**Protocol Amendment 02**

**Study ID:** 214075

**Official Title of Study:** A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability, and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD)

**Date of Document:** 28 Nov 2022

# TITLE PAGE

**Protocol Title:**

A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability, and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD)

**Protocol Number**: 214075/Amendment 02

**Compound Number:** GSK3923868

**Brief Title:**

A study to investigate safety, tolerability, and PK of GSK3923868 inhalation powder in COPD

**Study Phase:** Phase 1

**Eudra CT Number:** 2022-002337-34

**Sponsor Name and Legal Registered Address:**

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**Sponsor Signatory:**

Nicolas Wisniacki,
VP, Discovery Medicine
Clinical Pharmacology and Experimental Medicine

**Approval Date:** 28 Nov 2022

# PROTOCOL AMENDME'NT SUMMARY OF CHANGES TABLE

| **DOCUMENT HISTORY** | | |
|---|---|---|
| **Document** | **Date** | **Document Identifier** |
| Amendment 02 | 28 Nov 2022 | TMF-15098001 |
| Amendment 01 | 27 October 2022 | TMF-15074949 |
| Original Protocol 00 | 08 July 2022 | TMF-14593236 |

**Amendment 02:** 28 Nov 2022

**Overall Rationale for the Amendment:** This amendment has been made in response to CCI [redacted] and to update study procedures.

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 1.1: Synopsis and subsequent sections | The top dose was changed from 3000 mcg to 1500 mcg. | CCI [redacted]. |
| Section 1.1: Synopsis and subsequent sections | GSK3923868 was changed to GSK3923868 inhalation powder when it is referred as a product.<br>"dry powder" was replaced by "inhalation powder" | These edits were made to standardize the terminology used to describe GSK3923868 product. |
| Section 1.1: Synopsis and subsequent sections | Minor editorial changes were made, e.g., changing "a" to "an" in the first sentence of Single Dose of Section 1.1 Synopsis. | These changes were made to improve text flow. |

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 1.3.3: Repeat Dose (Treatment Period 3)<br><br>Section 4.1: Overall Design | Section 1.3.3 (update in bold):<br><br>Footnote #6: "**Dosing on Days 6 and 13 can be either at home or at the site**" was added; and "**home**" was removed from "**home-dosing**"<br><br>Patient diary card dispense was added to Day 14.<br><br>Footnote #7 was expended by adding patient diary card dispense on Day 14 as follows "**and dispense Day 14 (for evening entry) and Day 15 (morning entry) patient diary card before discharge on Day 14**. **The last diary card (dispensed on Day14) will be reviewed by the site via the phone call on Day 15, and returned to the site within 2 weeks from Day 15**"<br><br>Section 4.1 (update in bold):<br><br>"**after home dosing that day**" was removed from the sentence "Participants will then return to the unit on Day 6 after home dosing that day to receive a dose in the unit on Day 7 before being discharged on Day 7 to continue home dosing from Days 8 to 12". | The edits were made to: 1) provide options for participants to receive a dose either at home or at the unit upon arrival on Day 6 and Day 13; and 2) add one more patient diary card dispense on Day 14. |

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 2.2: Background | The last sentence of last paragraph (study 213499) has been updated as follows (update in bold):<br>"At the time of publishing this protocol **amendment, 13** participants have been dosed. No SAEs or notable AEs have been observed so far". | This edit was made to update an ongoing study referred in the protocol. |
| Section 2.3.1: Risk Assessment | Respiratory tract irritancy mitigation strategy (update in bold):<br>Safety margins were modified to "maximum observed clinical exposure following 14-day repeat doses of **1500 mcg** is expected to be below the rat mean gender-averaged NOAEL systemic exposure margins (AUC: **6-14** fold; Cmax: **26-64** fold; lung deposition cover at the rat NOAEL for lung pathology: **10** fold)" | These edits were made to update safety margins based on the new top dose of 1500 mcg. |

| | | |
|---|---|---|
| Section 4.1: Overall Design<br><br>Section 4.2: Justification for Dose | Section 4.1 (update in bold):<br><br>Single Dose Treatments - "**half of**" was added to the second last paragraph as follows "The planned doses may be modified based on emerging safety and tolerability data but will not exceed **half of** the maximum single and repeat dose level administered in the FTIH Study of 3000 mcg once daily".<br><br>Repeat Dose Treatment – "half of" was added to the third paragraph as follows "This planned dose may be modified based on emerging data but will not exceed **half of** 3000 mcg, the maximum repeat dose level administered in the FTIH Study".<br><br>Section 4.2.1: Starting Dose and Dose Escalation (update in bold):<br><br>The sentence "This dose was also the highest dose administered and was well tolerated in the FTIH Study" was edited to "This dose was **half of** the highest dose **(3000 mcg)** administered **that** was well tolerated in the FTIH Study".<br><br>Section 4.2.2: Safety Margins:<br><br>Safety margins for 1500 mcg have been updated in | These edits were made to justify 1500 mcg selection. |

| | | |
|---|---|---|
| | the following paragraph (update in bold).<br><br>"Based on the PK data generated from FTIH Study 213497, the systemic exposure of participants following **1500 mcg** GSK3923868 once daily for 14 days using the CCI device **would be** within the systemic exposure safety margins provided by the Rat IV study NOAEL (providing **26** to **64** fold cover for Cmax and **6** to **14** fold cover for AUC(0-24) based on the individual participant exposures on Day 14 **with 3000 mcg once daily** in the FTIH Study" .<br><br>Section 4.2.3: Predicted Target Engagement at Steady State:<br><br>Target engagement at 1500 mcg has been updated in the following paragraph and "In addition" was removed (update in bold).<br><br>"Modelling and simulation was conducted utilising the PBPK model and the PKPD model (incorporated the PI4KB enzyme kinetics data which accounted for competitive binding with ATP) prediction shows at steady state trough in lungs, the median TE of GSK3923868 following a | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | **1500 mcg** once daily dose was CCI [redacted] as illustrated in Figure 1 below".<br><br>The following sentence was deleted.<br><br>"Additionally, for a 1000 mcg dose given using the CCI [redacted] device (with the assumption of dose proportionality in PK), the model predicted about CCI [redacted]<br><br>Original Figure 1 was replaced with 1500 mcg target engagement prediction and the figure title was updated as follows (update in bold).<br><br>"Predicted Distribution of **Percent** Target Engagement **(TE)** at Steady State Trough **(1500 mcg OD)**" | |
| Section 6.1: Study Intervention(s) Administered | Table 3/Repeat Dose (Period 3):<br><br>Unit dose strength was changed from CCI [redacted].<br><br>Dose level was changed from CCI [redacted] | These edits were made to clarify that CCI [redacted] CCI [redacted] will be used for treatment period 3. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.2: Preparation, Handling, Storage and Accountability | The bullet "CCI should be kept in their primary packaging until dispensing into participant dosing bottles" was removed. | This edit was made to update the change in dispensing study intervention strategy, i.e., no sub-dispensing will be conducted. |
| Section 6.5.1.2: Study specific dose escalation stopping criteria | "**severe non-serious**" and "**and at least possibly related to the study drug**" was added to the bullet "Two participants experience any **severe non-serious** adverse event considered clinically important by the Investigator **and at least possibly related to the study drug**" | This edit was made to further clarify this stopping criterium. |
| Section 8.2.4.2: Peak Expiratory Flow | "**and recorded in the eCRF**" was removed from "PEF will be performed at time points outlined in the SoA and recorded in the eCRF" | This edit was made to clarify that PEF data will be collected for participants to monitor their lung functions only. |
| Section 9: Statistical Considerations | "**and in the OPS, respectively**" was added to the end of the second paragraph. | This edit was made to clarify study reporting details. |
| Section 9.4.2.2: Laboratory values, vital signs, 12-lead electrocardiogram and Spirometry | "**FVC**" was removed from the last bullet. | FVC data will be collected at screening only and not for analyses. |

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 10.10: Appendix 10: Protocol Amendment History<br><br>Section 10.11: Appendix 11: Abbreviations and Definitions and Trademarks | New Section 10.10 and Appendix 10 were inserted for Protocol Amendment History. Consequently, original Section 10.10 and Appendix 10 were updated to Section 10.11 and Appendix 11. | This edit was made to include protocol amendment history. |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A randomized, double-blind, placebo controlled, single and repeat dose study to assess the safety, tolerability and pharmacokinetics of inhaled GSK3923868 in participants with Chronic Obstructive Pulmonary Disease (COPD)

**Brief Title:** A study to investigate safety, tolerability, and PK of GSK3923868 inhalation powder in COPD

**Rationale:**

GSK3923868 is a selective and potent inhibitor of phosphatidylinositol 4-kinase beta (PI4KB) being developed for respiratory disease and specifically the treatment of rhinovirus associated exacerbations of chronic obstructive pulmonary disease (COPD) and asthma.

