Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan (for Group 1 reporting) for 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
Effective Date	:	08-MAY-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205920.
- This RAP is intended to describe the Group 1 analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable for Group 1.

Author(s):

Author	Date
Lead PPD Senior Statistician (FPD, Biostatistics)	NA
Co-Author PPD Statistics Director (FPD, Biostatistics)	

RAP Team Review Confirmations (Method: E-mail)

Approver	Date
PPD Clinical Development Manager, RD PCPS CPSSO	12-APR-2019
PPD Head, RD Respiratory HUP 2	17-APR-2019
PPD Manager, Clinical Pharmacology, CPMS	15-APR-2019
PPD Manager Data Management, CPSSO Data Management Respiratory	23-APR-2019
PPD Medical Director, SERM, CMO GCSP SERM US	12-APR-2019
PPD Principal Programmer/Analyst, RD PCPS Qsci Clinical Statistics 9B2	29-APR2019

Clinical Statistics and Clinical Programming Line Approvals

(Method: Pharma TMF eSignature)

Approver	Date
PPD Biostatistics and Programming Manager (Infectious Diseases), Biostatistics India On behalf of PPD (Line Manager, FPD, Biostatistics India)	08-MAY-2019
PPD Programming Manager (FPD) , RD PCPS Qsci Clinical Statistics 9B	08-MAY-2019

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses of Group 1 to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2016N281575_00	2016-AUG-22	Original
2016N281575_01	2016-OCT-10	Section 6.2: Inclusion of information on CE marking.
2016N281575_02	2018-JAN-04	Update to PK collection procedures and implementation of in-stream PK data analysis. Update to location of Secondary Medical Monitor contact information.
2016N281575_03	2018-MAY-30	Modification to informal interim and Group 2 analysis plans.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• To compare pharmacokinetics of IH oxytocin to 10 I.U. IM oxytocin in women in TSL.	• To produce summary statistics for IH and IM Oxytocin	• Due to sparse PK concentration available for IM and IH Oxytocin a formal statistical analysis comparison is not possible; summary statistics will be presented instead.
• To characterize the pharmacokinetics of single doses of IH oxytocin and 10 International Units (I.U.) IM oxytocin in women in TSL.	• To produce individual plasma concentration-time plots and summary statistics for PK parameters : Maximum observed plasma concentration (Cmax), Observed plasma concentrations at 10 minutes (min) postdose (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	• As only sparse PK concentration is available for IM and IH Oxytocin PK parameters will be derived wherever data permit. Terminal Phase half-life (t1/2) will not be calculated. AUC(0-3h) will not be calculated instead AUC(0-t) and time of last quantifiable concentration will be computed.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	concentration-time curve from time zero to the time of the last quantifiable concentration (AUC(0-t)),as data permit. Terminal Phase half-life (t1/2) will not be calculated	
• To compare pharmacokinetics of IH oxytocin between Group 1 and Group 2	• No statistical comparison will be done	• As only sparse PK concentration is available for IH Oxytocin in Group 1 as compared to Group 2, a statistical comparison will not be reported.
• All Subjects Population	• All Subjects population label changed to Safety population.	• To be compliant with the new RAP template
• 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 exists on the study database. This population will be used for summarizing screening failure reasons.	• All participants who passed screening and entered the study including randomized participants and run in failures **Note:** Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• To be compliant with the new RAP template

2.2. Study Objective(s) and Endpoint(s)

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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) postdose (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 Objectives	**Secondary Endpoints**
• 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).

Objectives	Endpoints
• 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 Objectives	**Exploratory Endpoints**
• 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.

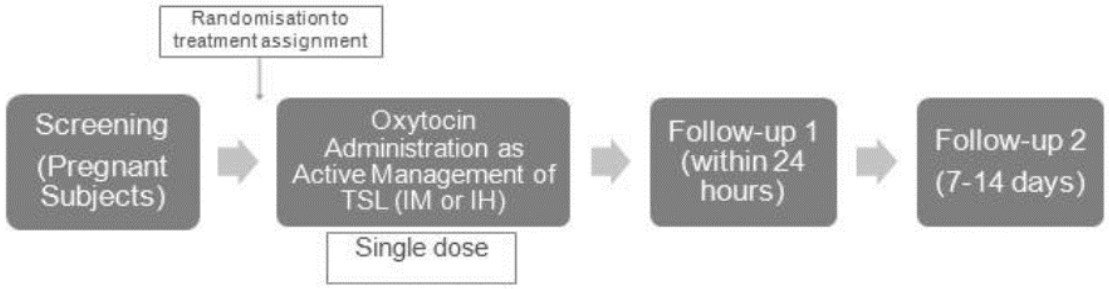
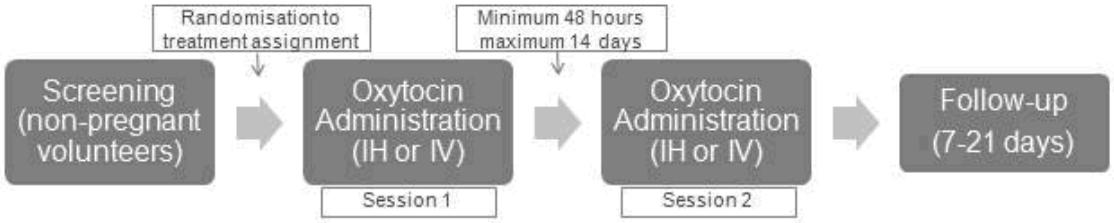
Group 2 – Non-pregnant, non-lactating females of child bearing potential

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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 Objectives	**Exploratory Endpoints**
• 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
Primary Objectives	**Primary Endpoints**
• 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.

2.3. Study Design

Overview of Study Design and Key Features	
Group 1 – Women in TSL  **Group 2 – Non-pregnant, non-lactating females of child bearing potential** 	
Design Features	• **Group 1:** This is an open-label, randomized, single dose study enrolling women in the third stage of labour who will receive either IH or IM oxytocin • **Group 2:** This is an open-label, randomized, two dosing, cross over study enrolling healthy, non-pregnant, non-lactating female subjects of childbearing potential who will receive IH oxytocin at one dosing session and IV oxytocin at the other dosing session. It will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive. Cohort B will enrol women who are not using a hormonal form of contraceptive.
Dosing	• **Group 1:** Subjects will receive 400 mcg IH oxytocin or 10 I.U. IM oxytocin in one dosing session. Follow Up 1 within approximately 24 hours post dose. Follow Up 2 at least 7 days and no greater than 14 days after study drug administration. • Total duration: 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:** Subjects will receive 400 mcg IH oxytocin and 5 I.U. IV oxytocin in two dosing sessions. Follow Up will take place at least 7 days and no greater than 21 days after last study drug administration. • Total duration: 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
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• **Group 1:** Subjects will be randomised to receive one of the following study treatments: A: 400 mcg IH oxytocin B: 10 I.U. IM oxytocin • **Group 2:** Subjects will receive both of the following study treatments over the course

Overview of Study Design and Key Features	
	of two dosing sessions: C: 400 mcg IH oxytocin D: 5 I.U. IV oxytocin
Interim Analysis	• No formal Interim Analysis are planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: 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), in order to assess if dose escalation is required.

