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

  NOTE: The method of documenting Medical Device Incidents is provided in Appendix 4.

7.3.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.

- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor or SAE coordinator.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.3.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.3.5. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen if palpable).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.6. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate (unless otherwise specified in T&E).

7.3.7. Documentation of Labour Events

The time that the following labour events occurred will be collected:

- Time of crowning
- Time of birth
- Time of delivery of placenta

7.3.8. Electrocardiogram (ECG) (Group 2 Only)

- Triplicate 12-lead ECGs will be obtained at screening as listed in Section 7.1.1.
- Single 12-lead ECGs will be obtained at each timepoint as listed in Section 7.1.2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At all single 12-lead ECG time-points if QTc >450, repeat twice and take average reading.

7.3.9. Continuous Cardiac Telemetry (Group 2 Only)

Continuous cardiac telemetry will be started at least 10 minutes pre-dose (to obtain a stable reading) and continue until at least the first hour after IV and IH placebo / oxytocin administration and then as deemed necessary by the investigator. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

7.3.10. Device Acceptability Questionnaire (Group 1 Only)

A device acceptability questionnaire will be administered to subjects in Group 1 following use of the ROTAHALER (Appendix 7).

7.3.11. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as required by Section 7.1 and defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Tests performed as part of routine care in Group 1.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Subjects in Group 1 are not required to undergo additional laboratory assessments beyond those done as part of their routine care. However, the investigator/designee may conduct any of the tests listed in Table 4 in order to confirm eligibility. Haematology, clinical chemistry, and additional parameters to be tested in all Group 2 subjects are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>White Blood Cell (WBC) count with Differential</u>:</td></tr>
<tr><td>Red Blood Cell (RBC) Count</td><td>Mean Corpuscular Volume (MCV)</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>Mean Corpuscular Hemoglobin (MCH)</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate aminotransferase (AST) (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine aminotransferase (ALT) (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>HIV

Hepatitis B (HBsAg)</td></tr>
</table>

Laboratory Assessments	Parameters
	Hepatitis C (Hep C antibody) Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of suspected non-child bearing potential only) Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) Serum or urine hCG Pregnancy test (Group 2 only) [2]
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2 and Appendix 2 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.	

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of oxytocin will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

At each time point, 4 mL of blood will be collected into K2 or K3 Ethylenediaminetetraacetic acid (EDTA) tubes and stored on ice for up to 2 hours prior to centrifugation in a refrigerated centrifuge. Further details regarding collection/shipping procedures are provided in the SRM

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of oxytocin will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

7.5. Biomarkers

7.5.1. Pharmacodynamic Markers

Pre and post-delivery full blood counts will be collected from Group 1 subjects to assess for a change in haemoglobin levels.

7.5.2. Immunogenicity

Blood samples will be taken at the time points specified in the Time and Events Table (Section 7.1) to assess the immunogenicity of oxytocin.

Pre- and post-dose samples will be retained in the event that further immunologic tests are deemed necessary to support observations of unexpected anaphylaxis/ hypersensitivity, and / or a PK profile for IH oxytocin in any Dosing Session which is regarded by the GSK Study Team to be reasonably attributable to circulating anti-oxytocin antibodies.

Details of the collection / shipping procedures are provided in the SRM.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to characterize the pharmacokinetics of 400 mcg IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

No formal hypotheses will be tested, however, the following comparisons are of interest, within Group 1, (IH vs. IM) and between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on oral contraception) and between Cohorts A and B in Group 2 (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive). For each PK endpoint of interest, point estimates and corresponding two-sided 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference) to provide the range of plausible values for the comparisons of interest.

9.2. Sample Size Considerations

A sufficient number of subjects will be enrolled to ensure approximately 20 evaluable subjects (10 in each of the IM and IH groups) complete all dosing and critical assessments in Group 1, as well as 5 subjects in each cohort in Group 2. Whilst sample size is based on feasibility, precision calculation was also done to approximate the estimate of the expected half width of 90% CI around point estimate for the main comparison of interest (IH oxytocin to 10 I.U. IM oxytocin in women in TSL) using a t-test.

Table 5 illustrates the associated 90% CIs for the mean treatment ratios, assuming between subject SDs of 0.424 and 0.601 (SDs are based on log transformed data) for AUC (0-3h) and CP10 respectively, for the comparisons of interest detailed in Section 9.1. Calculations are based on a symmetric two-tailed procedure on the loge scale and a type I error rate of 10%. These values represent estimates of the between-subject variability observed in the FTIH study 201558 [GlaxoSmithKline Document Number 2016N277949_00].

Table 5 Estimated 90% Confidence Intervals for Treatment Ratios

N	Parameter	Between Subject Standard Deviation (SD)	Estimated Treatment Ratio	Precision	Expected 90% CI
10	AUC(0-3h)	0.424 (CVb=44.35%)	1	38.30%	(0.72, 1.38)
10	Cp10	0.601 (Cvb=65.96%)	1	58.20%	(0.63,1.58)

The precision estimates are deemed acceptable to assess the study objectives at this stage of development.

9.2.1. Sample Size Sensitivity

Considering the variability of AUC(0-3h) and Cp10, Table 6 shows the scenarios for different sample size and the precision estimates for IH vs. IM in Group 1.

Table 6 Estimated 90% Confidence Intervals for Treatment Ratios for Sample Size Sensitivity

%CVb	N	Precision	Assuming ratio 1, the confidence interval
44.35%	5	61.90%	(0.61, 1.61)
	15	29.80%	(0.77,1.29)
65.96%	5	98.00%	(0.50, 1.98)
	15	44.80%	(0.69, 1.44)
	20	37.40%	(0.72,1.37)
85.35%*	5	131.90%	(0.43, 2.31)
	10	75.90%	(0.56, 1.75)
	15	57.60%	(0.63, 1.57)
	20	48.00%	(0.67, 1.48)

* 85.35% was the largest between subject CV for AUC(0-10) observed for FTIH study 201558 [GlaxoSmithKline Document Number:2016N277949_00]

9.2.2. Sample Size Re-estimation or Adjustment

No formal sample size re-estimation is planned for this study. However, if the variability is high (for example approaching 85%) then the sample size for Group 1 may be increased to a maximum of 10 additional subjects per treatment arm (IH and IM only).

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exist on the study database. This population will be used for summarizing screening failure reasons.
All Subjects Population	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays.
Pharmacokinetic Population	• Subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.

9.3.2. Interim Analysis

No formal interim analysis is planned. However, PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

9.4.1.1. Safety Analysis

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.1.2. Pharmacokinetic Analysis

Pharmacokinetics analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline. Plasma oxytocin concentration-time data will be analyzed by non-compartmental methods with WinNonlin V6.3 or greater. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-3h) and AUC(0-∞)], the last observed quantifiable concentration (Clast), time of the last quantifiable concentration (tlast), Cp10, Cp20, Cp30 (observed plasma concentrations at 10, 20 and 30minutes post-dose, respectively), plasma clearance (CL; IV only), volume of distribution (V; IV only) and apparent terminal phase half-life (t1/2). Other PK parameters may also be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

If appropriate, a population PK analysis may also be conducted, in addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis.

9.4.2. Secondary Analyses

Statistical analyses of the PK parameter data will be performed by, or under direct auspices of Clinical Statistics, QSci.

9.4.2.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons within Group 1 IH vs. IM, point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3. Exploratory Analyses

9.4.3.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on the combined oral contraceptive), and within Group 2 between Cohorts A and B (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive), point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3.2. Device Acceptability Questionnaire

In Group 1, subject satisfaction with device, including instructions and ease of use, will be assessed. The questionnaire is located in Section 12.7

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRFs <or> entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for

those required by local regulations to be maintained elsewhere), in a safe and secure location.

- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Frontiers in Pharmacology*. 2014. Volume 5. Article 65: 1-5.

GlaxoSmithKline Document Number 2015N234711_01. Study ID 201558. Clinical Pharmacology Study Protocol. A single centre, single blind study to investigate the safety, tolerability and pharmacokinetics of single doses of oxytocin (GR121619) administered via an inhaled route in healthy female volunteers. 16-NOV-2015.

GlaxoSmithKline Document Number 2015N239682_00. Study ID 201248 – Clinical Pharmacology Study Report. An enabling study to compare the inhalation profiles of women in the third stage of labour to those of non-pregnant female volunteers and to explore whether there are any differences which could impact the delivery of an inhaled medicinal product, 16-OCT-2016.

GlaxoSmithKline Document Number 2015N240749_01. GR121619 Investigator's Brochure, AUG-2015.

GlaxoSmithKline Document Number 2016N277949_00. Study ID 201558 – Clinical Study Report.. 30-JUN-2016.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.

Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2014, *Issue* 2. *Art. No.: CD003249. DOI:* 10.1002/14651858.CD003249.pub3.

Prankerd RJ, Nguyen T, Ibrahim JP, et al. Pulmonary Delivery of an Ultra-Fine Oxytocin Dry Powder Formulation: Potential for Treatment of Postpartum Haemorrhage in Developing Countries. 2013; *PLoS One*. Vol 8: 12: Article e82965

Syntocinon Summary of Product Characteristics, Novartis, 2014

Thornton S, Davison JM, Baylis PH. Effect of human pregnancy on metabolic clearance rate of oxytocin. *American Physiological Society*. 1990. 0363-6119: R21-R24.

Thornton S, Davison JM, Baylis PH. Plasma oxytocin during third stage of labour: comparison of natural and active management.*BMJ.* 1988. Volume 297:167-169.

WHO Model List of Essential Medicines 18th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO Model List of Essential Medicines for Children 4th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO, UNICEF, UNFPA. The World Bank World Health Organization (WHO) Press. Trends in Maternal Mortality: 1990 to 2008: Estimates Developed by WHO, UNICEF, UNFPA and The World Bank. Geneva*: WHO,* 2010.

12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

Abbreviations

ADAs	Anti drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANP	Atrial natriuretic peptide
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-3)	Area under the concentration-time curve from time zero (pre-dose) to three hours
AUC(0-∞)	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
Ca2+	Intracellular calcium
CI	Confidence Interval
CL	Plasma clearance
Clast	last observed quantifiable concentration
Cmax	Maximum observed plasma concentration
COC	Combined oral contraceptive
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
Cp10	Observed plasma concentrations at 10 minutes post-dose
Cp20	Observed plasma concentrations at 20 minutes post-dose
Cp30	Observed plasma concentrations at 30 minutes post-dose
CPK	Creatinine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry powder inhaler
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1.0	Forced expiratory volume at 1 minute
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram
GCP	Good Clinical Practice

GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care professional
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
I.U.	International units
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IH	Inhaled
IL	Interleukin
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
Kg	kilogram
LDH	Lactate dehydrogenase
m	Meter
mcg	Micrograms
MCH	Mean Corpuscular Hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
mmHg	Millimeter of mercury
MSDS	Material Safety Data Sheet
Msec	Milliseconds
MW	Molecular weight
OTR	Oxytocin receptor
PGF	Prostaglandin F
PI	Principal Investigator
PK	Pharmacokinetics
PPH	Post-partum haemorrhage
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis plan
RBC	Red blood cells
SAE	Serious Adverse Event

SD	Standard deviation
SMC	Smooth muscle cells
SPC	Summary of product characteristics
SpO2	Peripheral capillary oxygen saturation
SRM	Study reference manual
T&E	Time and event
t1/2	Terminal phase half-life
TB	Tuberculosis
tmax	Time to Cmax
TSL	Third stage of labour
UK	United Kingdom
ULN	Upper Limit of Normal
V	Vassopresin
VOD	Volume of distribution
WBC	White blood cells
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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ROTAHALER

Trademarks not owned by the GlaxoSmithKline group of companies
Syntocinon
Uniject
WinNonlin

12.2. Appendix 2 Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 4h of the last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or</td></tr>
</table>

recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; International normalized ratio (INR) measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism

- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4 Definition of and Procedures for Documenting Medical Device Incidents

12.4.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.4.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.5. Appendix 5 List of Acceptable Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Group 2, Cohort B Only: List of Acceptable Non-hormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Nonhormonal Intrauterine device or
2. Male condom combined with vaginal spermicide
3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

Group 2 Only

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication or be withdrawn from the study.