Data from this Phase 1 study will provide an assessment of the safety, tolerability, and pharmacokinetics of GSK3923868 inhalation powder in participants with stable COPD to support future studies in which COPD patients will be treated at the onset of cold-like symptoms and possibly at the beginning of an infective exacerbation. GSK3923868 is not an immunomodulatory drug.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the safety and tolerability of GSK3923868 following single and repeat inhaled administration in participants with COPD | • Occurrence of adverse events (AEs) and serious adverse events (SAEs).<br>• Clinically significant changes in laboratory values, vital signs,12-lead electrocardiogram (ECG) and spirometry measurements up to Follow Up. |

| Objectives | Endpoints |
|---|---|
| Secondary | |
| • To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in participants with COPD | Derived pharmacokinetic parameters as data permit, including (but not limited to):<br>• Area under the plasma-concentration time curve (AUC): area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose (AUC[0-24]) or area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC[0-t]) for single dose and area under the concentration-time curve from time 0 (predose) to 6 hours post dose administration following the first dose (AUC[0-6]) for repeat dose<br>• Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax) |

**Overall Design:**

This is a single cohort, randomized, double-blind, placebo controlled single and repeat dose study designed to assess the safety, tolerability and plasma PK of GSK3923868 administered as an inhalation powder blend (GSK3923868 CCI [redacted]) using the CCI [redacted] inhaler in participants with stable COPD. This study contains two parts, a single ascending dose followed by 14-days repeat dosing.

The single ascending dose part will assess two dose levels of GSK3923868 inhalation powder or placebo across two treatment periods in a single crossover cohort of participants.

The repeat dose part will assess one dose level of GSK3923868 inhalation powder or placebo in one treatment period in the same cohort of participants.

**Brief Summary:**

The purpose of this study is to measure safety, tolerability and pharmacokinetics of single or repeat inhaled doses of GSK3923868 in participants with stable COPD. The study treatment will be one day for the single dose assessments and 14 days for the repeat dose assessment. The study duration will be from 64 to 71 days. The visit frequency is detailed in the Schedule of Activities (SoA) in Section 1.3

**Number of Participants:**

A total of approximately 12 participants with COPD will be enrolled in this study. Sufficient patients will be screened and those who meet the study entry criteria will be randomized to receive GSK3923868 inhalation powder or placebo in a 3:1 ratio with the intention of a minimum of 8 and a maximum of 12 participants to complete the study.

**Note**: Enrolled means a participant agrees to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

**Intervention Groups and Duration:**

This single cohort, randomized, double-blind, placebo-controlled study contains two single and one repeat dose treatments.

**Single Dose**

The single dose treatments will assess two ascending single doses of GSK3923868 as an inhalation powder using the CCI inhaler in one cross-over cohort of participants with COPD. Participants will receive single ascending doses of GSK3923868 inhalation powder or matching placebo (3:1 ratio) in two treatment periods. The proposed starting dose is 500 mcg. Progression to the next single dose level of 1000 mcg will occur on an individual participant basis and only if, in the judgement of the Investigator, it is supported by the safety and tolerability profile in that patient taking 500 mcg.

Participants will be enrolled for approximately 42 days for the single dose assessments (up to 30 days screening, 2 assessment/washout periods up to 6 days each).

**Repeat Dose**

The repeat dose treatment will assess 1500 mcg of GSK3923868 in the same cohort of participants that has completed single dose assessments. Participants will receive either GSK3923868 or placebo as an inhalation powder via CCI inhaler (3:1 ratio) once daily for 14 days. Progression to repeat dosing will occur on an individual participant basis and only if the Investigator agrees it is supported by the safety and tolerability profile of single doses.

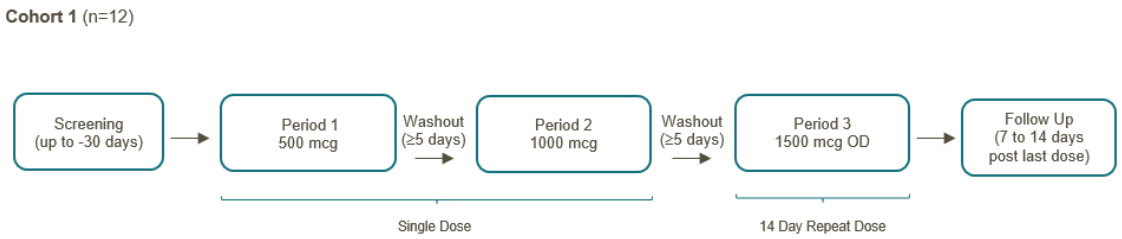
Participants will be enrolled for approximately 15 days for the repeat dose period and follow-up period from 7 to 14 days.

In total, participants will be enrolled for approximately 64 to 71 days in the study (42 days for two single dose periods including screen and washouts, and 15 days for one repeat dose period including a 7 to 14-day follow-up).

**Data Monitoring/ Other Committee:** No

Regular (i.e., every 4 weeks) meetings between the Investigator and Sponsor study teams will review all available safety data across all participants in the study.

## 1.2. Schema




## 1.3. Schedule of Activities (SoA)

### 1.3.1. Screen and Follow Up

| Procedure | Screening[1] (up to -30 days before Day 1) | Early Discontinuation/Withdrawal Visit (7 ± 2 days post last dose) | Follow Up Phone Call (7 to 14 days post last dose) |
|---|---|---|---|
| Phone Call | | | X |
| Informed Consent | X | | |
| Review Inclusion and Exclusion Criteria | X | | |
| Demography | X | | |
| Medical & Disease History | X | | |
| Full Physical Examination (includes height, weight and BMI) | X | | |
| Brief Physical Examination | | X | |
| Alcohol Urine Test | X | X | |
| Urine Drug Screen | X | X | |
| COVID-19 Screening[2] | X | X | |
| AE Review | | X | X |
| SAE Review | X | X | X |
| Concomitant Medication Review | X | X | X |
| Inhaler Training | X | | |
| Spirometry (FEV1 & FVC)[3] | X | X | |
| Vital Signs[4] | X | X | |
| 12-Lead Safety ECG[5] | X | X | |
| Safety Laboratory Assessment[6] | X | X | |
| Urinalysis | X | X | |
| Serum FSH and Estradiol[7] | X | | |
| Urine Pregnancy Test | X | X | |
| HIV, Hepatitis B and C Screening | X | | |

| Procedure | Screening[1] (up to -30 days before Day 1) | Early Discontinuation/Withdrawal Visit (7 ± 2 days post last dose) | Follow Up Phone Call (7 to 14 days post last dose) |
|---|---|---|---|
| PK Blood Sample | | X | |

1. Screening may be performed across multiple visits if necessary.
2. To be performed according to local site policy.
3. Pre- and post-bronchodilator FEV1, predicted FEV1 and FVC are needed at screen only.
4. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature
5. Triplicate ECGs will be obtained at screening and single ECGs at all other occasions.
6. Clinical chemistry, hematology.
7. As needed in women of nonchildbearing potential only