2.4. Statistical Hypotheses / Statistical Analyses

No formal hypotheses will be tested.

For IH and IM oxytocin, summary statistics will be produced separately for IH Oxytocin and IM Oxytocin. Due to sparse PK concentrations, it is not possible to include a formal statistical analysis to compare IH and IM Oxytocin. PK parameters will be derived as data permit. Individual plots, listings and summary tables will be produced for available PK concentration data. Only listings and summary tables will be produced for PK Parameter data.

3. PLANNED ANALYSES: GROUP 1

3.1. Interim Analyses: Group 1

No formal Interim Analysis are planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: 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), in order to assess if dose escalation is required.

Due to sparse PK concentration-time data available following administration of IH and IM oxytocin to women in TSL, only concentration time plots were presented at the interim analysis. The Study has been terminated early due the unanticipated inability to be able to quantify plasma oxytocin using a selective and sensitive (LLQ 2pg/mL) analytical assay due to low oxytocin concentrations (<2pg/mL) in the majority of samples collected from women in Third Stage Labour (TSL), following either IM or IH administration. Therefore, the Primary objective of the study to characterise the PK of single doses of IH and IM oxytocin in women in TSL, cannot be met, and the study is being terminated

3.2. Final Analyses

The final planned primary analyses for Group 1 will be performed after the completion of the following sequential steps:

1. All participants who had enrolled into the study prior to the termination of the study as defined in the protocol will be part of final analysis.
2. All required database cleaning activities have been completed for group 1 and final database release (DBR) and database freeze (DBF) for group 1 has been declared by Data Management.
3. All criteria for unblinding the randomization codes for group 1 have been met.
4. Randomization codes for group 1 have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Screen Failures
Enrolled	• All participants who passed screening and entered the study including randomized participants and run in failures **Note:** Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays. **Note:** This population will be based on the treatment the participants actually received	• Study Population • Safety
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- The SI dataset will include all protocol deviations; the analysis dataset will include only important protocol deviations. The analysis dataset will be used for the listing of important protocol deviations.
- The study endpoints will be reported using the populations detailed in Section 4 of this document regardless of whether the participants deviate from the protocol.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors: Group 1

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	400 mcg IH oxytocin	400 mcg IH	1
B	10 I.U. IM oxytocin	17 mcg IM	2

The treatment dosage will be included in the footnotes for the respective tables/listings. If treatment codes have been displayed in the tables/listings the treatment descriptions should be included as footnotes.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Unscheduled visits will not be used for baseline calculation

Baseline definitions for Group 1

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Vital Signs (blood pressure, heart rate, temperature, respiratory rate)	X	X	X	Day 1
LAB	X			Screening

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES: GROUP 1

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety & Enrolled population, with screen failures as an exception.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

7. SAFETY ANALYSES: GROUP 1

The safety analyses will be based on the Safety population, unless otherwise specified.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

8. PHARMACOKINETIC ANALYSES : GROUP 1

8.1. Primary Pharmacokinetic Analyses : Group 1

8.1.1. Endpoint / Variables : Group 1

- 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) postdose (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(0-t)), and time of last quantifiable concentration will be calculated as data permit.

8.1.1.1. Drug Concentration Measures : Group 1

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.2 and Section 10.5.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters: Group 1

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and GSK procedures using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Treatment	Parameter	Parameter Description
IH/IM	Cmax	Maximum observed concentration, determined directly from the concentration-time data.
IH/IM	Cp10	Quantified concentration in PK sample collected at 10 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH/IM	Cp20	Quantified concentration in PK sample collected at 20 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH/IM	Cp30	Quantified concentration in PK sample collected at 30 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH/IM	tmax	Time to reach Cmax, determined directly from the concentration-time data.
IH/IM	AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
IH/IM	tlast	Time of last quantifiable concentration

At least 2 quantifiable (3 including time 0 where NQ values at time zero will be set to 0) values per profile are required to calculate the AUC(0-t). For profiles with less than 2 quantifiable values, AUC(0-t) will be coded with NC in the PKPar file.

8.1.2. Summary Measure: Group 1

Pharmacokinetic concentration data will be presented in graphical and/or tabular form and will be summarized descriptively by IH oxytocin and IM Oxytocin.

The conversion factor to normalise IM doses is 1 IU = 1.7 mcg oxytocin

As a large number of PK parameter values will be reported as Non Calculable (NC: PK parameter cannot be derived due to the presence of non-quantifiable data) then the PK parameter will be summarised by following measures

- number of subjects with non-missing observations, n, (includes those reported as NC)
- number of subjects for whom parameter cannot be derived because of NQ concentrations, n*, (reported as NC)
- median, minimum and maximum

In addition a frequency table of the number of subjects with all concentrations NQ and the number of subjects with one, or 2 or more measurable concentrations will be produced.

8.1.3. Population of Interest : Group 1

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.2. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

PK samples will be analysed periodically throughout the study duration to enable development of a preliminary population PK model. If appropriate, a population PK analysis may also be conducted on the final data. In addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in POP PK RAP appendix.

8.3. Secondary Pharmacokinetic Analyses: Group 1

8.3.1. Endpoint / Variables : Group 1

• 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.

Due to sparse PK concentrations, it is not possible to include a formal statistical analysis to compare IH and IM Oxytocin therefore no statistical analysis will be performed.

8.4. Exploratory Pharmacodynamic Analyses: Group 1

8.4.1. Endpoint / Variables: Group 1

- Pre and post-delivery haemoglobin
- Questionnaire results from participants

8.4.2. Summary Measure: Group 1

Pre and post-delivery Haemoglobin will be summarized and listed along with other haematology parameters. A box plot will be produced for pre and post-delivery haemoglobin.

A listing and a summary table will be produced for the questionnaire results from the Rotahaler.

8.4.3. Population of Interest: Group 1

The exploratory analyses will be based on the Safety population, unless otherwise specified.

9. REFERENCES

GlaxoSmithKline Document Number 2016N281575_03: A randomized, open-label study to characterize the pharmacokinetics of IH 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. (amendment no.3 – 30-May-2018)

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

This section is not applicable as Per Protocol Population is not defined for this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events : Group 1

10.2.1.1. Time & Events 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).

10.2.1.2. Time & 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

10.3. Appendix 3: Assessment Windows

No assessment windows will be applied.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment.