12.5.3. References

Bolton TJ, Randall K, Yentis SM. Effect of the Confidential Enquiries into Maternal Deaths on the use of Syntocinon at Caesarean section in the UK. Anaesthesia 2003(58-3):277-9.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.6. Appendix 6 Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7 Device Acceptability Questionnaire

Device Acceptability Questionnaire

Please answer the following questions regarding your use of the ROTAHALER inhaler for oxytocin.

1. Did you feel confident you had received the medicine?

   Yes No Neutral Decline to answer

2. Did you find the inhaler easy to use?

   Yes No Neutral Decline to answer

3. Did you prefer to have your medicine from an inhaler instead of an injection?

   Yes No Neutral Decline to answer

4. Do you feel using this inhaler is an acceptable way to administer the medicine?

   Yes No Neutral Decline to answer

Thank you for answering these questions.

12.8. Appendix 8 Protocol Changes

Protocol Amendment 01

As part of the Medical Device Notification assessment process, the Medicines and Healthcare products Regulatory Agency (MHRA) requested that the protocol prominently reflect that although the investigational device (the ROTAHALER) bears a CE mark, it has not been CE marked in accordance with the Medical Device Directive 93/42/EEC as updated. This change applies to all sites.

Section 6.2 Medical Devices

Change From:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device).

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

Change to:

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device). **Although this investigational device bears a CE mark, it has not been CE marked in accordance with the Medical Devices Directive 93/42/EEC.**

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A randomized, open-label study to characterize the pharmacokinetics of inhaled oxytocin (GR121619) compared with IM oxytocin in women in the third stage of labour, and with IV oxytocin in non-pregnant, non-lactating women of childbearing potential.

Compound Number: GR121619

Development Phase I

Effective Date: 22-AUG-2016

Author(s): PPD **(Respiratory TAU);** PPD **(GCSP);** PPD PPD **(MNHU),** PPD **Clinical Statistics);** PPD **(GCSP);** PPD **(QSci CPMS);** PPD **(CPSSO)**

SPONSOR SIGNATORY:

PPD

Pauline Williams
Head of Global Health R&D

22nd August 2016
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				GSK Gunnels Wood Road Stevenage SG1 2NY UK
Secondary Medical Monitor					GSK Gunnels Wood Road Stevenage SG1 2NY UK
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline (GSK) Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **EudraCT 2016-002672-27**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 205920

Rationale

Post-partum hemorrhage is one of the main causes of maternal mortality in the developing world. The World Health Organization (WHO) lists oxytocin on its list of 'Essential Medicines' for Humanity as a preventative treatment for post-partum hemorrhage; however, because of its cold-chain storage requirement and parenteral administration route, high-quality oxytocin is not always available in resource-poor settings. GlaxoSmithKline (GSK) has developed a stable, dry-powder formulation of oxytocin to address this unmet need, with the goal of reducing post-partum hemorrhage morbidity and mortality in these settings.

This study is being conducted to further assess safety and tolerability of inhaled oxytocin, and to characterize the pharmacokinetic (PK) profile of inhaled oxytocin compared to oxytocin administered as standard of care. Two groups of subjects will be enrolled. Group 1 will enroll pregnant women, who will be randomized to receive either inhaled (IH) or intramuscular (IM) oxytocin as active management of the third stage of labour. Group 2 will enroll non-pregnant women of childbearing potential, who will receive IH oxytocin and intravenous (IV) oxytocin in a cross over design over two dosing sessions.

Objectives/Endpoints

Group 1 – Women in Third Stage of Labour (TSL)

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 International Units (I.U.) IM oxytocin in women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events (AE); absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h])

Objectives	Endpoints
	will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM oxytocin in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in the presence and absence of the combined oral contraceptive.	• Pre-dose plasma concentrations of oxytocin.
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as

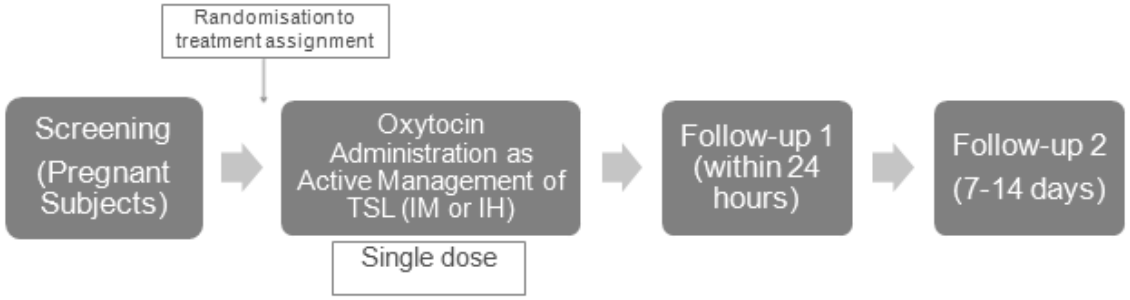
Objectives	Endpoints
oxytocin between Cohort A and Cohort B.	data permit.

Groups 1 and 2 – Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

Overall Design

Group 1 – Women in TSL



Group 2 – Non-pregnant, non-lactating females of child bearing potential

Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery). Group 2: All screening assessments to be completed within 28 days prior to the first dose.

Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions.
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 micrograms (mcg) IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 h post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 – 21 days = 64 days

Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2).

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor. Replacement subjects will complete all study procedures.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for inhaled and intramuscular oxytocin. In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose.

Analysis

The primary objective of this study is to characterize pharmacokinetics of IH oxytocin and IM oxytocin in women in the third stage of labour.

No formal hypotheses will be tested, however, comparisons of interest, within Group 1, and between Group 1 and Group 2 and between Cohorts A and B in Group 2 will be made and the point estimates and corresponding two-sided 90% confidence intervals (CI) will be presented to provide the range of plausible values for the comparisons.

2. INTRODUCTION

Maternal mortality associated with post partum hemorrhage (PPH) is one of the major public health problems in the developing world. Approximately half a million women worldwide die annually from causes directly related to pregnancy and childbirth, and up to one third of these deaths in Africa and Asia are caused by complications as a result of PPH [Khan, 2006;WHO, 2010]. A Cochrane Review meta-analysis of the data from multiple preventative trials with oxytocin at 10 international units (I.U.) given via the intramuscular (IM) route has confirmed this specific uterotonic, and this particular route of administration, to be the gold standard prophylactic therapy for PPH [Mousa, 2014]. For this reason, the World Health Organization (WHO) has designated oxytocin as one of its 'Essential Medicines' for humanity [WHOModel List of Essential Medicines 18th list, April 2013; WHOModel List of Essential Medicines for Children 4th list, April 2013].

However, in resource-poor settings within the developing world, the effectiveness of prophylactic IM oxytocin is diminished by a lack of appropriate refrigeration facilities and availability of trained health care professionals (HCPs) to administer IM injections [Mousa, 2014]. Although single-use, oxytocin prefilled, syringes for IM injection are available in many developing countries (e.g. UNIJECT device), the development of a needle-free and self-administered inhaled (IH) oxytocin product, which delivers comparable systemic exposure to 10 I.U. IM, would be a major step-change in the administration of this life-saving medicine to pregnant women in resource-poor regions of the developing world. This would be particularly relevant in rural areas where the mother has no routine access to a trained HCP and/or where there is no reliable electricity supply to permit refrigerated storage of oxytocin injection vials.

We have developed a stable, dry-powder formulation of oxytocin to be administered via the oral inhaled pulmonary route (compared to 10 I.U. of IM oxytocin) using a GlaxoSmithKline (GSK)-manufactured medical device (or device manufactured for GSK by a third party) which is a capsule-based inhaler (Modified Air Inlet ROTAHALER™ Dry Powder Inhaler (DPI) device, hereafter referred to as ROTAHALER). This

formulation and delivery method has the potential to be used in settings where effective oxytocin is currently unavailable to women in the third stage of labour (TSL).