## 1.3.2. Single Ascending Dose (Treatment Periods 1 and 2)

| Procedure | Treatment Periods 1 and 2 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D-1 | D1 | | | | | | | | | | D2 | D3 |
| | | Pre-dose | 0h | 5m | 15m | 30m | 45m | 1h | 2h | 4h | 6h | | |
| Site Visit | X | X | | | | | | | | | | | |
| Site Overnight Stay[1] | X | X | | | | | | | | | | | |
| Discharge from Site | | | | | | | | | | | | X | |
| Phone Call | | | | | | | | | | | | | X |
| Review Inclusion and Exclusion Criteria | X | | | | | | | | | | | | |
| Alcohol Urine Test | X | | | | | | | | | | | | |
| Urine Drug Screen | X | | | | | | | | | | | | |
| COVID-19 Testing[2] | X | | | | | | | | | | | | |
| Brief Physical Examination | X | | | | | | | | | | | | |
| Inhaler Training (refresher)[3] | X | | | | | | | | | | | | |
| Randomisation (Period 1 only) | | X | | | | | | | | | | | |
| Treatment Administration[4] | | | X | | | | | | | | | | |
| AE Review (include washout) | | ← | | | | | | | | | | | → |
| SAE Review (include washout) | ← | | | | | | | | | | | | → |
| Conmed Review | | ← | | | | | | | | | | | → |
| Spirometry (FEV1) | | X | | | | | | X | | | | X | |
| Vital Signs[5] | | X | | | | X | | | | | X | X | |
| 12-Lead Safety ECG (single) | | X | | | | | | X | | | | X | |
| Laboratory Safety Assessment[6] | X | | | | | | | | | | | X | |
| Urinalysis | X | | | | | | | | | | | | |
| Urine Pregnancy Test | X | | | | | | | | | | | | |
| PK Blood Sample | | X | | X | X | X | X | X | X | X | X | X | |
| Genetic sample[7] (optional) | | X | | | | | | | | | | | |

1. Day -1 site admission would be optional.
2. To be performed according to local site policy on Day -1.
3. To be provided before first dose administration. If necessary, another inhaler refresher training may be provided in treatment period
4. Participants should fast for at least 6 hours before dosing until 1 hour post-dose. No water from 1 hour before dosing until 1 hour post-dose. See Section 5.3 for details.
5. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature. Tympanic temperature will be measured once per day in the morning only.
6. Clinical chemistry and hematology only.
7. Genetic sampling can be conducted at any onsite visit during the study.

## 1.3.3. Repeat Dose (Treatment Period 3)

| Procedure | D -1 | D1 | | | | | | | | | | D 2 to 5 | D6 | D7 | | | D 8 to 12 | D 13 | D14 | | | | | | | | | | D15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre-dose | 0 h | 5 m | 15 m | 30 m | 45 m | 1 h | 2 h | 4 h | 6 h | | | Pre-dose | 0 h | 1 h | | | Pre-dose | 0 h | 5 m | 15 m | 30 m | 45 m | 1 h | 2 h | 6 h | |
| **Site Visit** | X | X | | | | | | | | | | | X | X | | | | X | X | | | | | | | | | |
| **Site Overnight Stay[1]** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Discharge from Site** | | | | | | | | | | | X | | | | | X | | | | | | | | | | | X | |
| **Phone Call[2]** | | | | | | | | | | | | X | | | | | X | | | | | | | | | | | X |
| **Review Inclusion and Exclusion Criteria** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Alcohol Urine Test** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Urine Drug Screen** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **COVID-19 Testing[3]** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Brief Physical Examination** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Inhaler Training (refresher)[4]** | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Site Treatment Administration[5]** | | | X | | | | | | | | | | | | X | | | | | X[6] | | | | | | | | |
| **Home Dosing[6]** | | | | | | | | | | | | X | X | | | | X | X[6] | | | | | | | | | | |
| **Dispense Patient Diary[7]** | | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | |

| Procedure | D -1 | D1 | | | | | | | | | | D 2 to 5 | D6 | D7 | | | D 8 to 12 | D 13 | D14 | | | | | | | | | D15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre-dose | 0 h | 5 m | 15 m | 30 m | 45 m | 1 h | 2 h | 4 h | 6 h | | | Pre-dose | 0 h | 1 h | | | Pre-dose | 0 h | 5 m | 15 m | 30 m | 45 m | 1 h | 2 h | 6 h | |
| **Site Visit** | X | X | | | | | | | | | | | X | X | | | | X | X | | | | | | | | | |
| **Review Patient Diary and Treatment Compliance** | | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **AE Review (continuous from treatment period 2)** | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → |
| **SAE Review (continuous from treatment period 2)** | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → |
| **Conmed Review** | | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → |
| **Spirometry (FEV1)** | | X | | | | | | X | | | | | | X | | X | | | X | | | | | | X | | | |
| **PEF[8]** | | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → |
| **Vital Signs[9]** | | X | | | | X | | | | | X | | | X | | X | | | X | | | | | | X | | | |
| **12-Lead Safety ECG (single)** | | X | | | | | | X | | | | | | X | | X | | | X | | | | | | X | | | |
| **Laboratory Safety Assessment[10]** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Urinalysis** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **Urine Pregnancy Test** | X | | | | | | | | | | | | X | | | | | X | | | | | | | | | | |
| **PK Blood Sample** | | X | | X | X | X | X | X | X | X | X | | | | | X | | | X | | X | X | X | X | X | X | X | |

1. Day -1, Day 6 and Day 13 site admissions would be optional.
2. Telephone call on Days 2, 4, 8, 10, 12 and 15.
3. To be performed according to local site policy.
4. If necessary, inhaler refresher training may be provided.
5. Participants should fast for at least 6 hours before dosing until 1 hour post dose. No water from 1 hour before dosing until 1 hour post-dose. See Section 5.3 for details.
6. Dosing on Days 6 and 13 can be either at home or at the site. Day 14 dosing will be timed according to the Day 13 dosing time so that Day 14 pre-dose PK sample can be used as 24h post-dose in PK parameter calculations.
7. Patient diary card will be used to capture study intervention information, PEF measurements, AE/SAE and concomitant medication use. Dispense Day 1 (for evening entry), Day 2 to 5 (full day entry), and Day 6 (for morning entry) patient diary card before discharge on Day 1, and dispense Day 7 (for evening entry), Day 8 to 12 (full day entry), and Day 13 (for morning entry) patient diary card before discharge on Day 7, and dispense Day 14 (for evening entry) and Day 15 (morning entry) patient diary card before discharge on Day 14. The last diary card (dispensed on Day14) will be reviewed by the site via the phone call on Day 15, and returned to the site within 2 weeks from Day 15.
8. PEF measurements will be taken in triplicate twice each day (once in morning upon waking and once in the evening before bedtime) from Day 1 morning until Day 15 morning. PEF will be reviewed by the Investigator at each site visit or phone call (Day 15).
9. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature. Tympanic temperature will be measured once per day in the morning only.
10. Clinical chemistry and hematology only.9

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

# 2. INTRODUCTION

## 2.1. Study Rationale

GSK3923868 is a selective and potent inhibitor of phosphatidylinositol 4-kinase beta (PI4KB) being developed for respiratory disease and specifically the treatment of rhinovirus associated exacerbations of COPD and asthma.

Data from this Phase 1 study will provide an assessment of the safety, tolerability, and pharmacokinetics of GSK3923868 inhalation powder in participants with stable COPD to support future studies in which COPD patients will be treated at the onset of cold-like symptoms and possibly at the beginning of an infective exacerbation. GSK3923868 is not an immunomodulatory drug.

## 2.2. Background

Human rhinovirus are small, non-enveloped, positive sense RNA viruses that cause the common cold. The symptoms related to HRV infection are generally mild and limited to the upper respiratory tract. However, in patients with chronic respiratory diseases such as COPD and asthma, HRV is the predominant viral stimulus leading to disease exacerbations [Hershenson 2013].

PI4KB is a human intracellular lipid kinase and is a host factor required for the replication of multiple picornaviruses, including HRV.

GSK3923868 is a selective inhibitor of PI4KB. Preclinical data has shown that GSK3923868 exhibits potent and slowly reversible inhibition of HRV replication.

A first time in human study designed to evaluate the safety, tolerability and PK profile of single and repeat inhaled doses of GSK3923868 in both healthy participants and participants with asthma is ongoing. This study uses the CCI [redacted] inhaler for drug delivery.

At the time of publishing this protocol, there are currently two on-going studies and no completed studies.

The study 213497 [GSK Document Number 2020N430088_03] is a FTIH study that has completed single ascending and repeat dosing in healthy participants. These healthy participants received inhaled GSK3923868 at doses up to 3000 mcg once daily for 14 days (the predefined maximum) dose which was found to be well tolerated.