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date +1
Post-Treatment	Date > Study Treatment Stop Date +1

10.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior to 18th week of pregnancy.
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +1.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software 9.4 will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound (Group 1 Dry Run)	: /arenv/arprod/gr121619/mid205920/final_03
HARP Compound (Group 1 Final)	/arenv/arprod/gr121619/mid205920/final_04
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset	
Generation of RTF Files	
• RTF files will be generated for summary tables	

10.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Summary table	Summary table will be produced as described in Section 8.1.2
Listing	All PK Parameters that are collected will be listed
Reporting of No treatment	
If in a situation where a subject has received no treatment, then the subject will be included only in Screened and enrolled population.	
Graphical Displays	
Refer to IDSL Statistical Principals 7.01 to 7.13. All figures will use coloured lines	

10.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	WNL file will be produced for PK parameters. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 9.1 Data Specification of the Pop-PK RAP (RAP-IVF116828-201558-205920-PopPK, located in Cabinets/Study File/GR121619/_Project/Meta Analysis/ RAP-IVF116828-201558-205920-PopPK)
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: Cp10, Cp20 and Cp30

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

10.6.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age. • Randomization date will be used as reference date to calculate age
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.6.3 Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : RR = [(QT/QTcB)^(2)]*1000 [2] If QTcF is machine read and QTcB is not provided, then: RR = [(QT/QTcF)^(3)]*1000 • If ECGs are manually read, the RR value preceding the measurement QT interval should be collected values THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided or calculated then missing QTcB and/or QTcF will be derived as : $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$
Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Decimal Points = '< x' becomes x – 0.01 o Example 2: 1 Decimal Point = '> x' becomes x + 0.1 o Example 3: 0 Decimal Points = '< x' becomes x – 1

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as who has completed all phases of the study including the follow-up visit(s). • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow for the possibility of partial dates. The eCRF and the site need to enter the full date or if not known, they would be required to complete an item level comment bubble to specify why the date is unknown. This would also be documented in the Data Quality Release Report by DM. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1			
		Female	0.3	0.54
		Δ from BL		
Haemoglobin	g/L			
		Female	80	180
		Δ from BL		
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	22

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 3x ULN
AST/SGOT	U/L	High	≥ 3x ULN
AlkPhos	U/L	High	≥ 3x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.8.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
COC	Combined Oral Contraceptive
non-COC	non-Combined Oral Contraceptive
CPSSO	Clinical Pharmacology Science & Study Operations
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
EMA	European Medicines Agency
F	Inhaled Bioavailability
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV1.0	Forced expiratory volume at 1 minute
FPD	Future Pipelines Discovery
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IH	Inhaled
IM	Intramuscular
IMMS	International Modules Management System
IP	Investigational Product
I.U.	International units
IV	Intravenous
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PCPS	Projects, Clinical Platforms and Sciences
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic

Abbreviation	Description
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SPDS	Statistics, Programming and Data Sciences
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TSL	Third stage of labour

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ROTAHALER

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

All displays (Tables, Figures & Listings) will use the term 'Subjects'. The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.7-1.12	N/A
Pharmacokinetic	2.6-2.8	2.8
Safety	3.17-3.28	3.1
Section	**Listings**	
ICH Listings	35-50	
Other Listings	51-53	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Safety	SAFE_FN	SAFE_TN	SAFE_LN
Pharmacokinetic	N/A	PK_TN	NA

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.3. Deliverables

Delivery [Priority] [1]	Description
DR [1]	Prior to DBR. Dry Run for Study Pop, Safety displays
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.7.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT	DR [1], SAC
1.8.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID	EudraCT/Clinical Operations	DR [1], SAC
Population Analysed					
1.9.	Screened	SP1	Summary of Study Populations		DR [1], SAC
Demographic and Baseline Characteristics					
1.10.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	DR [1], SAC
1.11.	Enrolled	DM11	Summary of Age Ranges	EudraCT	DR [1], SAC
1.12.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	DR [1], SAC

10.10.5. Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
2.6.	PK	pkct1	Summary of Plasma Concentration-time Data	Page by subjects before study restart, subjects after restart and all subjects together.	SAC
2.7.	PK	PK_T1	Summary of Derived Plasma Pharmacokinetic Parameters (untransformed data)	Page by subjects before study restart, subjects after restart and all subjects together. This will be an overall summary and will not be displayed by timepoints.	SAC
2.8.	PK	PK_T2	Summary of Number and Percentage of Subjects with Measurable Concentrations	Page by subjects before study restart, subjects after restart and all subjects together. This will be an overall summary and will not be displayed by timepoints.	SAC

10.10.6. Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
2.8.	PK	pkcf6	Individual Subject Plasma Concentration-time Plot (Linear and Semi-log) by Treatment	By Treatment, Page by subjects before study restart, subjects after restart and all subjects together	SAC

10.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.17.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		DR [1], SAC
3.18.	Safety	AE1	Summary of Drug-Related Adverse Events		DR [1], SAC
3.19.	Safety	AE1	Summary of Non-Serious Adverse Events		DR [1], SAC
3.20.	Safety	AE15	Summary of Common (>1 Subject) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	DR [1], SAC
Serious and Other Significant Adverse Events					
3.21.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	DR [1], SAC
3.22.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		DR [1], SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.23.	Safety	LB1	Summary of Haematology Values		DR [1], SAC
3.24.	Safety	LB1	Summary of Haematology Changes from Baseline		DR [1], SAC
Vital Signs					
3.25.	Safety	VS1	Summary of Vital Signs		DR [1], SAC
3.26.	Safety	VS1	Summary of Change from Baseline for Vital Signs		DR [1], SAC
3.27.	Safety	VS7	Summary of Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		DR [1], SAC
Exploratory : Questionnaire Results					
3.28.	Safety	SAFE_T1	Summary of Device Acceptability Questionnaire for Rotahaler Inhaler		DR[1], SAC

10.10.8. Safety Figure

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	LB10	Safety Summary Plot of Pre and Post-Delivery Haemaglobin	IDSL Include the timepoints in the x-axis and values in the y-axis	DR[1], SAC

10.10.9. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
35	Screened	ES7	Listing of Reasons for Screening Failure		DR [1], SAC
36.	Safety	ES2	Listing of Reasons for Withdrawal		DR [1], SAC
37.	Safety	TA1	Listing of Randomised and Actual Treatments		DR [1], SAC
Protocol Deviations					
38.	Safety	DV2	Listing of Important Protocol Deviations		DR [1], SAC
39.	Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		DR [1], SAC
Populations Analysed					
40.	Enrolled	SP3	Listing of Participants Excluded from Analysis Population		DR [1], SAC
Demographic and Baseline Characteristics					
41.	Safety	DM2	Listing of Demographic Characteristics		DR [1], SAC
42.	Safety	DM9	Listing of Race		DR [1], SAC
Prior and Concomitant Medications					
43.	Safety	CM3	Listing of Concomitant Medications		DR [1], SAC
Exposure and Treatment Compliance					
44.	Safety	EX3	Listing of Exposure Data		DR [1], SAC
Adverse Events					
45.	Safety	AE8	Listing of All Adverse Events		DR [1], SAC
46.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		DR [1], SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
47.	Safety	AE8	Listing of Serious Adverse Events		DR [1], SAC
48.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study		DR [1], SAC
All Laboratory					
49.	Safety	LB5	Listing of All Hematology Data	All PCI criteria will be flagged	DR [1], SAC
Vital Signs					
50.	Safety	VS4	Listing of All Vital Signs Data	All PCI criteria will be flagged	DR [1], SAC