2.1. Study Rationale

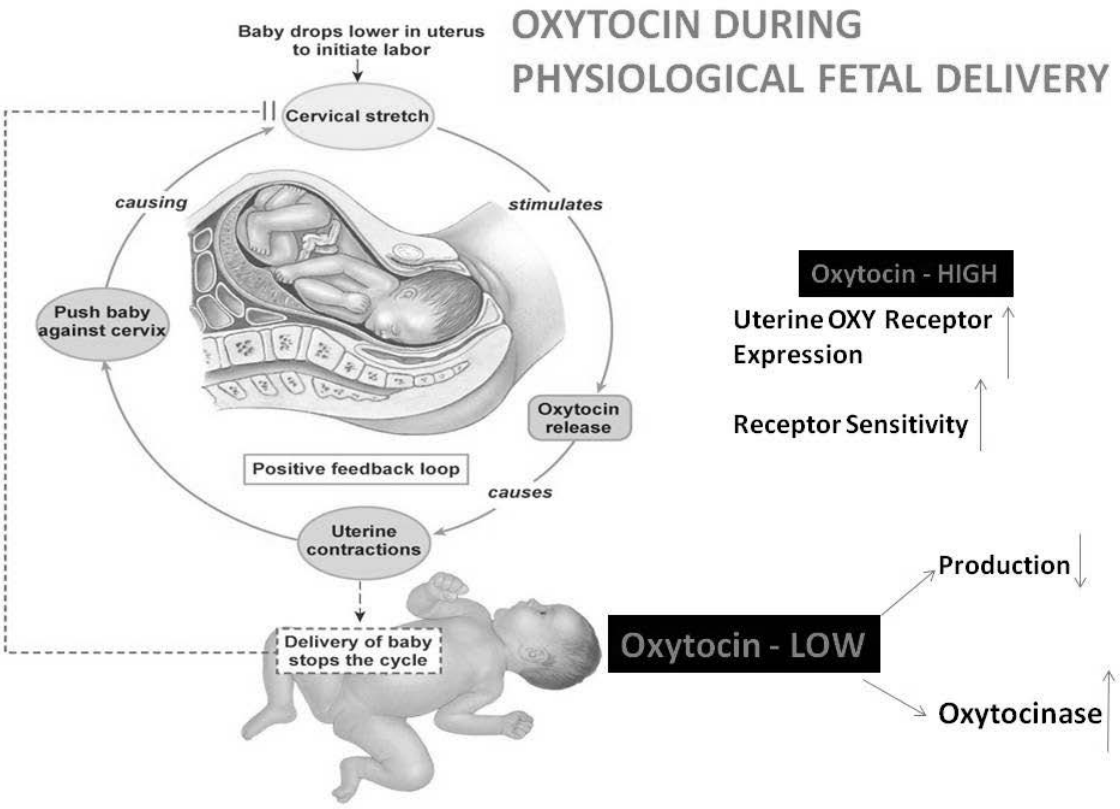
This study will be the second investigation of oxytocin in humans via the IH route, which follows the first time in human (FTIH) study, 201558 [GlaxoSmithKline Document Number 2015N234711_01, 2015; see Section 2.2.1 for more information on the FTIH trial)]. Published literature on the pharmacokinetics (PK) of oxytocin in non-pregnant and pregnant women is limited. There is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy; potentially related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy related changes in hepatic and renal function [Syntocinon Summary of Product Characteristics, Novartis, 2014; Thornton, 1990]. In addition, endogenous oxytocin plasma concentrations have been reported to either increase or remain constant after the delivery of the fetal anterior shoulder [Thornton, 1988]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in the TSL for a given dose and route of administration of oxytocin. To further understand the effect of pregnancy on the PK of oxytocin, this study will investigate the PK of oxytocin in pregnant women in TSL following either IH (400 micrograms [mcg]) or 10 I.U. IM (17 mcg) administration. A greater understanding of the PK of oxytocin in TSL will help facilitate extrapolation of data obtained in healthy non-pregnant women to women in TSL. An additional group of non-pregnant non-lactating female volunteers will also be included as a control group and will receive 400 mcg IH oxytocin and 5 I.U. intravenous (IV) oxytocin. This second group will enrol one cohort of subjects taking the combined oral contraceptive (COC), and another cohort using a non-hormonal form of contraception. This will assess if women need to be on an oral contraceptive vs. other methods of birth control in future clinical studies, since although the COC is believed to suppress endogenous oxytocin levels the literature is not consistent about this observation. As the requirement to be taking the COC makes recruitment more of a challenge it will be helpful to know if this inclusion is essential, or if women using non-hormonal forms of birth control might also have sufficiently low systemic oxytocin levels suitable for PK studies.

2.2. Brief Background

Oxytocin is a nonapeptide which is produced by the hypothalamus and released into the systemic circulation by the posterior pituitary gland. Within the brain, oxytocin, like most hypothalamic synthesized hormones, acts as a neurotransmitter. In human pregnancy, during the later phases of the third trimester, increasing circulating levels of oxytocin act as a potent endogenous uterotonic which facilitates the initiation of labour. Furthermore, a neurohormonal positive feedback loop exists between dilatation of the cervico-vaginal canal by fetal passage and the hypothalamus (i.e. Fergusson reflex) which augments oxytocin production, thus increasing uterine contraction intensity and frequency which facilitates vaginal delivery. However, once the fetus is delivered, plasma oxytocin levels rapidly diminish probably due to a combination of increased circulating levels of oxytocinase (the principal oxytocin deactivating enzyme), in the plasma, an overall reduction in hypothalamic oxytocin synthesis (Figure 1), and a reduction in uterine

oxytocin receptor (OTR) density. This oxytocin-depleted, relatively auterotonic, physiological environment puts the mother at risk of PPH during the subsequent placental delivery phase (i.e. TSL).

Figure 1 Oxytocin During Physiological Fetal Delivery



Oxytocin receptors are constitutively expressed in smooth muscle cells (SMCs) in the uterine myometrium, muscular walls of the bronchi and upper digestive tract, myoepithelial cells of the breast duct which are essential for the oxytocin-dependent postpartum breast milk let-down reflex, and in different regions of the brain. Although uterine OTR expression increases during the later stages of pregnancy, it is not known whether pregnancy increases OTR expression at non-uterine sites, such as the maternal brain, where neuronal oxytocin signalling has been implicated in postpartum bonding behaviour with the baby. Within the kidney, oxytocin is known to bind to vasopressin (V2) receptors, rather than OTR, in the medullary renal collecting duct which triggers an antidiuretic effect.

Binding of oxytocin to OTR triggers an increase in intracellular calcium (Ca2+), which is partly mediated through oxytocin-dependent up-regulation of prostaglandin F (PGF)2α synthesis, which in the uterine myometrium leads to physiological uterine contractions during 3rd-stage labour.

More recent research has shown oxytocin to be present in broncho-alveloar lavage fluid collected from the respiratory tract of adult humans of both sexes, but oxytocinase

expression was not assessed. In an in vivo pharmacology study [Prankerd , 2013] in pregnant ewes intratracheal insufflation of a dry-powder formulation of oxytocin was associated with poor absolute bioavailability (ca 5%), but despite low systemic exposure, this still caused a pharmacodynamic response that was manifested by increased electrical uterine activity measured by electromyography, probably as a result of increased OTR stimulation in the pregnant uterus.

2.2.1. IH Oxytocin FTIH Study 201558

Study 201558 [GlaxoSmithKline Document Number 2016N277949_00] was the FTIH study to evaluate safety, tolerability, and characterize the PK profile of 4 dose strengths of IH oxytocin compared to oxytocin 10 I.U. IM. The study enrolled 16 healthy, non-pregnant, premenopausal female subjects. One subject was withdrawn prior to IH oxytocin dosing due to inability to cannulate. Subjects were administered 10 I.U. IM oxytocin, IH placebo containing (only) the excipients found in the IH oxytocin formulation, and IH oxytocin. A minimum washout period of 48 hours (h) was required between each dose of active drug. This dose escalation study evaluated 4 doses of IH oxytocin: 50 mcg, 200 mcg, 400 mcg, and 600 mcg. The most frequently reported Adverse Event (AE) was headache, and occurred in at least one subject in each treatment arm. In general, IH oxytocin was well-tolerated, no safety concerns with IH dosing were identified, no clinically significant effect on respiratory parameters were observed, and no Serious Adverse Events (SAEs) were reported. The PK profile of the 400 mcg IH oxytocin dose was similar to that of 10 I.U. IM, and has been selected for further evaluation. See Section 4.5 for further information on PK characteristics.

3. OBJECTIVES AND ENDPOINTS

3.1. Group 1: Women in TSL

Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 I.U. IM oxytocinin women in TSL.	• Plasma concentration time profile for IH oxytocin and 10 I.U. IM oxytocin. • PK parameters: Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) post-dose (Cp10), Observed plasma concentrations at 20 min post-dose (Cp20), Observed plasma concentrations at 30 min post-dose (Cp30), Time to Cmax (tmax), Area under concentration-time curve (AUC), and Terminal phase half-life (t1/2) will be calculated as data permit.

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of inhaled oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate, respiratory rate, temperature).
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• Cmax ,Cp10, Cp20, Cp30, Area under the concentration-time curve from time zero (pre-dose) to three hours (h) (AUC[0-3h]) will be compared as data permit.
Exploratory	
• Pharmacodynamic effect of IH oxytocin and 10 I.U. IM in women in TSL.	• Pre and post-delivery haemoglobin.
• Participant feedback regarding ease of use, instructions, and perceived ability of patients to use the ROTAHALER.	• Questionnaire results from participants.

3.2. Group 2: Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of IH and IV oxytocin.	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, Corrected QT interval [QTc] intervals) from pre-dose values. • Specific respiratory safety parameters: adverse respiratory events as monitored by spirometry including Forced expiratory volume at 1 minute (FEV1.0), respiratory rate, and pulse oximetry.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 5 I.U. IV oxytocin.	• Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin. • PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC, Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit.
Exploratory	
• To evaluate endogenous plasma oxytocin concentrations in non-pregnant females in	• Pre-dose plasma concentrations of oxytocin.

Objectives	Endpoints
the presence and absence of the combined oral contraceptive.	
• To compare the IH pharmacokinetics of oxytocin between Cohort A (subjects on combined oral contraceptive) and Cohort B (subjects using a non-hormonal form of contraception).	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2, will be compared as data permit.
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• Cmax, AUC, t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

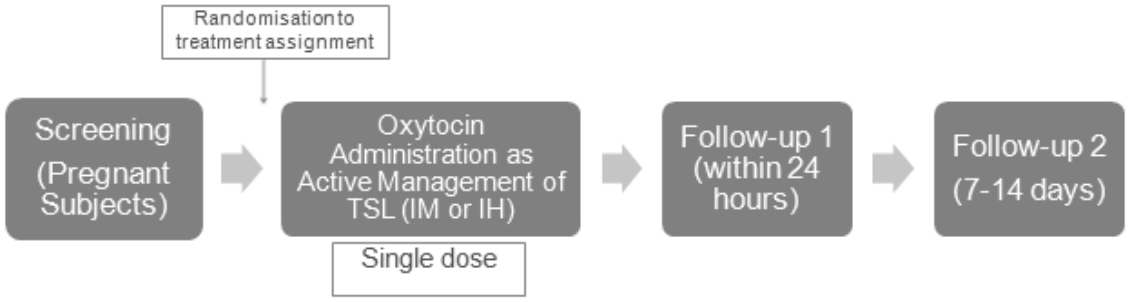
3.3. Groups 1 and 2: Women in TSL and Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Exploratory	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2.	• Cp10, Cp20, Cp30, AUC(0-3h) Cmax, AUC(0-3h) AUC(0-∞), and t1/2 will be compared as data permit.

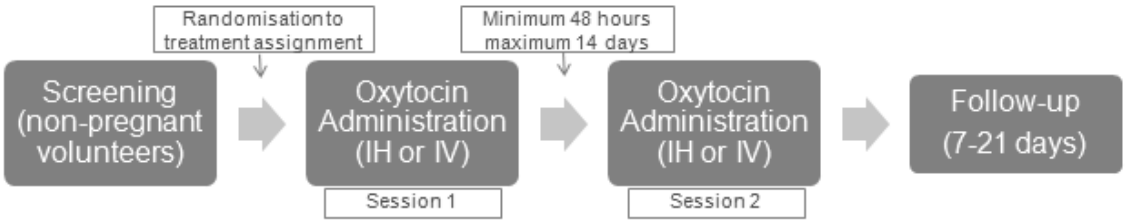
4. STUDY DESIGN

4.1. Overall Design

4.1.1. Study Schematic Group 1: Women in TSL



4.1.2. Study Schematic Group 2: Non-pregnant, non-lactating females of child bearing potential



4.1.3. Study Design Detail

This study will enrol two groups.

Group 1 - Women in TSL

Group 1 will enrol women with an uncomplicated pregnancy, and main phase procedures will occur during TSL. Subjects will be randomized to receive either IH or IM oxytocin as active management of TSL. The specific timing of this dose will be as per local standard of care.[1]

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Group 2 will enrol healthy, non-pregnant, non-lactating female subjects of childbearing potential, and each subject will participate in 2 dosing sessions. Group 2 will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive, and Cohort B will enrol women who are not using a hormonal form of contraceptive. Group 2 subjects will receive IH oxytocin at one dosing session, and IV oxytocin at the other dosing session; the order of IH versus IV oxytocin administration will be randomly assigned.