The repeat dose in asthmatics has completed recruitment, with 7 moderate and 4 mild asthmatics completing the study to date. Transient increases in ALT and AST were noted in two participants (one active and one placebo) with asthma, which normalized after dosing was stopped. Both participants were asymptomatic. There have been no other clinically significant findings or episodes of bronchospasm reported and the drug has been otherwise well tolerated. The plasma PK in asthmatics was also comparable to that observed in healthy participants.

Study 213499 [GSK Document Number TMF-14737217. ] is a Phase 1b study that is currently on-going and recruiting mild asthma patients to undergo experimental HRV infection and will receive doses of 3000 mcg GSK3923868 inhalation powder or placebo for up to 14 days. At the time of publishing this protocol amendment, 13 participants have been dosed. No SAEs or notable AEs have been observed so far.

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3923868 may be found in the Investigator's Brochure [GSK Document Number: RPS-CLIN-024977].

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention [GSK3923868]** | | |
| Bronchospasm | Can potentially occur with any inhaled treatment.<br><br>The FTIH study 213497 assessed single ascending (50 to 3000 mcg) and 3000 mcg repeat doses of GSK3923868 inhalation powder for 14 days in healthy participants and 7 days in asthmatics. There was no evidence of bronchospasm in adverse events or with daily pre- and post-dose FEV1 assessments.<br><br>The risk of bronchospasm in participants with COPD is therefore considered to be very low. | Inclusion/Exclusion criteria: only participants with stable COPD with a post-bronchodilator FEV1 $\geq$ 40% of predicted normal value will be recruited.<br><br>Monitoring: initial doses of study treatment will be administered in a clinical unit in the presence of clinical staff. Spirometry will be conducted pre and post dose to monitor participants.<br><br>Management: treatment with a short-acting inhaled bronchodilator will be available. If bronchospasm occurs, GSK3923868 will be discontinued immediately. The participant will be assessed and, if necessary, further therapy will be given as deemed appropriate by the Investigator or the attending physician. Participants will be withdrawn from the study if bronchospasm occurs. |
| Respiratory tract irritancy | In rats dosed for 4 weeks by inhaled administration, microscopic findings were noted in the lungs and bronchi, with minimal degeneration/regeneration of the epithelium at the bronchioloalveolar junction at 2060 µg/kg/day. In addition, an increased incidence | Appropriate safety margin: maximum observed clinical exposure following 14-day repeat doses of 1500 mcg is expected to be below the rat mean gender-averaged NOAEL systemic exposure margins (AUC: 6-14 fold; Cmax: 26-64 |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention [GSK3923868]** | | |
| | of inflammatory cell infiltrate (minimal or slight severity), composed predominantly of granulocytes, of the peribronchiolar/perivascular interstitium was also seen at 2060 µg/kg/day. Minimal or slight inflammatory cell infiltrate was seen at a higher than control incidence in females given 2060 µg/kg/day only. However, no microscopic findings in dog IH and rat IV studies. | fold; lung deposition cover at the rat NOAEL for lung pathology: 10-fold).<br><br>Monitoring: respiratory AEs will be monitored and spirometry will be conducted pre- and post-dose in all three initial single doses. In addition, PEF monitoring will be implemented. Single dose escalation will proceed in an individual participant basis and only proceed after a blinded review of safety, tolerability. |
| **Study Procedures** | | |
| Spirometry assessments | Shortness of breath, coughing, light headedness or fainting, and/or chest tightness during the spirometry assessments | As specified in the informed consent form for this study, if any of these symptoms should occur, the participant will receive appropriate medical treatment. |

### 2.3.2. Benefit Assessment

No clinical benefit is expected for the COPD participants enrolled in this study, as evidence for the potential of clinical benefits of GSK3923868 is yet to be determined. Furthermore, clinical benefit would not be expected in participants not experiencing a HRV infection.

Participants may benefit from the thorough medical assessments they receive during the course of the study.

### 2.3.3. Overall Benefit: Risk Conclusion

The potential risks associated with GSK3923868 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential participants is considered low. Enrolment of participants with stable COPD is considered justified by the anticipated benefits that may be afforded to participants with COPD and asthma in the future.

# 3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the safety and tolerability of GSK3923868 following single and repeat inhaled administration in participants with COPD | • Occurrence of AEs and SAEs<br>• Clinically significant changes in laboratory values, vital signs,12-lead ECG and spirometry measurements up to Follow Up |
| Secondary | |
| • To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in participants with COPD | Derived pharmacokinetic parameters as data permit, including (but not limited to):<br>• Area under the plasma-concentration time curve (AUC): AUC(0-24) or AUC(0-t) for single dose and AUC(0-6) for repeat dose<br>• Cmax, Tmax |

# 4. STUDY DESIGN

## 4.1. Overall Design

This randomized, double-blind, placebo controlled, single and repeat dose study will assess the safety, tolerability and plasma PK of GSK3923868 administered as an inhalation powder blend (GSK3923868 CCI for inhalation) using the CCI inhaler in three cross-over treatments to one cohort of participants with stable COPD. The study design schematic is presented in Section 1.2. Study treatment and post-treatment follow-up Schedule of Activities (SoA) Tables are provided in Section 1.3. Treatment sequence and randomization is shown in Table 1.

**Table 1 Study treatment sequence and randomization**

| Treatment Period | Planned Dose | Cohort 1 | | | |
|---|---|---|---|---|---|
| | | (n=3) | (n=3) | (n=3) | (n=3) |
| 1 (Single Dose) | 500 mcg GSK3923868 | A | A | A | P |
| 2 (Single Dose) | 1000 mcg GSK3923868 | P | A | A | A |
| 3 (14-Day Repeat Dose) | 1500 mcg GSK3923868 | A | P | A | A |

A = Active Treatment; P = Placebo Treatment

The total duration of study participation is shown in Table 2.

**Table 2 Study duration by treatment**

| Screen | Treatment Period 1 (500 mcg single dose) plus washout | Treatment Period 2 (1000 mcg single dose) plus washout | Treatment Period 3 (1500 mcg repeat dose) | Follow-up Period | Total Duration |
|---|---|---|---|---|---|
| Up to 30 days before first dose | 6 days (2 days inpatient + 4 days outpatient) | 6 days (2 days inpatient + 4 days outpatient) | 15 days (3 days inpatient + 12 days outpatient) | 7- 14 days post-dose | 64 - 71 days |

Participants who meet the study entry criteria will be randomized to receive GSK3923868 inhalation powder or placebo before study intervention administration on Day 1 of Treatment Period 1.

If a participant withdraws prematurely from the study or discontinues treatment early, additional participants may be recruited to start from 500 mcg single dose treatment sequence at the discretion of the Sponsor in consultation with the Investigator.

**Single Dose Treatments**

Sufficient participants will be screened and those who meet the study entry criteria will be randomized to receive GSK3923868 or placebo using a [redacted] inhaler in a 3:1 ratio with the intention of a minimum of 8 and a maximum of 12 participants to complete the study.

The proposed starting dose for the first treatment period is 500 mcg (refer to Section 4.2 for Dose Justification). Participants will be admitted to the unit on Day -1 and receive a single dose of 500 mcg in the unit on Day 1. Participants will then be discharged on Day 2 after completion of all SoA-specified procedures/activities, and followed up by a telephone call on Day 3.

Escalation to treatment period 2 (1000 mcg) will occur on **an individual participant basis**. A review of safety and tolerability will be conducted prior to administration of the next dose level. This review will occur after at least 3 days of data collection from the participant.

Participants will return for their next scheduled dosing period once all information for dose escalation has been received and reviewed, which is anticipated to be at least 5 days after administration of the study drug from the prior dosing period.

The planned doses may be modified based on emerging safety and tolerability data but will not exceed half of the maximum single and repeat dose level administered in the FTIH Study of 3000 mcg once daily [GSK Document Number 2020N430088_03].

Participants will be enrolled for approximately 42 days for the single dose assessments (up to 30 days screening, 2 assessment/washout periods up to 6 days each) (Table 2).