10.10.10. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety					
51.	Safety	SAFE_L1	Listing of Device Acceptability Questionnaire for Rotahaler Inhaler		DR [1], SAC
PK Concentration					
52.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data		SAC
53.	PK	PK13	Listing of Derived Plasma Pharmacokinetic Parameters		SAC

10.11. Appendix 11: Mock Shell

Example: SAFE_T1
Protocol: 205920
Population: Safety

Table x.xx
Summary of Device Acceptability Questionnaire for Rotahaler Inhaler

	Total (N=XX)
Feel Confident Received the Medicine	
n	xx
Yes	xx (xx%)
No	xx (xx%)
Neutral	xx (xx%)
Decline to Answer	xx (xx%)
Find This Inhaler Easy to Use	
n	xx
Yes	xx (xx%)
No	xx (xx%)
Neutral	xx (xx%)
Decline to Answer	xx (xx%)
Prefer Inhaler Instead of Injection	
n	xx
Yes	xx (xx%)
No	xx (xx%)
Neutral	xx (xx%)
Decline to Answer	xx (xx%)

Example: SAFE_T1
Protocol: 205920
Population: Safety

Table x.xx
Summary of Device Acceptability Questionnaire for Rotahaler Inhaler

	Total (N=XX)
This Inhaler Acceptable to Administer	
n	xx
Yes	xx (xx%)
No	xx (xx%)
Neutral	xx (xx%)
Decline to Answer	xx (xx%)

Example : SAFE_L1
Protocol : GR121619
Population : Safety

Listing SAFE_T1
Listing of Device Acceptability Questionnaire for Rotahaler Inhaler

Site Id./ Subj Id.	Visit	Date	Question	Response
Xxxx/PPD	PERIOD 1 GRP1	PPD	Feel Confident Received the Medicine	Yes
			Find This Inhaler Easy to Use	Yes
			Prefer Inhaler Instead of Injection	Yes
			This Inhaler Acceptable to Administer	Yes
Xxxx/PPD	PERIOD 1 GRP1	PPD	Feel Confident Received the Medicine	Neutral
			Find This Inhaler Easy to Use	Yes
			Prefer Inhaler Instead of Injection	Yes
			This Inhaler Acceptable to Administer	Yes

Table x.x
Summary of Derived [Analyte] [Matrix] Pharmacokinetic Parameters {by Group}

Parameter	Treatment	N	n	n*	Median	Range
AUC(0-t) (units)	400mcg	24	24	xxxx.xx	NC	NC to NC
			24	xxxx.xx	xxxx.xx	NC to xx
	17mg	24	24	xxxx.xx	xxxx.xx	xxxx.x
			23	xxxx.xx	xxxx.xx	xxxx.x
Cmax (units)	400mcg	24	24	xxxx.xx	xxxx.xx	xxxx.x
			23	xxxx.xx	xxxx.xx	xxxx.x
	17mg	24	24	xxxx.xx	xxxx.xx	xxxx.x
			21	xxxx.xx	xxxx.xx	xxxx.x

NC = non calculable due to NQ concentrations
NA = not applicable due to insufficient data to derive summary measure
n = Number of subjects with non-missing observations (including imputed NC values)
n* = Number of subjects for whom parameter cannot be derived because of NQ concentrations
Note: for Cmax and AUC, NCs were imputed prior to derivation of summary statistics; No NC values were imputed for tmax.
Cmax imputed with ½ LLQ (5 pg/mL)
AUC(0-t) imputed with ½ lowest observed AUC(0-t) (5.45 pg.h/mL)

Table x.x
Summary of Number and Percentage of Subjects with Measurable Concentrations

Treatment (mcg)	N	n	Number of measurable Concentrations in the Concentration-time Profile				
			0	1	2	3	>/=4 but <7
400	8	8	2(25%)	2 (25%)	1 (12.5 %)	1 (12.5%)	2 (25%)
17	7	7	5 (71%)	0 (0%)	0 (0%)	0 (0%)	2 (29%)

n=Number of subjects with non-missing observations (including NC values)

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan (for Group 2 reporting) for 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
Effective Date	:	16-JAN-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205920.
- This RAP is intended to describe the Group 2 analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable for Group 2.

RAP Author(s):

Approver	Date	Approval Method
PPD Associate Statistician (FPD, SPDS India)	N/A	N/A
PPD Statistics Director (FPD, SPDS)	09-JAN-2019	e-signature

RAP Team Approvals:

Approver	Date	Approval Method
PPD Clinical Development Manager, RD PCPS CPSSO	09-JAN-2019	e-signature
PPD Head, RD Respiratory HUP 2	09-JAN-2019	e-mail
PPD Manager, Clinical Pharmacology, CPMS	09-JAN-2019	e-signature
PPD Manager Data Management, CPSSO Data Management Respiratory	09-JAN-2019	e-signature
PPD Medical Director, SERM, CMO GCSP SERM US	16-JAN-2019	e-mail
PPD Principal Programmer/Analyst, RD PCPS Qsci Clinical Statistics 9B2	10-JAN-2019	e-signature

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Biostatistics and Programming Manager, SPDS India	09-JAN-2019	e-signature
PPD Programming Manager, RD PCPS Qsci Clinical Statistics 9B	09-JAN-2019	e-signature

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205920

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses of Group 2 to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2016N281575_00	2016-AUG-22	Original
2016N281575_01	2016-OCT-10	Section 6.2: Inclusion of information on CE marking.
2016N281575_02	2018-JAN-04	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	Modification to informal interim and Group 2 analysis plans.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• To compare the IV pharmacokinetics of oxytocin between Cohort A and Cohort B.	• To produce summary statistics for IV Bolus and IV infusion by Cohort	• Some participants, received IV Bolus dose and some participants received IV infusion dose. As the number of participants that received IV bolus and IV infusion are too small to allow for a formal stats analysis comparison, summary statistics will be presented instead.
• All Subjects Population	• All Subjects population label changed to Safety population.	• To be compliant with the new RAP template
• 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 exists on the study database. This population will be used for summarizing screening failure reasons.	• All participants who passed screening and entered the study including randomized participants and run in failures **Note:** Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used)	• To be compliant with the new RAP template

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	are excluded from the Enrolled population as they did not enter the study.	