PK samples will be analysed periodically throughout the study duration to enable development of the population PK model and derivation of PK parameters via non-compartmental methods, as data permits.

No formal interim analysis is planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: IH, IM in Group 1 and IH in Group 2 Cohort A in order to assess if dose escalation is required.

[1] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

4.1.3.1. Pregnant Females (Group 1)

Subjects will review the study information and if they agree to participate, sign the informed consent form. For most subjects this is expected to take place at an outpatient antenatal visit, or additional study-specific screening visit. If a subject meets all inclusion/exclusion criteria for the study, she will be eligible for enrolment in the study.

To facilitate recruitment, and provide subjects ample time to consider participation, screening may occur any time after 18 weeks gestation (based on estimated date of delivery). See time and events (T&E) table in Section 7.1 for details.

4.1.3.2. Non-pregnant Females (Group 2)

Subjects will review the study information and if they agree to participate, sign the informed consent form. If a subject meets all inclusion/exclusion criteria for the study, she will be enrolled in the study.

Screening may occur within 28 days prior to randomization for non-pregnant volunteers. If a subject falls outside this window prior to randomization and enrolment, she must be re-screened. Certain screening procedures may not be required to be repeated; see T&E (Section 7.1) for details.

Group 2 subjects will take part in 2 dosing sessions, which must be conducted a minimum of 48 hours apart. It is recommended that subjects complete Session 2 within 14 days of Session 1. Subjects will be randomized to receive either IH or IV oxytocin during Session 1, and to receive the other treatment during Session 2, such that all subjects in Group 2 receive both treatments over the course of the 2 sessions.

4.1.4. ROTAHALER Inhaler Training

The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner (refer to Section 6.7). Subjects will be instructed by the investigator/designee to use an inspiration technique (2 inhalations) that enables maximal inhalation of the ROTACAPS powder capsule contents (refer to Section 6.7 for full details). This will ensure optimal and consistent drug delivery (full instructions available in the Study Reference Manual [SRM]).

4.1.5. Length of Stay for All Subjects

Group 1 - Women in TSL

Subjects in Group 1 will be admitted to hospital during labour as part of their routine care, and will be required to remain inpatient for a minimum of 4 hours after receiving any study-related dose of oxytocin. After final PK collection, subjects will be finished with study procedures and the main phase of the study will be considered complete. Discharge from hospital will be determined by the subject's medical provider.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

Subjects in Group 2 will be admitted to the clinical unit prior to dosing on Day 1 and are to remain inpatient until at least 4 hours after dosing. Discharge will occur at the discretion of the investigator.

4.2. Treatment Arms and Duration

Screening	Group 1: All screening assessments to be completed after the 18th week of pregnancy (based on estimated date of delivery) Group 2: All screening assessments to be completed within 28 days prior to the first dose
Treatment Session	Group 1: Each subject will take part in 1 dosing session. Group 2: Each subject will take part in 2 dosing sessions
Treatment Arms[1]	Group 1: Subjects will be randomised to receive one of the following study treatments: • 400 mcg IH oxytocin • 10 I.U. IM oxytocin Group 2: Subjects will receive both of the following study treatments over the course of two dosing sessions: • 400 mcg IH oxytocin • 5 I.U. IV oxytocin
Follow-up	**Group 1:** Follow Up 1 – Within approximately 24 hours post dose. **Group 1:** Follow Up 2 – At least 7 days and no greater than 14 days after study drug administration. Both visits may be conducted in-person or via telephone. **Group 2:** At least 7 days and no greater than 21 days after last study drug administration. This visit will be conducted in-person. If warranted, additional follow-up visits may be scheduled for both Groups.
Total Duration	Group 1: Screening after 18th week of pregnancy (i.e. within 168 days of 1 dosing session) + follow up of 7 - 14 days = approximately 183 days Group 2: Screening within 28 days of dosing session 1 + 2 dosing sessions with a maximum of 14 days between dosing + follow-up of 7 –

	21 days = 64 days

[1] See Section 6.4 for possible dose adjustment to IH oxytocin.

4.3. Type and Number of Subjects

Sufficient subjects will be screened such that approximately 20 subjects complete all study procedures in Group 1, and approximately 10 subjects complete all study procedures in Group 2 (approximately 5 in each cohort of Group 2). Refer to Section 6.3 for treatment assignment information.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited and assigned to the same treatment at the discretion of the Sponsor. Replacement subjects will complete all study procedures as outlined in Section 7.1.

If the PK variability between subjects in Group 1 is higher than expected, it may be required to increase the sample size up to a maximum of 10 additional subjects per treatment group for IH and IM. In the event of this, sufficient subjects will be screened such that a maximum of 45 subjects complete Group 1.

If a dose adjustment is required in either group, additional subjects may be recruited such that a full 10 subjects receive the final IH or IV dose. See Section 6.4.1 for more details.

4.4. Design Justification

Group 1 - Women in TSL

This trial uses a randomized, single-dose approach to assign women in TSL to receive oxytocin by one of two routes: IM or IH. No placebo is being used, as the current standard of care is to administer oxytocin as active management of TSL to prevent PPH.

Group 2 - Non-pregnant, non-lactating females of child bearing potential

A group of non-pregnant, non-lactating women of childbearing potential will receive IH and IV oxytocin. This group will be divided into two cohorts: Cohort A will enrol women on the combined oral contraceptive. This cohort will serve as a control group, as they most closely resemble the population enrolled in the FTIH study. Cohort B will enrol women using a non-hormonal form of contraception. This comparison group will help characterize the effect of oral contraceptives on endogenous oxytocin production and the PK profile of oxytocin.

Blinding

This study uses an open-label design.

4.5. Dose Justification

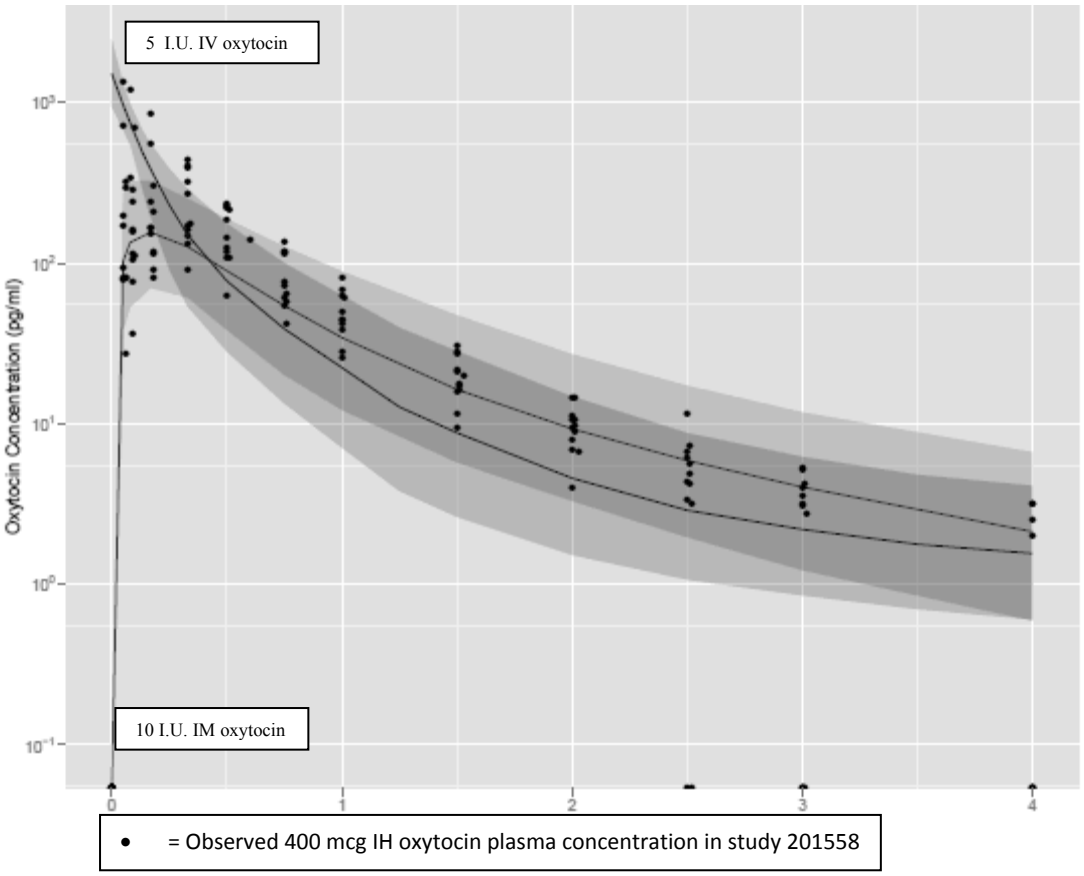
Single inhaled doses of oxytocin (50-600 mcg) have been generally well tolerated in the FTIH study, with no emerging safety signals, in healthy, non-pregnant, premenopausal female subjects (Study 201558) [GlaxoSmithKline Document Number 2016N277949_00; see also Section 2.2.1]. Following inhaled administration oxytocin was rapidly absorbed into the systemic circulation (tmax ranging from 0.05 to 0.50 h) with systemic exposure (Cmax and AUC) increasing with inhaled dose in an approximately proportional manner between 200 and 600 mcg. In general, the shape of the observed oxytocin concentration-time profile following inhaled administration was consistent with that following IM administration.

Based on the data from the FTIH study, and assuming that the PK characteristics of IH and IM oxytocin are similar in TSL compared with non-pregnant women, the 400 mcg inhaled dose is predicted to be an effective dose in women in TSL by ensuring that the systemic exposure (Cp10, Cp30 and AUC(0-3 h) following IH dosing is at least that following IM administration at the approved dose of 10 I.U. This would be based on the adjusted geometric mean ratio (90% Confidence Interval [CI]) treatment comparisons for Cp10, Cp30 and AUC (0-3 h) following 400 mcg IH compared with 10 I.U. IM, namely 1.10 (0.85,1.43), 1.65 (1.30, 2.09) and 1.27 (1.07, 1.50) respectively in study 201558. The PK parameters (Cp10, Cp30 and AUC(0-3 h)) have been selected to ensure onset and duration of action of the IH product is at least comparable to IM.

The clinical safety and reported AEs with oxytocin correlates to Cmax, with the Cmax of 10 I.U. IV representing the upper bounds of what could be considered safe in current clinical practice (AEs include flushing, which can cause a transient decrease in blood pressure and reflex tachycardia; see the Oxytocin Summary of Product Characteristics for more information). The recommendation in the United Kingdom (UK) in clinical practice has been to reduce the IV dose to 5 I.U. IV or administer by a controlled IV infusion [Bolton, 2003].