**Repeat Dose Treatment**

Escalation to treatment period 3 (1500 mcg) will also occur on **an individual participant basis.** Once participants completed the single dose treatment and all information for dose adjustment/ escalation has been reviewed, the participants may start a 14-day repeat dose treatment (period 3) following at least a 6-day washout after administration of last single dose. Participants will receive either GSK3923868 in inhalation powder or placebo administered using a [redacted] inhaler as described in Table 1

The proposed dose for the repeat dose is 1500 mcg. The repeat dose period requires three single-night unit stays (Days -1, 6 and 13). Participants will be admitted on Day -1 to receive their first dose of 1500 mcg in the unit on Day 1. Participants will be discharged on Day 1 after completion of all procedures/activities to continue repeat dosing at home from Days 2 to 6. Participants will then return to the unit on Day 6 to receive a dose in the unit on Day 7 before being discharged on Day 7 to continue home dosing from Days 8 to 12. Participants will be admitted once more on Day 13 to receive their last dose of the period in the unit on Day 14. Participants will be discharged on Day 14 and followed up by telephone call on Day 15 with final telephone follow up approximately 7 to 14 days after their final dose.

This planned dose may be modified based on emerging data but will not exceed half of 3000 mcg, the maximum repeat dose level administered in the FTIH Study [GSK Document Number 2020N430088_03].

Participants will be enrolled for approximately 29 days for the repeat dose assessment (one treatment assessment up to 15 days and follow-up period from 7 to 14 day) (Table 2 Scientific Rationale for Study Design).

This study will be the first administration of GSK3923868 inhalation powder to participants with stable COPD and the first outpatient-based study with GSK3923868 inhalation powder. GSK3923868 inhalation powder is being studied in healthy participants and participants with mild to moderate asthma and has been found to be well tolerated in both populations.

As this study represents a change in population a cautious approach is being adopted. Two single dose treatment periods of 500 mcg and 1000 mcg, respectively, have been incorporated to allow for review of safety and tolerability and ensure the safety of participants before progression to repeat 1500 mcg once daily treatment for 14-days.

The randomized, placebo-controlled study design is a well-established methodology in experimental studies to allow for the valid evaluation of effects attributable to treatment versus those independent of treatment. The double-blind design is a standard methodology for randomized controlled trials to avoid potential bias. The crossover randomisation approach will reduce the potential impact of inter-individual variability on the study outputs.

A minimum washout period of 5 days between single doses and before repeat dosing is based on observed PK data from the FTIH Study [GSK Document Number 2020N430088_03]. The time points for monitoring safety and tolerability endpoints are based on the experience with administration of GSK3923868 inhalation powder as both single and repeat doses to healthy participants and mild to moderate asthmatics.

### 4.1.1. Participant Input into Design

There was no specific elicitation of participant input into the design of this study.

## 4.2. Justification for Dose

For this CCI device, the term “dose” refers to the nominal content of active pharmaceutical ingredient contained within the GSK3923868 CCI for inhalation, administered using the CCI inhaler.

Dose selection was based on the emerging safety, tolerability and plasma PK data of single and repeat dose treatment of GSK3923868 inhalation powder using the CCI inhaler in healthy participants and participants with mild to moderate asthma.

### 4.2.1. Starting Dose and Dose Escalation

The first dose to be administered in this study will be a single dose of 500 mcg GSK3923868 inhalation powder in treatment period 1 followed by a single dose escalation to 1000 mcg GSK3923868 inhalation powder in treatment period 2.

The 1500 mcg GSK3923868 inhalation powder once daily dose given for 14-days in treatment period 3 will be the highest dose level to be evaluated in this study. This dose was half of the highest dose administered (3000 mcg) that was well tolerated in the FTIH Study [GSK Document Number 2020N430088_03], including administration for 7 days to participants with asthma.

### 4.2.2. Safety Margins

Based on the PK data generated from FTIH Study 213497, the systemic exposure of participants following 1500 mcg GSK3923868 inhalation powder once daily for 14 days using the CCI device would be within the systemic exposure safety margins provided by the Rat IV study NOAEL (providing 26 to 64 fold cover for Cmax and 6 to 14 fold cover for AUC(0-24) based on the individual participant exposures on Day 14 with 3000 mcg once daily in the FTIH Study [GSK Document Number 2020N430088_03].

### 4.2.3. Predicted Target Engagement at Steady State

Modelling and simulation was conducted utilising the PBPK model and the PKPD model (incorporated the PI4KB enzyme kinetics data which accounted for competitive binding with ATP) prediction shows at steady state trough in lungs, the median TE of GSK3923868 following a 1500 mcg once daily dose was CCI and there is a CCI probability that steady state trough TE would be above CCI as illustrated in Figure 1 below.

**Figure 1 Predicted Distribution of Percent Target Engagement (TE) at Steady State Trough (1500 mcg OD)**


This level of target engagement is expected to be relevant for the assessment of efficacy in future studies in COPD patients.

## 4.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA.

# 5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

| AGE |
|---|
| 1. Between 40 and 70 years of age inclusive, at the time of signing the informed consent.<br>• ***Note:*** *Participants must show evidence of complete COVID-19 vaccination before being eligible to participate. A complete COVID-19 vaccination is currently defined as having taken either two basic vaccinations plus one booster three months afterwards or two vaccinations plus a confirmed COVID-19 infection before vaccinations.* |

| TYPE OF PARTICIPANT |
|---|
| 2. The participant has a confirmed diagnosis of COPD for > 6 months, as defined by the GOLD guidelines.<br>3. The participant has a post-bronchodilator FEV1/FVC ratio < 0.7 within 30 min after administration of 400 µg salbutamol or equivalent and post-bronchodilator FEV1 ≥ 40% to < 80% of predicted value.<br>• ***Note:*** *Predicted values based on ERS guidelines*, [Quanjer 2012] .<br>4. Participant is a smoker or an ex-smoker with a smoking history of at least 10 pack years.<br>• ***Notes:***<br>*The following equation should be used to calculate pack years.*<br>$pack\ years = \left(\frac{cigarettes\ smoked\ per\ day}{20}\right) \times number\ of\ years\ smoked$ |

| WEIGHT |
|---|
| 5. Body weight at least 45 kg and BMI within the range 18.0 to 32 kg/m$^2$ (inclusive). |

| SEX |
|---|
| 6. Males and female participants, as follows:<br>**Male Participants:** No additional requirements.<br>**Female Participants:** A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:<br>• Is a WONCBP.<br>OR<br>• Is a WOCBP and using an acceptable contraceptive method as described in Appendix 4 during the intervention period for at least 10 days after the last dose of study intervention.<br>A WOCBP must have both:<br>○ A confirmed menstrual period before the first dose of study intervention.<br>AND<br>○ A negative highly sensitive (see Appendix 4) pregnancy test (urine or serum as required by local regulations) within 30 days before the first dose of study intervention.<br>▪ ***Note****: If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant will be excluded from participation if the serum pregnancy result is positive.* |

| SEX |
| --- |
| Note: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4. |

| INFORMED CONSENT |
| --- |
| 7. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. |

## 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

| MEDICAL CONDITIONS |
|---|
| 1. Participant has poorly controlled or unstable COPD, defined as the occurrence of any of the following:<br>• Acute worsening of COPD (an exacerbation) that is managed with oral corticosteroids and/or antibiotics within 4 weeks of screening.<br>OR<br>• More than two exacerbations in the previous 3 months before screening that required a course of oral corticosteroids and/or antibiotics, or for which the participant was hospitalised. |
| 2. Participant has a past or current medical condition(s) or disease(s) that is/are not well controlled and, which in the judgement of the Investigator, may affect participant safety or affect study endpoints.<br>• ***Note:*** *Participants with adequately treated and well controlled concurrent medical conditions (e.g., hypertension) ARE permitted to be entered into this study.* |
| 3. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's Syndrome, and asymptomatic gallstones). |
| 4. Evidence of concurrent significant pulmonary diseases, other than COPD, including (but not limited to): active tuberculosis, lung cancer, clinically symptomatic bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that, in the opinion of the Investigator, may compromise the safety of the participants or affect the interpretation of results. |

| PRIOR/CONCOMITANT THERAPY |
|---|
| 5. Participant has had a respiratory tract infection treated with antibiotics within 4 weeks prior to screening. |
| 6. Participant requires regular treatment with oral corticosteroids or has received a course of oral or parenteral corticosteroids within 4 weeks prior to screening. |
| 7. Participant requires long-term oxygen therapy. |
| 8. Participant requires treatment with medications considered as strong inhibitors of CYP3A4 (e.g., macrolide antibiotics) up to 14 days before first dose. |