2.2. Study Objective(s) and Endpoint(s)

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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) postdose (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 Objectives	**Secondary Endpoints**
• 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]) will be compared as data permit.
Exploratory Objectives	**Exploratory Endpoints**
• 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

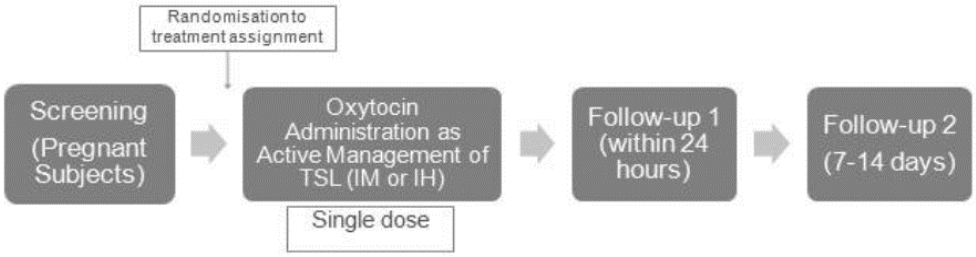
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of IH and IV Oxytocin	• General safety parameters: adverse events; absolute values and changes over time of vital signs (blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters (PR, 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	• Plasma concentration time profile for IH oxytocin and 5

Objectives	Endpoints
of single doses of IH oxytocin and 5 I.U. IV oxytocin.	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 Objectives	**Exploratory Endpoints**
• 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
Primary Objectives	**Primary Endpoints**
• 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.

2.3. Study Design

Overview of Study Design and Key Features	
Group 1 – Women in TSL  **Group 2 – Non-pregnant, non-lactating females of child bearing potential** 	
Design Features	• **Group 1:** This is an open-label, randomized, single dose study enrolling women in the third stage of labour who will receive either IH or IM oxytocin • **Group 2:** This is an open-label, randomized, two dosing, cross over study enrolling healthy, non-pregnant, non-lactating female subjects of childbearing potential who will receive IH oxytocin at one dosing session and IV oxytocin at the other dosing session. It will be divided into two cohorts: Cohort A will enrol women on a combined oral contraceptive. Cohort B will enrol women who are not using a hormonal form of contraceptive.
Dosing	• **Group 1:** Subjects will receive 400 mcg IH oxytocin or 10 I.U. IM oxytocin in one dosing session. Follow Up 1 within approximately 24 hours post dose. Follow Up 2 at least 7 days and no greater than 14 days after study drug administration. • Total duration: 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:** Subjects will receive 400 mcg IH oxytocin and 5 I.U. IV oxytocin in two dosing sessions. Follow Up will take place at least 7 days and no greater than 21 days after last study drug administration. • Total duration: 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
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• **Group 1:** Subjects will be randomised to receive one of the following study treatments: A: 400 mcg IH oxytocin B: 10 I.U. IM oxytocin • **Group 2:** Subjects will receive both of the following study treatments over the course

Overview of Study Design and Key Features	
	of two dosing sessions: C: 400 mcg IH oxytocin D: 5 I.U. IV oxytocin
Interim Analysis	• No formal Interim Analysis are planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: 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), in order to assess if dose escalation is required.

2.4. Statistical Hypotheses / Statistical Analyses

No formal hypotheses will be tested, however, the following comparison is of interest:

- Cohort A (inhaled oxytocin) vs Cohort B(inhaled oxytocin)

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.

For IV oxytocin, summary statistics will be produced separately for IV Bolus Oxytocin and IV Infusion Oxytocin. Due to small participant numbers, a formal statistical analysis to compare Cohort A vs Cohort B is not possible for IV Bolus or for IV infusion.

3. PLANNED ANALYSES: GROUP 2

3.1. Interim Analyses: Group 2

No formal Interim Analysis are planned, however, PK samples will be analysed and preliminary PK parameters derived following completion of approximately 5 women on each treatment group: 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), in order to assess if dose escalation is required.

3.2. Final Analyses

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.

The final planned primary analyses for Group 2 will be performed after the completion of the following sequential steps:

1. All participants in group 2 have completed the study as defined in the protocol
2. All required database cleaning activities have been completed for group 2 and final database release (DBR) and database freeze (DBF) for group 2 has been declared by Data Management.
3. All criteria for unblinding the randomization codes for group 2 have been met.
4. Randomization codes for group 2 have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Screen Failures
Enrolled	• All participants who passed screening and entered the study including randomized participants and run in failures **Note:** Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• Comprise of subjects who receive at least one dose of study medication. This population will be used for the study population and safety displays. **Note:** This population will be based on the treatment the participants actually received	• Study Population • Safety
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed. PK population will be the population for reporting PK data.	• PK

Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- The SI dataset will include all protocol deviations; the analysis dataset will include only important protocol deviations. The analysis dataset will be used for the listing of important protocol deviations.
- The study endpoints will be reported using the populations detailed in Section 4 of this document regardless of whether the participants deviate from the protocol.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors: Group 2

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
C	400 mcg IH oxytocin	400 mcg IH	1
D1	5 I.U. IV oxytocin	8.5 mcg IV bolus	2
D2	5 I.U. IV oxytocin	8.5 mcg IV Infusion	3

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. IH Oxytocin (COC) vs IH Oxytocin (non-COC)

If the duration of IV oxytocin dose administered is less than or equal to 2min then the IV dose administered is an IV Bolus dose. If the duration of IV oxytocin dose administered is greater than 2 min then the IV dose administered is an IV Infusion dose. The tables/listings that would display the statistics should display IV oxytocin administered as IV Bolus Oxytocin and IV Infusion Oxytocin. Subjects assigned to treatment code D and received the IV via bolus will be labelled as D1 and those who received IV via infusion will be labelled as D2.

The treatment dosage will be included in the footnotes for the respective tables/listings. If treatment codes have been displayed in the tables/listings the treatment descriptions should be included as footnotes. COC refers to Combined Oral Contraceptive and non-COC refers to non-Combined Oral Contraceptive.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Baseline definitions for Group 2

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Vital Signs (pressure, heart rate, temperature, respiratory rate)	X	X	X	Day 1
LAB	X	X	X	Day 1
ECG	X	X	X	Day 1
FEV1	X	X	X	Day 1

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES : GROUP 2

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety & Enrolled population, with screen failures as an exception. The study population displays will be produced page wise, grouped by cohorts A and B

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards.

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

7. SAFETY ANALYSES : GROUP 2

The safety analyses will be based on the Safety population, unless otherwise specified.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

8. PHARMACOKINETIC ANALYSES : GROUP 2

8.1. Primary Pharmacokinetic Analyses : Group 2

8.1.1. Endpoint / Variables : Group 2

- Plasma concentration time profile for IH oxytocin and 5 I.U. IV oxytocin.