Minimising the risk of high Cmax levels of oxytocin following the IH administration is therefore important. Based on a comparison of model predicted systemic exposure following IV administration to non-pregnant, premenopausal female subjects with observed PK profiles following 400 mcg IH oxytocin, it is anticipated that Cmax following administration of the 400 mcg dose will not markedly exceed values following 5 I.U. IV bolus oxytocin (Figure 2). The inclusion of the 5 I.U. IV dose will allow an assessment of the potential safety and PK of the inhaled formulation compared to IV route of administration.

Figure 2 **Model predicted profiles (median (95%PI)) following IM (10 I.U. and IV bolus (5 I.U. administration of oxytocin overlaid with observed plasma concentrations of oxytocin following 400 mcg IH oxytocin to healthy non-pregnant females**



Whilst published literature on the PK of oxytocin in non-pregnant and pregnant women is limited there is some evidence to suggest that the metabolic clearance of oxytocin may increase during pregnancy. This may be related to degradation by the circulating aminopeptidase, oxytocinase, and/or pregnancy-related changes in hepatic and renal function [Syntocinon, 2014;Thornton, 1990]. In addition, there may be circulating levels of endogenous oxytocin in the plasma in women in TSL [Thornton, 1988] and increases in blood volume (40-50%) and total body water [Costantine, 2014]. As a result of these pregnancy related changes, systemic exposure to oxytocin may differ between healthy non-pregnant women and women in TSL for a given dose and route of administration of oxytocin. However, given that any pregnancy-related changes in systemic clearance, and/or distribution and baseline oxytocin levels, are considered to equally impact on each route of administration (IV, IM and IH), it is considered that the relative ratio of IV to IM and IH exposure observed in non-pregnant women is likely to be maintained in pregnancy. The only exception may be if pregnancy results in marked changes in absorption profiles. However, in a study of inhalation profiles of non-pregnant and women in the third stage of labour, the inhalation endpoints appeared to be broadly similar across the two cohorts and any small changes are not considered to markedly impact the delivery of an inhaled product in the third stage of labour [GlaxoSmithKline

Document Number 2015N239682_00]. In addition, in a pre-clinical sheep model the ratio IH:IV was generally similar in non-pregnant and post-partum ewes (Data on file Monash). In the event of enhanced pulmonary absorption in pregnancy, the selected 400 mcg inhaled dose is predicted to have an approximate 2-fold safe cover for Cmax compared with an 10 I.U. IV bolus oxytocin (assumes linearity from 5 -10 I.U. IV).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GR121619 can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2015N240749_01] and oxytocin for parenteral administration [Syntocinon, 2014] . The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) – Inhaled Oxytocin – GR121619		
Bronchospasm, cough and dyspnoea, with increased *theoretical* risk in asthmatic subjects.	Oxytocin receptors are known to be expressed in human bronchial smooth muscle and up regulated by interleukin (IL)-13. Therefore, there is a hypothetical risk of bronchospasm, cough and dyspnoea.	See Section 5.2 for exclusion criteria. The oxytocin summary of product characteristics (SPC) does not list asthma as a contraindication to administration. Symptomatic wheezing may be treated with bronchodilator at the discretion of the investigator. Forced expiratory volume at 1 minute (FEV1) monitoring for both paradoxical and oxytocin induced bronchospasm Subjects with asthma or known pulmonary disease are excluded.
Hypotension, tachycardia and prolongation of QTc interval	Transient flushing, hypotension and tachycardia could be observed if the IH PK profile is comparable to an IM or IV oxytocin profile. Effects of oxytocin on the	Ongoing assessments of study subjects' cardiovascular function including blood pressure (BP), heart rate (HR) and ECG. Only single-dose IH, IM, or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Cardiovascular system (CVS) is unclear and contradictory in the literature but IV administered oxytocin can have a vasodilatory and negative inotropic effect in humans. Hypotension is thought to arise as a result of vascular smooth muscle relaxation and oxytocin binding to cardiac atrial OTR which leads to atrial natriuetic peptide (ANP) being transiently released into the systemic circulation. Prolongation of the QTc interval has been reported at the time of caesarean delivery with 10 IU IV oxytocin administration, rather than IM injection, in susceptible individuals	5 IU IV bolus injection routes of administration will be used as study treatment. Telemetry and frequent 12-lead ECGs will be used to monitor the healthy subject cohorts The 5 IU IV dose of oxytocin is the standard dose administered at the Rosie Maternity hospital post Caesarean Section. IV bolus will be given as a slow IV injection over 30 seconds with the option to change to a 5 minute infusion if frequent CV adverse effects are observed Exclusion of subjects with long QT syndrome, congenital cardiac abnormalities, and subjects taking anti-arrhythmic drugs. 12-lead ECG and telemetry covering Cmax in healthy subjects administered IH, IM and IV oxytocin
Insufficient uterotonic effect	The altered physiology and pharmacokinetics of women in the TSL my lead to a sub-optimal dose of inhaled oxytocin, resulting in a reduced or absent uterotonic effect.	In this setting, women in TSL and post-delivery are intensively observed. Therefore, any adverse events, including excessive blood loss due to unenhanced uterine contraction, will be managed in accordance with current local practice guidelines. This will usually include administration of additional uterotonic agents in the first instance. A follow-up within 24 h of discharge by the study team will be performed to specifically enquire if any late bleeding problems had

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		occurred. An interim analysis of IH and IM PK in the TSL group will be performed to ensure that the PK is in the acceptable range for efficacy to be anticipated.
Reference Intervention - IM Oxytocin / IV Oxytocin		
Hypotension, tachycardia and prolongation of QTc interval	See above section.	See above section. Subjects receiving the IV Oxytocin are required to have a systolic BP ≥ 90 Millimeter of mercury (mmHg) prior to dosing.
Myocardial Ischaemia and ST change on ECG	ECG changes consistent with myocardial ischaemia have been observed with 10 IU oxytocin IV bolus in healthy women associated with hypotension and tachycardia.	Oxytocic cardiovascular effects appear to be transient and persistent myocardial damage very rare and associated with 10 IU IV. Study is only using 5 IU IV as a slow IV bolus which is associated with a short lived increase in heart rate and reduction in BP but not ST changes on ECG in women undergoing Caesarean Section. Telemetry and 12-lead ECG monitoring in healthy subjects.
Abdominal pain	There is a hypothetical risk that IM oxytocin may trigger abdominal pain through contractions of the non-pregnant uterus in healthy women. Given the short half-life of oxytocin (approximately 30 minutes), the duration of a single abdominal pain episode	This is a theoretical possibility and not expected to occur. Ongoing assessments of study subjects' well-being along with vital signs and laboratory evaluations will be completed throughout the duration of the study. Abdominal pain which is clinically uncomfortable to the subject may be treated with paracetamol at the local

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	would be expected to be brief, not sustained and not recurrent in the absence of further oxytocin administration. Furthermore, no abdominal pain was observed in the FTiH study.	investigator's discretion.

4.6.2. Immunogenicity Risk

The oxytocin material used in the inhaled product is produced synthetically and so does not include any other protein/cell impuritites which might be intrinsically immunogenic. A review of the risk of immunogenicity of oxytocin and/or excipients was considered as part of the non-clinical safety studies but as the lymphoid tissues were not deemed to be pathologically affected and there were difficulties in generating a suitable assay, anti-drug antibodies (ADAs) were not measured. The FTIH study involved repeat dosing, and did not reveal any unexpected differences in PK which may have signalled the development of ADAs.

Oxytocin is an endogenous human peptide with a short systemic half-life and there are no reports of immunogenicity with oxytocin via parenteral administration. Thus it is considered unlikely that inhaled delivery of a small molecular weight (MW) peptide molecule like oxytocin would invoke an immunogenic response.

However, blood samples will be retained for anti-oxytocin antibody analysis if required in the event of an anaphylactic / allergic reaction (refer to Section 5.4.2) or other observation which would suggest an immunogenic effect.

4.6.3. Benefit Assessment and Overall Benefit:Risk Conclusion

Oxytocin has been administered to postpartum women for over 40 years via both the IM and IV routes, and has an established safety profile for each of these routes of administration. The FTIH study into IH oxytocin revealed no safety concerns for any of the subjects who received this new formulation. There are no direct clinical benefits to the volunteers within this study. The main contribution to their participation will be in the further development of a therapy (i.e. inhaled oxytocin) which may be ultimately used as a preventative therapy for postpartum haemorrhage in women during TSL in resource poor settings. It is fundamental to the project to clearly understand the PK of oxytocin following IH and IM administration to women in TSL in order to confirm the dose level that delivers a PK profile comparable to that of 10 I.U. IM (i.e. current standard of care in the developed world setting). Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with oxytocin (IH IM, and IV) are justified by the supporting data and overall benefit anticipated for women's health worldwide.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the investigator brochure for GR121619 [GlaxoSmithKline Document Number 2015N240749_01] and SPC for oxytocin administered IM or IV.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
All Groups: 1. Between 18 and 40 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
All Groups: 2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, and laboratory tests as required per protocol. Note: At time of randomisation, investigator or designee should confirm the subject feels fit and well, and is safely able to participate in the study. 3. Subject clinical chemistry and haematology values within an acceptable range for the population recruited and not of abnormal clinical significance. Note: Additional laboratory tests beyond those which are done as part of routine care (e.g. 28-week visit) are not required for subjects in Group 1. The investigator/designee may use his/her judgment in deciding whether to perform additional laboratory assessments to determine eligibility. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 4. Adequate peripheral venous access for cannulation.

Group 1 Only:

5. Currently pregnant, with an uncomplicated pregnancy as determined by the investigator or designee.
6. Estimated date of delivery within 24 weeks of screening.
7. Planned spontaneous vaginal birth and considered by investigator at low risk for PPH.
8. Planned birth in between the 37th and 42nd week of pregnancy.

   Note: Subjects can only receive study treatment if the onset of labour is between approximately 37 and 42 weeks estimated gestation. If a subject goes into labour before or after this timeframe, she should not receive study treatment.
9. Women who qualify for oxytocin as appropriate for active management of TSL and who agree to have active management.

Group 2 Only:

10. ECG normal, or abnormal and not clinically significant.
11. FEV1 >80% of predicted.
12. Systolic blood pressure ≥90 mmHg.

WEIGHT
Group 2 Only: 13. Body mass index (BMI) within the range 18 – 32 Kilogram (kg)/ meter $(m)^2$ (inclusive).

SEX
14. Female. Group 2, Cohort A Only: A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test), not lactating, and the following condition applies: a. Is of reproductive potential and agrees to use the same **combined estrogen and progestogen oral contraceptive** from 3 months prior to the first dose of study medication and until the follow-up contact. This method of contraception is only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method of contraception.

Group 2, Cohort B Only:

A female subject is eligible to participate if she is confirmed to be not pregnant at screening and on Day 1 (as confirmed by a negative serum or urine hCG test), not lactating, and one of the following conditions applies:

a. Is of reproductive potential and has been using the same **non-hormonal contraceptive method** (see List of Accep+ Nonhormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential [see Appendix 5] from 3 months prior to the first dose of study medication and until the follow-up contact.

b. Would be of reproductive potential, but has undergone bilateral tubal ligation or occlusion or bilateral salpingectomy at least 12 months prior to first dose of study medication.

c. Is of reproductive potential with only same sex partners or who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

These methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use their method(s) of contraception.