| PRIOR/CONCOMITANT CLINICAL STUDY EXPERIENCE |
|---|
| 9. Participation in this study would result in loss of blood or blood products in excess of 500 mL within a 56-day period. |
| 10. Exposure to more than 4 new chemical entities within 12 months before the first dosing day. |

| PRIOR/CONCOMITANT CLINICAL STUDY EXPERIENCE |
|---|
| 11. Current enrolment or past participation in a clinical trial and has received an investigational product within the following period before the first dosing day in this study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). |

| DIAGNOSTIC ASSESSMENTS |
|---|
| 12. Positive human immunodeficiency virus (HIV) antibody test.<br>13. Positive pre-study drug (except for as results of opioids prescribed for medical reasons and/or inadvertent consumption of poppy seeds, see Section 6.8) /alcohol screening result.<br>14. Presence of HBsAg/anti-hepatitis B core antibodies (IgM) at screening or within 3 months prior to first dose of study intervention.<br>15. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.<br>16. QTcF > 450 msec at screening visit based on the average of triplicate ECGs.<br>17. A positive laboratory confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19 |

| OTHER EXCLUSIONS |
|---|
| 18. History of regular alcohol consumption within 6 months prior to the study defined in Germany as:<br>• An average daily intake of pure alcohol of > 24 g per day for males and >12 g per day for females.<br>19. Sensitivity to the study intervention or components thereof (including CCI [redacted]), or drug or other allergy that, in the opinion of the Investigator or medical monitor, or vulnerable participants (e.g., participants in detention, protected adults under guardianship, trusteeship, or committed to an institution by government or juridical order) contraindicate participation in the study. |

## 5.3. Lifestyle Considerations

### 5.3.1. Meals and Dietary Restrictions

- Standardized meals will be provided while the participant is confined to the clinical unit. At all mealtimes, food will be served only after the completion of protocol specific procedures.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, from 7 days before the start of study intervention until after the final dose.

- No water is allowed 1 hour before and after dosing, water is allowed ad libitum at all other times
- Participants should fast for at least 6 hours until 1 hour after each dose.

### 5.3.2. Caffeine, Alcohol, and Tobacco

- Inpatient
    a. During PK sampling days, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 12 hours before the start of dosing until after collection of the final PK sample.
    b. Use of tobacco products will be allowed, but not between 1 hour before and after drug inhalation (see Section 5.1).
    c. Alcohol consumption is not permitted in the clinical unit or for at least 12 hours prior to clinical visits.
- Outpatient
    a. Use of tobacco products will be allowed, but not between 1 hour before and after drug inhalation (see Section 5.1).

### 5.3.3. Activity

- Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (e.g., watching television, reading).

## 5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, information from any previous trials with the same IP, any protocol deviations and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, especially for COVID-19-related screen failures. Participants recovered from COVID-19 infections may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Unused reserve participants that meet eligibility criteria are not considered screen failures.

## 5.5. Criteria for Temporarily Delaying

Not applicable.

# 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

**Table 3 Study Intervention(s) Administered**

| Study Intervention | | | | |
|---|---|---|---|---|
| **Treatment:** | Single Dose Period 1 | Single Dose Period 2 | Repeat Dose (Period 3) | All Treatment Periods |
| **Intervention name:** | GSK3923868 CCI for inhalation. | | | Placebo to match GSK3923868 CCI for inhalation. |
| **Type:** | Drug | | | Placebo |
| **Dose Formulation:** | CCI containing inhalation powder blend. Delivered via CCI device. | | | |
| **Unit Dose Strength:** | 500 mcg | 1000 mcg | 500 mcg | N/A |
| **Dosage Level(s)[1]:** | CCI | CCI | CCI | Number CCI to match active treatment. |
| **Route of Administration:** | Inhalation | | | |
| **Use:** | Experimental | | | Placebo |
| **IMP and NIMP:** | IMP | | | |
| **Sourcing:** | Provided centrally by the Sponsor | | | |
| **Packaging and Labelling:** | Study Intervention will be provided in a CCI. CCI and one 8 g 20% RH maintaining desiccant sachet. Each CCI will be labelled as required per country requirement. | | | |
| **Current Name:** | N/A | N/A | NA | N/A |

[1] CCI .

### 6.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are CCI
- Instructions for medical device use are provided in the SRM.

- All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.3.7 and Section 10.7) and appropriately managed by the sponsor.

## 6.2. Preparation, Handling, Storage and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- CCI [redacted] devices will be supplied in bulk. After use, the devices will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date. Devices will be disposed of at site after reconciliation is verified by Study Monitor.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct contact with the study intervention. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be randomized, according to the randomization schedule generated prior to the study by the Biostatistics Department at GSK. Each participant will be dispensed blinded study intervention, labelled with his/her unique randomisation number, throughout the study. Each participant scheduled to receive study drug will receive a treatment allocation number when randomized. Participants will be randomized in a 3:1 ratio to receive study treatment (active drug: placebo) in this study.

This will be a double-blind study with participants and the site staff blinded. The site pharmacy will be unblinded.

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Unblinded monitors, and in the event of a Quality Assurance audit, the auditor(s), will be allowed access to un-blinded study treatment records at the site to verify that randomization/dispensing has been done accurately.

A participant will be withdrawn from the study if that participant's intervention assignment is unblinded. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF.

GSK's GCSP staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

## 6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- When participants self-administer study intervention at home (treatment period 3), compliance with study intervention will be assessed by direct questioning and counting returned CCI during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.
- A record of the quantity of GSK3923868 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

## 6.5. Dose Modification

This protocol allows alteration from the currently outlined dosing schedule, but the maximum daily dose will not exceed 1500 mcg. Refer to Section 4.3 for dose justification.

The decision to proceed to the next dose level (either an increase or a decrease) will be made by the investigator and the study team on **an individual participant basis** and based on safety and tolerability data obtained in that participants at the prior dose level. The Investigator and Sponsor study team will review all available data for dose selection and/or modification. See Section 10.1.5 for more information.

### 6.5.1. Dose Escalation Stopping Criteria

#### 6.5.1.1. Participant specific dose escalation stopping criteria

Participants who experience an exacerbation during the study will stop dose escalation and be withdrawn from the study. Refer to Section 7.1.4 for COPD exacerbation definition and stopping criteria.

In case of excessive use of rescue medication above 3-fold the participant's normal usage and in the absence of a precipitating cause such as Upper or Lower Respiratory Tract Infection, the participant will be urgently reviewed by the Investigator with a view to being withdrawn. The rescue medication usage will be specifically reviewed at next phone call and/or site visits.

#### 6.5.1.2. Study specific dose escalation stopping criteria

Dose escalation and study will be temporarily halted and no further participants will be dosed until completion of a full safety review if one or more of the following criteria are met:

- One participant experiences a serious adverse event that is considered at least possibly related to the study drug.
- Two participants experience a severe adverse event or bronchospasm that is considered at least possibly related to the study drug.
- Two participants meet liver chemistry stopping criteria outlined in Section 7.1.1.
- Two participants meet QTc stopping criteria outlined in Section 7.1.2.
- Two participants meet spirometry stopping criteria outlined in Section 7.1.3.
- Two participants experience any severe non-serious adverse event considered clinically important by the Investigator and at least possibly related to the study drug.

Relevant reporting and discussion with the medical monitor, relevant GSK personnel, and the IRB/IEC will take place before resumption of dosing.

### 6.5.2. Pharmacokinetic Criteria for Dose Modification

There are no PK criteria for dose modification.

### 6.5.3. Retreatment Criteria

Retreatment is not permitted in this study.

## 6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment with GSK3923868 after completion of the study.

## 6.7. Treatment of Overdose

For this study, any dose of GSK3923868 inhalation powder greater than the planned nominal dose for the treatment period within a 24-hour time period up to minus 2 hour will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgement to treat any overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for 24 hours.
3. Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

## 6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start

of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants are also permitted to use any medicines (e.g., beta-2 agonists, anticholinergics, methylxanthines, inhaled corticosteroids) to control their COPD. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

Concomitant medication for concurrent well controlled medical conditions (e.g., hypertension, arthritis) may be continued, including opioids such as codeine.