- PK parameters: Cmax, Cp10, Cp20, Cp30, tmax, AUC(including AUC(0-t), AUC(0-inf) and AUC(0-3h)), Plasma clearance (CL), volume of distribution and t1/2 will be calculated as data permit

8.1.1.1. Drug Concentration Measures : Group 2

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3. Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters: Group 2

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and GSK procedures using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Treatment	Parameter	Parameter Description
IH/IV	Cmax	Maximum observed concentration, determined directly from the concentration-time data.
IH/IV	Pre - dose	Quantified concentration in PK sample collected at predose, determined directly from the concentration-time data.
IH	Cp10	Quantified concentration in PK sample collected at 10 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH	Cp20	Quantified concentration in PK sample collected at 20 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH	Cp30	Quantified concentration in PK sample collected at 30 minutes (nominal time) post-dose, determined directly from the concentration-time data.
IH/IV	tmax	Time to reach Cmax, determined directly from the concentration-time data.
IH/IV	AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
IH/IV	AUC (0-inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
IH/IV	AUC(0-3h)	Area under the concentration-time curve from time zero to 3 h post-dose
IV	Plasma clearance (CL)	Plasma clearance (a volume per time, i.e. a flow) expresses the overall ability of the body to eliminate a drug by scaling the drug elimination rate (amount per time) by the corresponding plasma concentration level.

Treatment	Parameter	Parameter Description
IV	VOD	Volume of distribution of a drug gives information on its distribution in the body. Calculated as VD=Total amount of blood in the body/Drug blood plasma concentration.
IH/IV	t1/2	Apparent terminal half-life will be calculated as: t½ = ln2 / Lambda_z (NOTE: Lambda_z is the terminal phase rate constant).
IH/IV	Clast	Last observed quantifiable concentration
IH/IV	tlast	Time of the last observed quantifiable concentration
IH/IV	Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
IH/IV	Lambda_z_lower	First time point used in computing Lambda_z.
IH/IV	Lambda_z_upper	Last time point used in computing Lambda_z.
IH/IV	#pts	Number of points used in computing Lambda_z.
IH/IV	r-squared	R-squared of Lambda_z computation.
IH/IV	AUC(0-inf)/D	AUC(0-inf) corrected for dose

NOTES:

- Additional parameters may be included as required.

The absolute bioavailability (F) will be derived for each subject using the formula outlined below. If dose normalised AUC(0-∞) cannot be determined this will be substituted with dose normalised AUC(0-t) for that profile. All PK parameters (including the derived inhaled bioavailability, F) will be listed and summarised.

$$F = \frac{AUC(0-\infty)_{inhaled} / Dose_{inhaled}}{AUC(0-\infty)_{IV} / Dose_{IV}}$$

The conversion factor to normalise IV doses is 1 IU = 1.7 mcg oxytocin

8.1.2. Summary Measure: Group 2

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively by IH oxytocin , IV Bolus Oxytocin, IV Infusion Oxytocin for each Cohort (Cohort A and Cohort B). In addition data for the derived absolute bioavailability, F will also be summarised by cohort.

For each of the parameters the following summary statistics will be calculated

• **Untransformed Data:** N, n, arithmetic mean, 90% confidence interval (CI) for the

arithmetic mean, standard deviation (SD), median, minimum, maximum.

• **Loge-transformed Data:** Geometric mean, 90% CI for the geometric mean, standard deviation (SD) of loge-transformed data and %CVb.

For tmax, and t½ the summary statistics specified for untransformed data above will be

generated.

8.1.3. Population of Interest : Group 2

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.2. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

PK samples will be analysed periodically throughout the study duration to enable development of a preliminary population PK model. If appropriate, a population PK analysis may also be conducted on the final data. In addition the oxytocin plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in POP PK RAP appendix.

8.3. Exploratory Pharmacokinetic Analyses: Group 2

8.3.1. Endpoint / Variables : Group 2

• Pre-dose plasma concentrations of oxytocin.

• For IH formulation: - Cp10, Cp20, Cp30, Cmax, Tmax, 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.

• For IV formulation: - Cmax, AUC(0-inf), AUC(0-3h), t1/2, CL and Volume of distribution (VOD) will be compared as data permit.

8.3.2. Summary Measure: Group 2

Descriptive Statistics will be produced for Pre-dose plasma concentrations of oxytocin. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively by cohort

As the number of subjects required to statistically compare IV Bolus Oxytocin and IV Infusion Oxytocin between Cohort A and Cohort B is not sufficient, only summary statistics will be produced for IV Bolus Oxytocin and IV Infusion oxytocin. The Inhaled oxytocin will be statistically compared between Cohort A and Cohort B as described in Section 8.3.4

8.3.3. Population of Interest: Group 2

The exploratory pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified

8.3.4. Statistical Analyses / Methods: Group 2

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles). Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics (CS).

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), point estimates and corresponding two-sided 90% confidence intervals will be computed for Cp10, Cp20, Cp30, Cmax, Tmax, AUC(0-3h), Area under the concentration-time curve from time zero to infinity (AUC[0-∞]) and t1/2.

Data will be loge-transformed prior to analysis using a mixed effect model with a fixed effect term for cohort and a random effect term for subject, with the exception of T1/2 and Tmax which will be analysed non-parametrically using Mann Whitney test.

8.3.4.1. Statistical Methodology Specification

Endpoint / Variables
• For IH: - Cp10, Cp20, Cp30, AUC(0-3h), Cmax, Area under the concentration time curve from time zero to infinity (AUC[0-∞]) will be compared as data permit. Note: These endpoints will be log transformed for analysis.
Model Specification
• Mixed Effect model will be used to analyze the data. **Endpoint:** log transformed PK parameter **Fixed effect:** Cohort (COC/Non-COC) **Random effect:** Subject • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • An unstructured covariance structure for the G matrix will be used. • In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS. • Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

Model Checking & Diagnostics
• For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored. • Non-parametric analyses will be conducted if the normality assumption does not hold.
Model Results Presentation
• Point estimates and corresponding two-sided 90% confidence intervals for the comparison of interest that is Cohort A (COC) vs Cohort B (non-COC) for IH Oxytocin. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios (COC/Non-COC)
Endpoint / Variables
• t1/2 , Tmax Note: This endpoint will not be log transformed for analysis
Model Specification
• Mann-Whitney test • The test will be performed for IH oxytocin only
Model Results Presentation
• Point estimate and 90% confidence interval for the median difference COC-non COC

9. REFERENCES

GlaxoSmithKline Document Number 2016N281575_03 (amendment no.3 – 30-May-2018): A randomized, open-label study to characterize the pharmacokinetics of IH 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.

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

This section is not applicable as Per Protocol Population is not defined for this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events : Group 2

10.2.1.1. Time & Events General Overview

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.