Of Note: Group 2, Cohort B will enrol women of reproductive potential if they agree to use a nonhormonal contraceptive method from at least one month prior to receiving study drug and until the follow-up assessment. Although condoms with spermicide are not considered a highly effective method of contraception, the risk of receiving study drug during pregnancy is minimal for the following reasons:

- Pregnancy testing must be negative at screening and on the first day of dosing.
- Dosing is completed no greater than 14 days from the start of dosing.
- Oxytocin has a well established rapid half-life.

If a patient happened to conceive during the time of dosing, study drug would be eliminated before implantation would occur.

INFORMED CONSENT
All Groups: 15. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
All Groups: 1. Postmenopausal as defined by gynaecological history. 2. Chronic lung condition of any etiology including asthma, Chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease or active Tuberculosis (TB). Note: Childhood asthma (resolved) is not exclusionary. 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 4. Blood pressure >140 systolic or >90 diastolic. **Group 1 Only:** 5. Females with planned Caesarean Section. 6. Females with significant medical complications as determined by investigator. **Group 2 Only:** 7. Currently breastfeeding or lactating. 8. QT duration corrected for heart rate by Fridericia's formula (QTcF) >450 milliseconds (msec). 9. Alanine aminotransferase (ALT) and bilirubin >1.5 Upper Limit of Normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 10. Subjects with highly-active or symptomatic gynaecological disorders (such as large symptomatic fibroids).

CONCOMITANT MEDICATIONS
All Groups: 11. Prescription or non-prescription drugs not approved by the investigator (refer to Section 6.12.1 for approved medications). 12. Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) prior to administration of study-related oxytocin.

RELEVANT HABITS
All Groups: 13. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >14 units. One unit is equivalent to 8 grams (g) of alcohol: a half-pint (~240 milliliter [ml]) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 14. Current smokers or subjects with a history of smoking within 6 months of screening, or with a total pack year history of >5 pack years. a. Confirmatory use via a Smokerlyzer is at the discretion of the local investigator, but is advised if the subject's recent smoking history is in doubt.

CONTRAINDICATIONS
All Groups: 15. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation (e.g. allergy to any previous inhaler use). 16. Participation in another clinical trial, which in the opinion of the investigator, jeopardizes the subject's safety or study outcomes.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
All Groups: 17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 18. The subject has participated in a clinical trial and has received an investigation product within the following time period prior to the first dosing day in the current study: 30 days or twice the duration of the biological effect of the investigational product (whichever is longer). 19. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. **Group 2 Only:** 20. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result. 21. A positive Human Immunodeficiency Virus (HIV) antibody test. 22. A positive pre-study drugs of abuse test (not explained by diet or approved concomitant medications). 23. A positive alcohol breath test.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.4).

5.3.1. Re-screening

If a subject fails screening, she may be rescreened one additional time.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Pregnancy Complication Stopping Criteria (Group 1 Only)

Any complication requiring clinical intervention which no longer allows for a vaginal delivery or safe completion of study procedures will be cause for immediate withdrawal from the study. Investigators should continue to manage any pregnancy complication per local guidelines, and record any associated AE/SAE or concomitant medication. This includes the need for additional uterotonic administration.

5.4.2. Anaphylaxis Stopping Criteria

Clinical signs or symptoms of anaphylaxis / allergic reaction to IH oxytocin will be an automatic stopping criterion. Stored serum samples will be analysed for anti-oxytocin antibody analysis for affected subjects as detailed in Section 7.5.2. The samples will be analysed for Immunoglobulin E (IgE)/ Immunoglobulin G (IgG) anti-oxytocin titres ± biochemical markers of mast cell degranulation (e.g. tryptase) in the event of an anaphylactic / allergic reaction occurring.

5.4.3. QTc Stopping Criteria (Group 2 Only)

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

QTcF is proposed to be used for this study. If a subject meets either of the following bulleted criterion below, she will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline: Increase in QTcF >60 msec.

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be withdrawn from the study.

5.4.4. Blood Pressure Stopping Criteria (Group 2 Only)

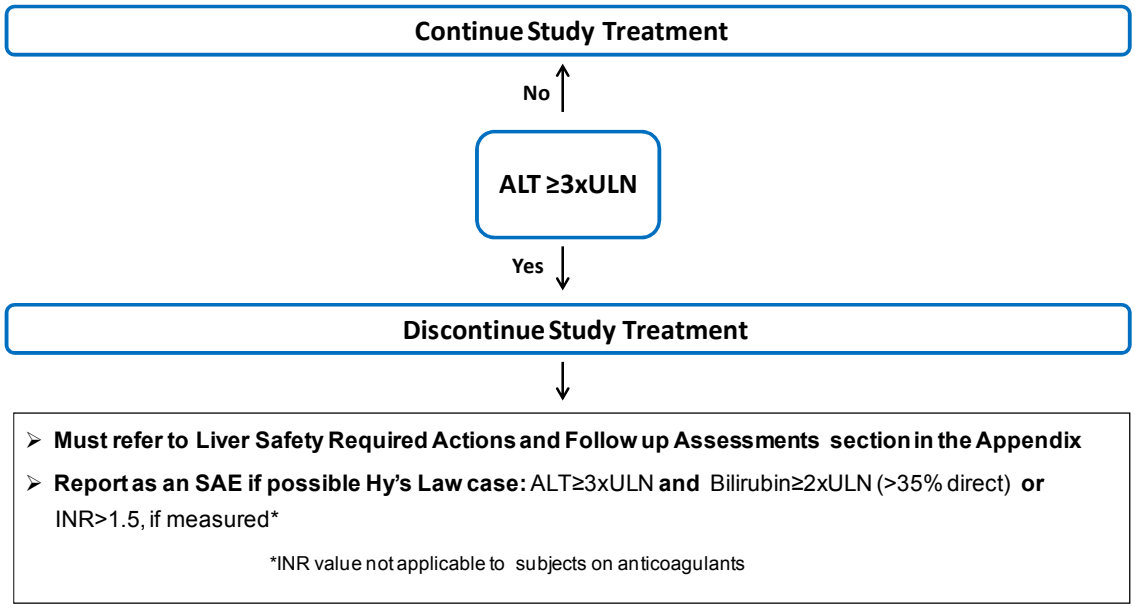
Subjects with a pre-dose systolic blood pressure of <90 mm Hg should not be dosed until systolic blood pressure is ≥90 mm Hg.

5.4.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit(s).

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Table 1 Study Treatment Information

	Study Treatment		
Product name:	Oxytocin (GR121619 capsule for inhalation)	Oxytocin	Oxytocin
Formulation description:	Powder Blend for Inhalation	Solution for Infusion	Solution for Infusion
Dosage form:	Inhalation powder, hard capsule	1ml ampoule	1ml ampoule
Unit dose strengths:	400 mcg 200 mcg	5 I.U./mL, or 10 I.U./mL	5 I.U./mL, or 10 I.U./mL
Route of Administration	For oral inhalation	Intramuscular (thigh)	Intravenous
Dosing instructions:	Capsule unit dose dispensed by ROTAHALER inhaler	Standard intramuscular injection	Adminster as a 30-second bolus
Physical description:	Colourless and clear HPMC capsules containing a white powder	Colourless and clear sterile solution	Colourless and clear sterile solution
Device:	ROTAHALER inhaler	Needle/Syringe	Intravenous Infusion Device

6.2. Medical Devices

The GSK manufactured medical device (or device manufactured for GSK by a third party) provided for use in this study is a high airflow resistance capsule-based inhaler (Modified Air Inlet ROTAHALER DPI device).

Instructions for medical device use are provided in Section 6.7. Further details on use of the device are provided in the SRM.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 12.4.

6.3. Treatment Assignment

Subjects in Group 1 will be assigned to one of two treatments (IH oxytocin or IM oxytocin). Subjects in Group 2 will receive both IH and IV oxytocin in separate dosing sessions in a cross over design. Treatment assignment in Group 1, and order of dosing in Group 2, will be done in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in Table 2:

Table 2 Treatment Assignment

Group	Session	Treatment [1]	Number of Subjects[2]
Group 1	1	400 mcg IH oxytocin	10
		10 I.U. IM Oxytocin	10
Group 2, Cohort A	1	400 mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	
Group 2, Cohort B	1	400mcg IH oxytocin or 5 I.U. IV oxytocin	5
	2	400 mcg IH oxytocin or 5 I.U. IV oxytocin	

[1] See Section 6.4 for possible dose adjustment.

[2] See Section 9.2.2 for possible adjustment to subject numbers to Group 1

6.4. Planned Dose Adjustments

There is no plan to adjust the dose of IH oxytocin in this study. However, if systemic exposure seen in 400 mcg IH oxytocin in TSL subjects is less than expected and not comparable to the 10 I.U. IM profile, a consideration to escalate the dose to 600 mcg may be made as detailed in Section 6.4.1.

For Group 2, if an exaggerated physicological response is seen with the IV dose, such as increased heart rate and decreased blood pressure, then consideration will be given to changing to a 5-minute infusion.

6.4.1. Dose Adjustment

The decision to adjust the IH dose in women in TSL will be determined by the GSK study team based on Group 1 PK data in TSL and Group 2, Cohort A PK data. After a minimum of n=5 women in TSL have received 400 mcg IH and 10 I.U. IM and a minimum of n=5 non-pregnant women on the combined oral contraceptive (Group 2, Cohort A) have received 400 mcg IH oxytocin, PK samples will be analysed and PK parameters derived (including but not limited to Cp10, Cp30 and AUC(0-3h)).

The median Cp10 will be estimated for women in TSL for each dose group (IH or IM) and the median ratio (IH/IM; n=5) derived. Based on the estimated ratio, the dose of IH

oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased per the criteria described in Table 3:

Table 3 Dose Adjustment Decision Criteria

Median Ratio IH/IM	Decision
< 0.5	Consider study halt and review data.
≥ 0.5 to <0.7	Consider dose adjust to 600 mcg IH in women in TSL.
≥ 0.7	Continue with 400 mcg IH dose.

If a decision to increase the dose is made, additional subjects will be enrolled into Group 1 such that 10 subjects receive the 600 mcg IH oxytocin dose.

6.5. Blinding

This will be an open-label study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

- The investigator/designee will be trained to load the ROTACAPS powder capsule into the device, prime the dose and instruct the subjects to inhale from the ROTAHALER inhaler in the appropriate manner. The investigator/designee will always load and prime the ROTACAPS powder capsule in the device before the subject self-administers an IH oxytocin dose
- All subjects will be taught by the investigator/designee to use the device in the "full-tilt" position and to use a "fast and deep" inspiration technique per inhalation, to achieve two rapidly consecutive maximal inhalations for IH oxytocin administration. This will ensure optimal and consistent treatment delivery. For subjects, the training session will be at any time during the 28-day Screening Period, as deemed appropriate by the investigator/designee.
- ROTACAPS powder capsules should be kept in their sealed packaging at room temperature (15-25°Centigrade [C]). The packaging should only be opened immediately prior to use.
- ROTAHALER inhaler devices will be supplied in bulk and unlabelled to the site. After dosing all ROTAHALER inhaler devices will be uniquely labelled and retained after each dosing session. The devices (which should not be opened up at the clinical study site) will be stored until further instruction from the sponsor is received.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.8. Compliance with Study Treatment Administration

Per ROTACAPS powder capsule dose, each subject will be asked to inhale twice from the ROTAHALER inhaler to reduce the possibility of inadequate administration due to a single poor inhalation manoeuvre. If failure of the ROTACAPS powder capsule actuation is suspected by the investigator (i.e. due to failure to open the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose using the same capsule.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Group 1 – Women in TSL

Following randomisation and any pre-dose procedures, subjects will receive a single study treatment as active management of TSL. The specific timing of this dose will be as per local standard of care.[2]

Administration will be documented in the source documents and reported in the Case report form (CRF).