Although GSK3923868 is not expected to be a perpetrator or victim of pharmacokinetic drug-drug interactions, strong CYP3A4 inhibitors (e.g., macrolides) are not permitted.

### 6.8.1. Rescue Medicine

Short-acting beta-2 agonists (e.g., salbutamol) or inhaled anticholinergic (e.g., ipratropium bromide) will be permitted to be used as rescue medication. This will be provided by the participant or, if necessary, supplied by the study site.

The use of rescue medications is allowable and at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Study discontinuation specifics are detailed in Appendix 1

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will then be withdrawn from the study. See the SOA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If the following criteria are met, the study will be temporarily paused, and all available safety data will be reviewed by the Sponsor and Investigator:

- One SAE occurring in 1 or more participants receiving GSK3923868 that is considered at least possibly related to the study drug

Further participants may be dosed only if, after review, the Sponsor and Investigator considers it safe to do so.

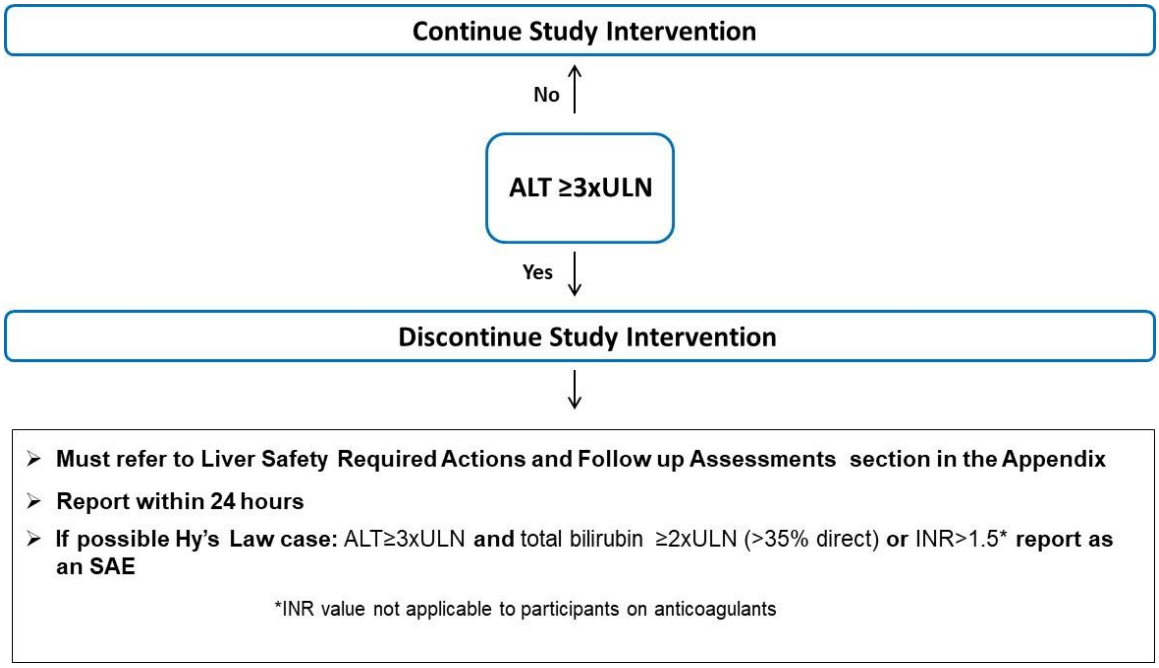
### 7.1.1. Liver Chemistry Stopping Criteria

**Liver chemistry stopping, and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 2 or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

**Figure 2 Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm**




Refer to Section 10.6 (Appendix 6) for liver safety actions and follow-up assessments. The investigator should consider that intensive muscular exercise can also cause asymptomatic elevations of liver function tests such as ALT and AST in using this algorithm [Pettersson, 2007].

### 7.1.2. QTc Stopping Criteria

The Fridericia QT correction (QTcF) formula will be used in the study.

A participant that meets either bulleted criteria based on the average of triplicate ECG readings will be considered for withdrawal from the study intervention:

- QTcF > 500 msec
- Change from baseline: QTcF > 60 msec

Baseline QTcF will be based on the pre-dose ECGs collected before the first dose.

If a clinically significant finding is identified after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

**Note**: Single safety ECG assessments are performed following enrolment in this study. If a single ECG should meet the criteria above, obtain two further ECGs over a brief period (e.g., 5 to 10 minutes). The averaged QTcF value of the 3 ECGs should be used to determine whether the participant should be withdrawn from the study.

### 7.1.3. Spirometry Stopping Criteria

Any participant experiencing a reduction in FEV1 at the 1-hour post-dose compared to daily pre-dose value of > 20% will be withdrawn from the study.

### 7.1.4. COPD Exacerbation Stopping Criteria

Any participant experiencing an exacerbation of COPD must be withdrawn from the study. A COPD exacerbation is defined as follows:

- Episodes characterised by a progressive increase in symptoms of shortness of breath, cough, sputum, wheezing or chest tightness and progressive decrease in lung function, i.e., they represent a change from the patient's usual status that is sufficient to require a change in treatment [GOLD,2020].

### 7.1.5. Pharmacokinetic Stopping Criteria

There are no PK stopping criteria in this study.

### 7.1.6. Temporary Discontinuation

Participant withdrawn from the study treatment will be withdrawn from the study.

### 7.1.7. Rechallenge

Study intervention restart or rechallenge after stopping criteria are met by any participant in this study is not allowed.

## 7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- If participants prematurely discontinue in the study, they may be replaced at the discretion of the Medical Monitor in consultation with the Principal Investigator. The replacement participant will be assigned to treatment period 1 regardless of when/where the last participant prematurely discontinued.

## 7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of the study as a whole is handled as part of Appendix 1.

## 7.4. Management of Participants who Develop COVID-19 Symptoms During the Study

If a participant develops COVID-19 like symptoms during the course of the study the following actions should be taken:

- During single dose treatment of the study (periods 1 and 2), when in the Unit participants who develop a high clinical index of suspicion for COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures. Participants who develop symptoms suspicious of COVID-19 during washout periods should inform the site immediately.
- During repeat dose of the study (period 3), study treatment should be halted for any participants who develop a high clinical index of suspicion for COVID-19 disease; they should be isolated and tested for COVID-19 in accordance with site procedures.

- In all cases, for participants who are in the Unit, assessments should be continued as per the protocol during this period. Participants with a confirmed COVID-19 test may continue to complete safety monitoring assessments but will receive no further doses of the study treatment. In other cases, withdrawal of participants from the study will be at the discretion of the Principal Investigator and discussed with the GSK Medical Monitor if required.
- Refer to Appendix 9 for further COVID-19 related study management details.

# 8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.
- Safety/laboratory/analyte results that could unblind the study will not be reported to the investigative site or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Additional considerations around Covid-19 can be found in Appendix 9.

## 8.1. Efficacy Assessments

There are no planned efficacy assessments in this study.

## 8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

### 8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height (at the screen only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Refer to the SRM for further information.

### 8.2.2. Vital Signs

- Vital signs will be measured in semi-supine position after at least 10 minutes rest and will include systolic and diastolic blood pressure, heart rate, respiratory rate and tympanic temperature. Temperature will be measured once per day in the morning only.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Refer to the SRM for further information.

### 8.2.3. Electrocardiograms

- 12-lead ECG safety ECGs will be performed in semi-supine position after at least 10 minutes rest.
- All safety ECGs must be obtained using an ECG machine that automatically calculates the heart rate and measures, PR, QRS, QT and QTcF intervals.
- Safety ECGs will be interpreted on-site by the Investigator to ensure participant safety. At time points where triplicate ECGs are required, the ECGs will be obtained at least 2 minutes apart and over a recording period of up to 10 minutes.
- Baseline QTcF will be based on the predose ECGs collected before the first dose.
- Refer to Section 7.1.2for QTc specific stopping criteria.
- Refer to the SRM for further information.

### 8.2.4. Lung function Measurements

#### 8.2.4.1. Spirometry

Spirometry will be performed at time points outlined in the SoA. Spirometry will be performed at the site using available equipment.

For each time point, at least 3 acceptable spirometry manoeuvres (from a maximum of 8 attempts) should be achieved. The highest FEV1 will be entered into the eCRF.