10.2.1.2. Time & Events - Main Phase Procedures

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

10.3. Appendix 3: Assessment Windows

No assessment windows will be applied.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

10.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• Any AE's occurring after Period 1 dosing and before Period 2 dosing (predose), will be considered as Period 1 AE's. Any AE's occurring after Period 2 dosing will be considered as Period 2 AE's. • For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period it would be counted in both periods.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software 9.4 will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: /arenv/arprod/gr121619/mid205920/final_01
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset	
Generation of RTF Files	
• RTF files will be generated for summary tables	

10.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Loge Transformed)	N, n, geometric mean, 90% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = √ (exp(SD2) - 1) * 100 [NOTE: SD = SD of loge transformed data] Following steps can be used to calculate 90% CI for PK parameters: Standard Error = [(Geometric Stdev-1)/Sqrt(N)], Margin of Error = [Standard Error * 1.645], and CI = [Geometric Mean ± Margin of Error]
Parameters Not Being Loge Transformed	Tmax, and t1/2
Summary Tables	The following PK parameters will not be summarised: tlast, Lambda_z, Lambda_z_lower, Lambda_z_upper, #pts and r-squared . The following PK parameters will not be log-transformed: Tmax. t1/2 All other parameters will be summarised as log-transformed and non-log-transformed data as described in Section 8.1.2.
Listings	Include PK Parameters Cmax, Clast, tmax, tlast, AUC(0-3h), AUC(0-t), AUC (0-∞)),Cp(10), Cp(20), Cp(30) , t1/2, Clearance (IV only), Volume of distribution (IV only), F (Inhaled Bioavailability) Lambda_z, Lambda_z_lower, Lambda_z_upper, #pts and r-squared as data permit
Reporting of Partial Dose / No treatment	
If in a situation where a subject has received partial dose or a subject has received no treatment in a particular period, then they will be handled as given below:	

	Enrolled, Screened Population	**Safety, PK Population**
Listings, individual PK figures, Study Population tables without period treatment information	Include	Include
Summary PK figures, Safety and PK tables with treatment information	Include	Exclude

Graphical Displays
Refer to IDSL Statistical Principals 7.01 to 7.13.

10.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to IDSL Standards. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 9.1 Data Specification of the Pop-PK RAP (RAP-IVF116828-201558-205920-PopPK, located in Cabinets/Study File/GR121619/_Project/Meta Analysis/ RAP-IVF116828-201558-205920-PopPK)
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: Cp10, Cp20 and Cp30 and pre-dose
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to Standards for the Transfer and Reporting of PK Data using HARP

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

10.6.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age. • Randomization date will be used as reference date to calculate age
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.6.3 Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : RR = [(QT/QTcB)^(2)]*1000 [2] If QTcF is machine read and QTcB is not provided, then: RR = [(QT/QTcF)^(3)]*1000 • If ECGs are manually read, the RR value preceding the measurement QT interval should be collected values THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided or calculated then missing QTcB and/or QTcF will be derived as : $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as who has completed all phases of the study including the follow-up visit(s). • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow for the possibility of partial dates. The eCRF and the site need to enter the full date or if not known, they would be required to complete an item level comment bubble to specify why the date is unknown. This would also be documented in the Data Quality Release Report by DM. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.80	1.60
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18.0	32.0

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	>110

10.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

10.9. Appendix 11: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
COC	Combined Oral Contraceptive
non-COC	non-Combined Oral Contraceptive
CPSSO	Clinical Pharmacology Science & Study Operations
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
EMA	European Medicines Agency
F	Inhaled Bioavailability
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV1.0	Forced expiratory volume at 1 minute
FPD	Future Pipelines Discovery
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IH	Inhaled
IM	Intramuscular
IMMS	International Modules Management System
IP	Investigational Product
I.U.	International units
IV	Intravenous
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PCPS	Projects, Clinical Platforms and Sciences
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan

Abbreviation	Description
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SPDS	Statistics, Programming and Data Sciences
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TSL	Third stage of labour

10.9.2. Trademarks

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10.10. Appendix 12: List of Data Displays

10.10.1. Data Display Numbering

All displays (Tables, Figures & Listings) will use the term 'Subjects'. The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.6	N/A
Pharmacokinetic	2.1 to 2.5	2.1 to 2.7
Safety	3.1 to 3.16	N/A
Section	**Listings**	
ICH Listings	1 to 24	
Other Listings	25 to 29	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic	N/A	PK_Tn	N/A

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.3. Deliverables

Delivery [Priority] [1]	Description
DR [1]	Prior to DBR. Dry Run for Study Pop, Safety & PK concentration displays (Summary Table and Mean/Median plots)
DR [2]	Post DBF, prior to SAC. Dry Run for displays not part of Dry run [1]
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Participant Disposition for the Participant Conclusion Record	By Cohort ICH E3, FDAAA, EudraCT	DR [1], SAC
1.2.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID	By Cohort EudraCT/Clinical Operations	DR [1], SAC
Population Analysed					
1.3.	Screened	SP1	Summary of Study Populations	By Cohort	DR [1], SAC
Demographic and Baseline Characteristics					
1.4.	Safety	DM3	Summary of Demographic Characteristics	By Cohort ICH E3, FDAAA, EudraCT	DR [1], SAC
1.5.	Enrolled	DM11	Summary of Age Ranges	By Cohort EudraCT	DR [1], SAC
1.6.	Safety	DM5	Summary of Race and Racial Combinations	By Cohort ICH E3, FDA, FDAAA, EudraCT	DR [1], SAC

10.10.5. Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
2.1.	PK	pkct1	Summary of Plasma Concentration-time Data	By Cohort	DR [1], SAC
PK Derived Parameters					
2.2.	PK	pkpt1	Summary of Derived Plasma Pharmacokinetic Parameters (untransformed data)	By Cohort	DR [2], SAC
2.3.	PK	pkpt3	Summary of Derived Plasma Pharmacokinetic Parameters (log-transformed data)	By Cohort	DR [2], SAC
Statistical Analysis Tables					
2.4.	PK	PK_T1	Summary of Statistical Analysis of Loge-transformed Pharmacokinetic Parameters (IH Formulation)	For Cp10, Cp20, Cp30, Cmax, AUC(0-3h) and AUC(0-inf) only. Include treatment dosage in the footnote (Refer Section 5.1)	DR [2], SAC
2.5.	PK	PK_T2	Summary of Statistical Analysis of un-transformed Pharmacokinetic Parameter (IH Formulation)	For t1/2 and Tmax only Include treatment dosage in the footnote (Refer Section 5.1)	DR [2], SAC

10.10.6. Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
2.1.	PK	pkcf1x	Individual Plasma Concentration-time Plot (Linear and Semi-log) by Subject	By Cohort, By Subject	DR [2], SAC
2.2.	PK	pkcf6	Individual Subject Plasma Concentration-time Plot (Linear and Semi-log) by Treatment	By Cohort, By Treatment	DR [2], SAC
Mean/Median Plots					
2.3.	PK	pkcf4	Arithmetic Mean (±SD) Plasma Concentration-time Plot (Linear and Semi-log) – Cohort Comparison	Use nominal times in X Axis. By treatment. Produce two curves one for COC and one for non-COC.	DR [1], SAC
2.4.	PK	pkcf5	Median (range) Plasma Concentration-time Plot (Linear and Semi-log) (IH Formulation)– Cohort Comparison	Use nominal times in X Axis, By treatment	DR [1], SAC
2.5.	PK	pkcf4	Arithmetic Mean (±SD) Plasma Concentration-time Plot (Linear and Semi-log) – Treatment Comparison	Use nominal times in X Axis. By Cohort. Produce three curves. One each for IH, IV Bolus, IV infusion	DR [1], SAC
2.6.	PK	pkcf5	Median (range) Plasma Concentration-time Plot (Linear and Semi-log) (IH Formulation)– Treatment Comparison	Use nominal times in X Axis, By Cohort	DR [1], SAC
Comparative plots					
2.7.	PK	pkpf3	Comparative Plot of Individual Subject Plasma Pharmacokinetic Parameter Versus Treatment	For all PK Parameter page by Treatment sequence; By Cohort	DR [2], SAC