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Following randomisation and all pre-dose procedures, subjects will receive two doses of oxytocin, separated by at least 48 hours. Randomisation will determine the order in which the IH and IV formulation is administered.

Administration will be documented in the source documents and reported in the Case report form (CRF).

6.9. Treatment of Study Treatment Overdose

For this study, any dose of the following compounds will be considered an overdose when administered as part of study procedures:

- IH oxytocin > 400 mcg
    - If study dose is increased to 600 mcg, then an overdose will be considered any dose > 600 mcg.
- Oxytocin > 10 I.U. IM
- Oxytocin > 5 I.U. IV

Note: Group 1 subjects may receive additional doses of oxytocin (IM or IV) when required as part of their general care and as clinically indicated. Additional doses of oxytocin will be recorded as concomitant medications, as will any related AEs.

General medical management consists of supportive care.

GSK does not recommend specific treatment for an overdose.

In the event of a study drug overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

[2] For information only: Standard of care at proposed clinical site is to administer the oxytocic drug by IM injection with the birth of the anterior shoulder, or immediately after the birth of the baby and before the cord is clamped and cut.

2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until oxytocin can no longer be detected systemically (at least 4 hours).
3. Obtain an additional plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because either only healthy volunteers are eligible for study participation, or there are other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of postpartum subjects' medical conditions, whether or not GSK is providing specific post-study treatment.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Meals and Dietary Restrictions

There are no dietary restrictions for subjects in either cohort.

6.11.2. Caffeine and Alcohol

Group 1 – Women in TSL

- There are no restrictions for Group 1.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 12 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

6.11.3. Activity

Group 1 – Women in TSL

There are no activity restrictions.

Group 2 – Non-pregnant, non-lactating females of child bearing potential

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses equal to or below the maximum recommended daily dose, is permitted for use during the screening period or at any time deemed necessary by the investigator or subject. All concomitant medication related to routine care during pregnancy and delivery is allowed (including pain relief [e.g. gas/air mixture] and epidural), and other medication may be considered on a case by case basis by the investigator or designee (in consultation with the Medical Monitor if required).

The start and stop time of any concomitant medications administered at any time during labour (including nitrous oxide gas/air mixtures) should be documented on the CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications will result in immediate withdrawal of subject:

- Oxytocin for any reason (including, but not limited to, induction or augmentation of labour) before or after administration of study-related oxytocin.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table in Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
    1. 12-lead ECG

2. vital signs
3. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic, immunogenic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

7.1.1. Time and Events Table – General Overview

Group 1

Procedure	Study Day			
	Screening[4]	Main Phase	Follow – Up 1 (approx. 24 hours post dose)	Follow – Up 2 (7-14 days post dose)
Informed Consent and Demography	X			
Brief Physical Examination	X			
Medical history (incl. substance abuse)	X			
Inhaler device training / education session	X			
Laboratory assessments[1]	X			
Vital signs[2]	X	X		
Pharmacokinetic blood sample		X		
Oxytocin Administration (IM/IH)		X		
Full blood count		X		
Labour Events Documentation		X		
Device acceptability questionnaire[3]		X		
Prior / concomitant medication review	X	X	X	X
AE review		---------- continuous review ----------		
SAE review	---------- continuous review ----------			

1. Only required if done as part of routine care. Additional study-specific laboratory assessments not required.
2. Includes blood pressure, heart rate, temperature, respiratory rate
3. Only to be used when randomized to IH oxytocin
4. To be completed after 18th week of pregnancy (based on estimated date of delivery).

Group 2

Procedure	Study Day		
	Screening[5]	**Main Phase**	**Follow - Up (7-21 days post dose)**
Informed Consent and Demography	X		
Brief Physical Examination	X	X	
Medical history	X		
Pregnancy test	X	X	
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X	X	
HIV, Hep B and Hep C screen[2]	X		
Inhaler device training / education session	X		
Laboratory assessments (including liver chemistries)	X	X	
Immunogenicity sample		X	X
12-lead ECG	X[4]	X	
CardiacTelemetry		X	
Vital signs[3]	X	X	
Spirometry (FEV-1)[4]	X	X	
Admission to unit		X	
Pharmacokinetic blood sample	X	X	
Oxytocin Administration (IH or IV)		X	
Prior / concomitant medication review	X	X	X
AE review		------ continuous review ----------	
SAE review	---------- continuous review ----------		
Discharge from unit		X	

1. Smokerlyzer at PI/designee discretion if smoking history in question.
2. If test otherwise performed within 3 months prior to first dose of study treatment, repeat testing at screening is not required.
3. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2.
4. Performed in triplicate.
5. To be completed within 28 days of randomization.

7.1.2. Time and Events – Main Phase Procedures

Group 1

		Time post dose										
Procedure	Pre-dose	3 min	5 min	10 min	15 min	20 min	30 min	1 hr	2 hr	2.5 hr	3 hr	4 hr
Vital signs[1]							X		X			
Pharmacokinetic blood sample	X[2]	X	X	X	X	X	X	X	X	X	X	X
Prior medication review	X											
Concomitant medication review		---------- continuous review ----------										
AE review		---------- continuous review ----------										
SAE Review	---------- continuous review ----------											
Device Acceptability Questionnaire[3]												X
Full Blood Count	X											X

1. Includes blood pressure, heart rate, temperature, respiratory rate
2. Predose PK sample to be taken immediately prior to administration of study treatment
3. Only to be administered when randomized to IH oxytocin

Group 2 – Sessions 1 and 2

		Time Post Dose														
Procedure	Pre-dose	2 min	3 min	5 min	8 min	10 min	15 min	20 min	30 min	45 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr
Brief Physical Exam	X															
Pregnancy Test	X															
Alcohol Breath Test, Smokerlyzer, Urine Drug Screen[1]	X															
Vital signs[2]	X			X			X		X		X					X
12-lead ECG	X	X				X		X	X		X					X
CardiacTelemetry	----------Continuous----------															
Spirometry[3]	X										X					
Pharmacokinetic blood sample	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sample	X															
Laboratory assessments (including liver chemistries)	X															X
Prior medication review	X															
Concomitant medication review		---------- continuous review ----------														
AE review		---------- continuous review ----------														
SAE Review	---------- continuous review ----------															
Discharge from unit[4]																X

1. Smokerlyzer at Principal Investigator (PI)/designee discretion if smoking history in question.
2. Includes blood pressure, heart rate, temperature, respiratory rate, and SpO2
3. FEV 1.0 will be performed in triplicate at each time point. Record all three values on source document, and record best effort in eCRF.
4. Discharge at PI discretion, no sooner than 4-hours post-dose.
5. 3 pre-dose samples: approximately 1 hr pre-dose, 30 minutes pre-dose, and 15 minutes pre-dose

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management [e.g. brief physical exam, laboratory assessments] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (see Section 12.3).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF or appropriate source document.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigators Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Adverse Events of Special Interest (AESI)

Any problem related to the delivery of the placenta or postpartum haemorrhage should be documented as an AESI using the appropriate case report form (CRF).

7.3.3. Pregnancy

Group 2 Only:

- Details of all pregnancies will be collected after the start of dosing and until follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.3.4. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Section 12.4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 12.3.6 and Appendix 3 of the Protocol.

7.3.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

  NOTE: The method of documenting Medical Device Incidents is provided in Appendix 4.

7.3.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.

- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor or SAE coordinator.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.3.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.3.5. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen if palpable).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.6. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate (unless otherwise specified in T&E).

7.3.7. Documentation of Labour Events

The time that the following labour events occurred will be collected:

- Time of crowning
- Time of birth
- Time of delivery of placenta

7.3.8. Electrocardiogram (ECG) (Group 2 Only)

- Triplicate 12-lead ECGs will be obtained at screening as listed in Section 7.1.1.
- Single 12-lead ECGs will be obtained at each timepoint as listed in Section 7.1.2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At all single 12-lead ECG time-points if QTc >450, repeat twice and take average reading.

7.3.9. Continuous Cardiac Telemetry (Group 2 Only)

Continuous cardiac telemetry will be started at least 10 minutes pre-dose (to obtain a stable reading) and continue until at least the first hour after IV and IH placebo / oxytocin administration and then as deemed necessary by the investigator. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

7.3.10. Device Acceptability Questionnaire (Group 1 Only)

A device acceptability questionnaire will be administered to subjects in Group 1 following use of the ROTAHALER (Appendix 7).

7.3.11. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as required by Section 7.1 and defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Tests performed as part of routine care in Group 1.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Subjects in Group 1 are not required to undergo additional laboratory assessments beyond those done as part of their routine care. However, the investigator/designee may conduct any of the tests listed in Table 4 in order to confirm eligibility. Haematology, clinical chemistry, and additional parameters to be tested in all Group 2 subjects are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>White Blood Cell (WBC) count with Differential</u>:</td></tr>
<tr><td>Red Blood Cell (RBC) Count</td><td>Mean Corpuscular Volume (MCV)</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>Mean Corpuscular Hemoglobin (MCH)</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate aminotransferase (AST) (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine aminotransferase (ALT) (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>HIV

Hepatitis B (HBsAg)</td></tr>
</table>

	Hepatitis C (Hep C antibody) Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of suspected non-child bearing potential only) Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) Serum or urine hCG Pregnancy test (Group 2 only) [2]
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2 and Appendix 2 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.	

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of oxytocin will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

At each time point, 4 mL of blood will be collected into K2 or K3 Ethylenediaminetetraacetic acid (EDTA) tubes and stored on ice for up to 2 hours prior to centrifugation in a refrigerated centrifuge. Further details regarding collection/shipping procedures are provided in the SRM

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of oxytocin will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

7.5. Biomarkers

7.5.1. Pharmacodynamic Markers

Pre and post-delivery full blood counts will be collected from Group 1 subjects to assess for a change in haemoglobin levels.

7.5.2. Immunogenicity

Blood samples will be taken at the time points specified in the Time and Events Table (Section 7.1) to assess the immunogenicity of oxytocin.

Pre- and post-dose samples will be retained in the event that further immunologic tests are deemed necessary to support observations of unexpected anaphylaxis/ hypersensitivity, and / or a PK profile for IH oxytocin in any Dosing Session which is regarded by the GSK Study Team to be reasonably attributable to circulating anti-oxytocin antibodies.