10.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term	By Cohort	DR [1], SAC
3.2.	Safety	AE1CP	Summary of Drug-Related Adverse Events	By Cohort	DR [1], SAC
3.3.	Safety	AE1CP	Summary of Non-Serious Adverse Events	By Cohort	DR [1], SAC
3.4.	Safety	AE15	Summary of Common (>1 Subject) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	By Cohort FDAAA, EudraCT	DR [1], SAC
Serious and Other Significant Adverse Events					
3.5.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	By Cohort FDAAA, EudraCT	DR [1], SAC
3.6.	Safety	AE1CP	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	By Cohort	DR [1], SAC
Laboratory: Chemistry					
3.7.	Safety	LB1	Summary of Chemistry Laboratory Values	By Cohort	DR [1], SAC
3.8.	Safety	LB1	Summary of Change from Baseline for Chemistry Laboratory Values	By Cohort	DR [1], SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.9.	Safety	LB1	Summary of Haematology Laboratory Values	By Cohort	DR [1], SAC
3.10.	Safety	LB1	Summary of Change from Baseline for Haematology Laboratory Values	By Cohort .	DR [1], SAC
Spirometry					
3.11.	Safety	LB1	Summary of Spirometry data	By Cohort.	DR [1], SAC
ECG					
3.12.	Safety	EG1	Summary of ECG Findings	By Cohort	DR [1], SAC
3.13.	Safety	EG2	Summary of ECG Values	By Cohort	DR [1], SAC
Vital Signs					
3.14.	Safety	VS1	Summary of Vital Signs	By Cohort	DR [1], SAC
3.15.	Safety	VS1	Summary of Change from Baseline for Vital Signs	By Cohort	DR [1], SAC
3.16.	Safety	VS7	Summary of Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	By Cohort	DR [1], SAC

10.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screening Failures	By Cohort	DR [1], SAC
2.	Safety	ES3	Listing of Reasons for Withdrawal	By Cohort	DR [1], SAC
3.	Safety	TA2	Listing of Randomized and Actual Treatments	By Cohort	DR [1], SAC
Protocol Deviations					
4.	Safety	DV2A	Listing of Important Protocol Deviations	By Cohort .	DR [1], SAC
5.	Safety	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations	By Cohort	DR [1], SAC
Populations Analysed					
6.	Enrolled	SP3A	Listing of Participants Excluded from Analysis Population	By Cohort	DR [1], SAC
Demographic and Baseline Characteristics					
7.	Safety	DM4	Listing of Demographic Characteristics	By Cohort	DR [1], SAC
8.	Safety	DM10	Listing of Race	By Cohort	DR [1], SAC
Prior and Concomitant Medications					
9.	Safety	CM5	Listing of Concomitant Medications	By Cohort	DR [1], SAC
Exposure and Treatment Compliance					
10.	Safety	EX4	Listing of Exposure Data	By Cohort	DR [1], SAC
Adverse Events					
11.	Safety	AE9	Listing of All Adverse Events	By Cohort	DR [1], SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	By Cohort	DR [1], SAC
Serious and Other Significant Adverse Events					
13.	Safety	AE9	Listing of Serious Adverse Events	By Cohort	DR [1], SAC
14.	Safety	AE9	Listing of Adverse Events Leading to Withdrawal from Study	By Cohort	DR [1], SAC
All Laboratory					
15.	Safety	LB6	Listing of Laboratory Values of Potential Clinical Importance	By Cohort	DR [1], SAC
16.	Safety	LB6	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	By Cohort	DR [1], SAC
17.	Safety	LB6	Listing of Hematology Values of Potential Clinical Importance	By Cohort	DR [1], SAC
18.	Safety	LB6	Listing of All Hematology Laboratory Data for Subjects with Any Value of Potential Clinical Importance	By Cohort	DR [1], SAC
19.	Safety	UR2B	Listing of Urinalysis Data	By Cohort	DR [1], SAC
ECG					
20.	Safety	EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	By Cohort	DR [1], SAC
21.	Safety	EG4	Listing of ECG Values of Potential Clinical Importance	By Cohort	DR [1], SAC
22.	Safety	EG6	Listing of Abnormal ECG Findings	By Cohort	DR [1], SAC
Vital Signs					
23.	Safety	VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	By Cohort	DR [1], SAC
24.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance	By Cohort	DR [1], SAC

10.10.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety					
25.	Safety	EG4	Listing of Spirometry data	By Cohort	DR [1], SAC
PK Concentration					
26.	PK	PK08	Listing of Plasma Pharmacokinetic Concentration-Time Data	By Cohort	DR [2], SAC
PK Parameter					
27.	PK	PK14	Listing of Derived Plasma Pharmacokinetic Parameters	By Cohort	DR [2], SAC
28.	PK	N/A	Raw SAS output for Summary of Statistical Analysis of Loge-transformed Pharmacokinetic Parameters for IH formulation	For Cp10, Cp20, Cp30, Cmax, AUC(0-3h) and AUC(0-inf) only. Include treatment dosage in the footnote (Refer Section 5.1). Include footnotes present in the corresponding analysis table	DR [2], SAC
29.	PK	N/A	Raw SAS output for Summary of Statistical Analysis of un-transformed Plasma Pharmacokinetic Parameter for IH formulation	For t/2 and Tmax only Include treatment dosage in the footnote (Refer Section 5.1). Include footnotes present in the corresponding analysis table	DR [2], SAC

10.11. Appendix 13: Example Mock Shells for Data Displays

Example : PK_T1
Protocol : GR121619
Population : Pharmacokinetic

Table PK_T1
Summary of Statistical Analysis of log transformed GR121619 Pharmacokinetic Parameters for IH formulation

Parameter (units)	Comparison	Geom.LsMean				Ratio	90% Confidence Interval
		n	Test	n	Ref		
AUC(0-t)(µg.h/mL)	COC vs non-COC	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx, x.xxx)

Note:1. Mixed Effect Model has been used for the analysis. Cohort (COC/Non-COC is fitted as Fixed Effect. Subject is fitted as Random Effect.
2. _____ covariance structure is used

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Example : PK_T2
Protocol : GR121619
Population : Pharmacokinetic

Table PK_T2
Summary of Statistical Analysis of un-transformed Pharmacokinetic Parameter IH Formulation

Parameter (units)	Comparison	Median				Diff	90% Confidence Interval
		n	Test	n	Ref		
T1/2	COC vs non-COC	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx, x.xxx)

Appropriate footnotes to be used