Details of the collection / shipping procedures are provided in the SRM.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to characterize the pharmacokinetics of 400 mcg IH oxytocin and 10 I.U. IM oxytocin in women in TSL.

No formal hypotheses will be tested, however, the following comparisons are of interest, within Group 1, (IH vs. IM) and between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on oral contraception) and between Cohorts A and B in Group 2 (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive). For each PK endpoint of interest, point estimates and corresponding two-sided 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference) to provide the range of plausible values for the comparisons of interest.

9.2. Sample Size Considerations

A sufficient number of subjects will be enrolled to ensure approximately 20 evaluable subjects (10 in each of the IM and IH groups) complete all dosing and critical assessments in Group 1, as well as 5 subjects in each cohort in Group 2. Whilst sample size is based on feasibility, precision calculation was also done to approximate the estimate of the expected half width of 90% CI around point estimate for the main comparison of interest (IH oxytocin to 10 I.U. IM oxytocin in women in TSL) using a t-test.

Table 5 illustrates the associated 90% CIs for the mean treatment ratios, assuming between subject SDs of 0.424 and 0.601 (SDs are based on log transformed data) for AUC (0-3h) and CP10 respectively, for the comparisons of interest detailed in Section 9.1. Calculations are based on a symmetric two-tailed procedure on the loge scale and a type I error rate of 10%. These values represent estimates of the between-subject variability observed in the FTIH study 201558 [GlaxoSmithKline Document Number 2016N277949_00].

Table 5 Estimated 90% Confidence Intervals for Treatment Ratios

N	Parameter	Between Subject Standard Deviation (SD)	Estimated Treatment Ratio	Precision	Expected 90% CI
10	AUC(0-3h)	0.424 (CVb=44.35%)	1	38.30%	(0.72, 1.38)
10	Cp10	0.601 (Cvb=65.96%)	1	58.20%	(0.63,1.58)

The precision estimates are deemed acceptable to assess the study objectives at this stage of development.

9.2.1. Sample Size Sensitivity

Considering the variability of AUC(0-3h) and Cp10, Table 6 shows the scenarios for different sample size and the precision estimates for IH vs. IM in Group 1.

Table 6 Estimated 90% Confidence Intervals for Treatment Ratios for Sample Size Sensitivity

%CVb	N	Precision	Assuming ratio 1, the confidence interval
44.35%	5	61.90%	(0.61, 1.61)
	15	29.80%	(0.77,1.29)
65.96%	5	98.00%	(0.50, 1.98)
	15	44.80%	(0.69, 1.44)
	20	37.40%	(0.72,1.37)
85.35%*	5	131.90%	(0.43, 2.31)
	10	75.90%	(0.56, 1.75)
	15	57.60%	(0.63, 1.57)
	20	48.00%	(0.67, 1.48)

* 85.35% was the largest between subject CV for AUC(0-10) observed for FTIH study 201558 [GlaxoSmithKline Document Number:2016N277949_00]

9.2.2. Sample Size Re-estimation or Adjustment

No formal sample size re-estimation is planned for this study. However, if the variability is high (for example approaching 85%) then the sample size for Group 1 may be increased to a maximum of 10 additional subjects per treatment arm (IH and IM only).

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exist on the study database. This population will be used for summarizing screening failure reasons.
All Subjects Population	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays.
Pharmacokinetic Population	• Subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.

9.3.2. Interim Analysis

No formal interim analysis is planned. However, PK samples will be analysed and preliminary PK parameters derived following completion of 5 women on each of the following treatments: 400 mcg IH and 10 I.U. IM to women in TSL (Group 1) and 400 mcg IH to non-pregnant women on the combined oral contraceptive (Group 2 Cohort A). Based on the PK profiles the dose of IH oxytocin to be administered to women in TSL will either remain at 400 mcg or be increased (to 600 mcg) (See Section 6.4.1). This decision will be made by the study team in collaboration with the Principal Investigator.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

9.4.1.1. Safety Analysis

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.1.2. Pharmacokinetic Analysis

Pharmacokinetics analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline. Plasma oxytocin concentration-time data will be analyzed by non-compartmental methods with WinNonlin V6.3 or greater. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-3h) and AUC(0-∞)], the last observed quantifiable concentration (Clast), time of the last quantifiable concentration (tlast), Cp10, Cp20, Cp30 (observed plasma concentrations at 10, 20 and 30minutes post-dose, respectively), plasma clearance (CL; IV only), volume of distribution (V; IV only) and apparent terminal phase half-life (t1/2). Other PK parameters may also be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

If appropriate, a population PK analysis may also be conducted, in addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis.

9.4.2. Secondary Analyses

Statistical analyses of the PK parameter data will be performed by, or under direct auspices of Clinical Statistics, QSci.

9.4.2.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons within Group 1 IH vs. IM, point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3. Exploratory Analyses

9.4.3.1. Pharmacokinetic Analysis

For evaluating pharmacokinetic treatment comparisons between Group 1 and Group 2 (IH oxytocin comparison in TSL vs. non-pregnant women on the combined oral contraceptive), and within Group 2 between Cohorts A and B (IH and IV oxytocin comparison in non-pregnant women in the presence and absence of oral contraceptive), point estimates and corresponding two-sided 90% confidence intervals will be computed using a mixed effect model. Loge-transformed PK parameters will be analysed using the model with a fixed effect term for treatment and a random effect term for subject.

Further details of analysis and reporting of PK data will be given in the Reporting Analysis Plan (RAP).

9.4.3.2. Device Acceptability Questionnaire

In Group 1, subject satisfaction with device, including instructions and ease of use, will be assessed. The questionnaire is located in Section 12.7

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRFs <or> entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for

those required by local regulations to be maintained elsewhere), in a safe and secure location.

- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Frontiers in Pharmacology*. 2014. Volume 5. Article 65: 1-5.

GlaxoSmithKline Document Number 2015N234711_01. Study ID 201558. Clinical Pharmacology Study Protocol. A single centre, single blind study to investigate the safety, tolerability and pharmacokinetics of single doses of oxytocin (GR121619) administered via an inhaled route in healthy female volunteers. 16-NOV-2015.

GlaxoSmithKline Document Number 2015N239682_00. Study ID 201248 – Clinical Pharmacology Study Report. An enabling study to compare the inhalation profiles of women in the third stage of labour to those of non-pregnant female volunteers and to explore whether there are any differences which could impact the delivery of an inhaled medicinal product, 16-OCT-2016.

GlaxoSmithKline Document Number 2015N240749_01. GR121619 Investigator's Brochure, AUG-2015.

GlaxoSmithKline Document Number 2016N277949_00. Study ID 201558 – Clinical Study Report.. 30-JUN-2016.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.

Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2014, *Issue* 2. *Art. No.: CD003249. DOI:* 10.1002/14651858.CD003249.pub3.

Prankerd RJ, Nguyen T, Ibrahim JP, et al. Pulmonary Delivery of an Ultra-Fine Oxytocin Dry Powder Formulation: Potential for Treatment of Postpartum Haemorrhage in Developing Countries. 2013; *PLoS One*. Vol 8: 12: Article e82965

Syntocinon Summary of Product Characteristics, Novartis, 2014

Thornton S, Davison JM, Baylis PH. Effect of human pregnancy on metabolic clearance rate of oxytocin. *American Physiological Society*. 1990. 0363-6119: R21-R24.

Thornton S, Davison JM, Baylis PH. Plasma oxytocin during third stage of labour: comparison of natural and active management.*BMJ.* 1988. Volume 297:167-169.

WHO Model List of Essential Medicines 18th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO Model List of Essential Medicines for Children 4th list (April 2013). Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed May 26, 2015.

WHO, UNICEF, UNFPA. The World Bank World Health Organization (WHO) Press. Trends in Maternal Mortality: 1990 to 2008: Estimates Developed by WHO, UNICEF, UNFPA and The World Bank. Geneva*: WHO,* 2010.

12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

Abbreviations

ADAs	Anti drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANP	Atrial natriuretic peptide
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-3)	Area under the concentration-time curve from time zero (pre-dose) to three hours
AUC(0-∞)	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
Ca2+	Intracellular calcium
CI	Confidence Interval
CL	Plasma clearance
Clast	last observed quantifiable concentration
Cmax	Maximum observed plasma concentration
COC	Combined oral contraceptive
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
Cp10	Observed plasma concentrations at 10 minutes post-dose
Cp20	Observed plasma concentrations at 20 minutes post-dose
Cp30	Observed plasma concentrations at 30 minutes post-dose
CPK	Creatinine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry powder inhaler
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1.0	Forced expiratory volume at 1 minute
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First time in human
g	Gram
GCP	Good Clinical Practice

GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care professional
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
I.U.	International units
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IH	Inhaled
IL	Interleukin
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
Kg	kilogram
LDH	Lactate dehydrogenase
m	Meter
mcg	Micrograms
MCH	Mean Corpuscular Hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
mmHg	Millimeter of mercury
MSDS	Material Safety Data Sheet
Msec	Milliseconds
MW	Molecular weight
OTR	Oxytocin receptor
PGF	Prostaglandin F
PI	Principal Investigator
PK	Pharmacokinetics
PPH	Post-partum haemorrhage
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis plan
RBC	Red blood cells
SAE	Serious Adverse Event

SD	Standard deviation
SMC	Smooth muscle cells
SPC	Summary of product characteristics
SpO2	Peripheral capillary oxygen saturation
SRM	Study reference manual
T&E	Time and event
t1/2	Terminal phase half-life
TB	Tuberculosis
tmax	Time to Cmax
TSL	Third stage of labour
UK	United Kingdom
ULN	Upper Limit of Normal
V	Vassopresin
VOD	Volume of distribution
WBC	White blood cells
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ROTACAPS
ROTAHALER

Trademarks not owned by the GlaxoSmithKline group of companies
Syntocinon
Uniject
WinNonlin

12.2. Appendix 2 Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 4h of the last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or</td></tr>
</table>

recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; International normalized ratio (INR) measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism

- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4 Definition of and Procedures for Documenting Medical Device Incidents

12.4.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section for the list of GSK medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.4.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.5. Appendix 5 List of Acceptable Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Group 2, Cohort B Only: List of Acceptable Non-hormonal Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Nonhormonal Intrauterine device or
2. Male condom combined with vaginal spermicide
3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

Group 2 Only

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication or be withdrawn from the study.

12.5.3. References

Bolton TJ, Randall K, Yentis SM. Effect of the Confidential Enquiries into Maternal Deaths on the use of Syntocinon at Caesarean section in the UK. Anaesthesia 2003(58-3):277-9.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.6. Appendix 6 Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7 Device Acceptability Questionnaire

Device Acceptability Questionnaire

Please answer the following questions regarding your use of the ROTAHALER inhaler for oxytocin.

1. Did you feel confident you had received the medicine?

   Yes No Neutral Decline to answer

2. Did you find the inhaler easy to use?

   Yes No Neutral Decline to answer

3. Did you prefer to have your medicine from an inhaler instead of an injection?

   Yes No Neutral Decline to answer

4. Do you feel using this inhaler is an acceptable way to administer the medicine?

   Yes No Neutral Decline to answer

Thank you for answering these questions.