Participants should withhold use of short-acting bronchodilators for at least 6 hours and LABA for at least 12 hours prior to each spirometry measurement. Further details on performing the spirometry assessments are provided in the SRM.

#### 8.2.4.2. Peak Expiratory Flow

PEF will be performed at time points outlined in the SoA.

Further information on PEF assessments is outlined in the SRM.

### 8.2.5. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

### 8.2.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted per SoA (Section 1.3).
- If a pregnancy is reported then the Investigator should inform GSK within 24 hours of learning of pregnancy and should follow the procedures outlined in Section 10.4.3.
- Additional urine or serum pregnancy tests may be performed, as determined necessary by the Investigator or as required by local regulation, to establish the

absence of pregnancy at any time during the participant's participation in the study.

## 8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs or SAEs can be found in Section 10.3.

The definitions of device-related safety events, ADEs and SADEs, can be found in Section 10.7. Device deficiencies are covered in Section 10.7

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

### 8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the timepoints specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

### 8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

### 8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 10 days post-intervention (Section 5.1).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant /pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

### 8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

### 8.3.7. Medical Device Deficiencies

A medical device CCI is being provided for use in this study. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such a device.

The definition of a medical device deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

#### 8.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting medical device deficiencies is provided in Section 10.7.

#### 8.3.7.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### 8.3.7.3. Prompt Reporting of Medical Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The medical device deficiency report form will be sent to the sponsor by facsimile transmission. If facsimile transmission is unavailable, then notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The sponsor will be the contact for the receipt of device deficiency reports.

#### 8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

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

## 8.4. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of GSK3923868 as specified in the SoA (Section 1.3). Details of sample collection will be provided in the SRM.

- A maximum of 3 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of GSK3923868 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- PK Samples will be analyzed using an appropriately validated assay method by or under the supervision of the sponsor.
- Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

- Intervention concentration information that may unblind the study will not be reported to the investigative site or blinded personnel until the study has been unblinded.

## 8.5. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 [Genetics and Pharmacogenomics] for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

## 8.6. Biomarkers

Biomarkers are not evaluated in this study.

## 8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

## 8.8. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GlaxoSmithKline.

Reporting of study data will be performed in accordance with applicable GSK and/or CRO standards. Complete details of the planned statistical analyses will be provided in the SAP and in the OPS, respectively.

Any deviations from the planned analyses will be described in the SAP addendum and justified in the final integrated clinical study report.

## 9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested. The primary objective is to evaluate the safety and tolerability of GSK3923868 inhalation powder in participants with COPD.

## 9.2. Sample Size Considerations

No formal statistical techniques were used to calculate the sample size for this study.

The number of participants included is deemed an adequate number to provide an assessment of safety and tolerability and pharmacokinetics measurements.

Sufficient participants with COPD will be screened and randomized to receive GSK3923868 inhalation powder or placebo in a 3:1 ratio with the intention of a minimum of 8 and a maximum of 12 participants to complete the study.

In total, up to 9 participants are planned to receive each dose of active drug in each period. If the true adverse outcome rate is 5%, the chance of observing at least one adverse event at a given dose is 37%. If the true adverse outcome rate is 20%, the chance of observing at least one adverse event at a given dose level is 87%. For sample size of 6 participants on active drug in each period, if the true adverse outcome rate is 5%, the chance of observing at least one adverse event at a given dose is 27%. If the true adverse outcome rate is 20%, the chance of observing at least one adverse event at a given dose level is 74%.

This level of predictivity is deemed adequate within this phase of development.

## 9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined

| **Participant Analysis Set** | **Description** |
|---|---|
| Screened | All participants who were screened for eligibility. |
| Enrolled | All participants who passed screening and entered the study. |
| Randomized | All randomized participants. Participants will be included in the analyses according to the intervention they were randomized to. |
| Safety | All participants who received at least 1 dose of study treatment. This population will be based on the treatment the participant received. |
| Pharmacokinetic (PK) | All randomized participants in the Safety population who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values).<br><br>Participants will be analyzed according to the treatment they received. |

## 9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to FPFV and it will include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Exploratory analyses will be described in the SAP.

### 9.4.1. General Considerations

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

### 9.4.2. Primary Endpoints Analysis

All safety analyses will be performed on the Safety Population and details will be provided in the SAP.

#### 9.4.2.1. Adverse Events and Serious Adverse Events

The proportion of participants reporting AEs will be tabulated by study intervention and by dose for participants on GSK3923868. AEs will also be tabulated by severity and relationship to study product. AEs will be tabulated using MedDRA preferred terms.

The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product.

AEs leading to withdrawal will also be summarized.

#### 9.4.2.2. Laboratory values, vital signs, 12-lead electrocardiogram and Spirometry

Whilst all data collected will be summarized, only measurements which are clinically significant at any timepoint between randomization and follow up will be reported as part of the primary endpoint. Potential clinical interest (PCI) ranges will be defined in the SAP.

This data includes:

- Laboratory results for hematology, clinical chemistry and urinalysis (see Appendix 2 for full details).
- Vital Signs measurements for semi supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature.
- 12-lead safety electrocardiogram (ECG) measurements for heart rate, PR, QRS, QT and QT interval corrected for heart rate according to Frederica's formula (QTcF) intervals.
- Spirometry measurements for FEV1.

### 9.4.3. Secondary Endpoint Analysis

All pharmacokinetic analyses will be performed on the PK Population.

Pharmacokinetic analysis will be the responsibility of the CPMS department within GlaxoSmithKline.

Plasma GSK3923868 concentration-time data will be analyzed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined if data permitting, for each dose of GSK3923868:

- Treatment period 1 & 2 (single ascending doses): AUC(0-t), AUC(0-24), Cmax and Tmax
- Treatment period 3 (repeat dose): Cmax, Tmax and AUC(0-6) on Day 1 and Day 14

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. Analysis of dose proportionality and dose accumulation following repeated dosing (period 3 only) will be conducted. A population PK model (POP PK) may be developed with all available data from this and historical studies as appropriate and will be reported separately. Further details of the analysis plan and methods will be defined within the SAP.

## 9.5. Interim Analysis

No interim analysis planned.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:

  Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (Somerset West, Republic of South Africa, October 1996) and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

  Applicable ICH E6 (R2) GCP guidelines

  Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and/or other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:

  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3923868 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3923868 approved for medical use or approved for payment coverage.

### 10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by

the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.5. Committees Structure

There are no formal data review committees to be established for this study.

- Participant safety will be continuously monitored by the investigator and sponsor study team.
- An initial safety review for this study is planned for the first participant who is dosed and has provided safety data for 3 days after administration of 500 mcg.
- The data may be unblinded should a safety concern arise during the blinded review.
- Dose modification and escalation stopping criteria are outlined in Section 6.5.
- Further details on the dose escalation process are outlined in the Dose Escalation Plan.

### 10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data

provided by study participants are used to maximum effect in the creation of knowledge and understanding

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

### 10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines Document Veeva Vault Location.
- Quality tolerance limits will be pre-defined in the Veeva Vault system to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study-specific monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent CRO document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### 10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 10.1.9. Study and Site Start and Closure

**First Act of Recruitment**

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

**Study/Site Termination**

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development due to strategic considerations
- The study has met its stopping criteria defined in Section 6.5 and Section 7
- Any safety concerns arising from other studies with GSK3923868 (preclinical or clinical) that warrant the study discontinuation

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

### 10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 4 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 4 Protocol-required Safety Laboratory Tests**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count<br>RBC count<br>Hemoglobin<br>Hematocrit | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry[1] | BUN | Potassium | AST)/SGOT | Total and direct bilirubin |
| | Creatinine | Sodium | ALT)/SGPT | Total protein |
| | Glucose (non-fasting) | Calcium (corrected) | Alkaline phosphatase[2] | Albumin |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick<br>• Upon a positive urine test from leucocytes, blood, nitrite or protein, the Investigator may require further urine analysis such as flow cytometry. Results of the additional analyses will be kept in the database. If the flow cytometry examination shows a different result than the urine sticks, the urine will be investigated by fully automated digital imaging where leukocytes, erythrocytes, and casts in the urine will be analyzed. | | | |
| Pregnancy testing | • Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test for women of childbearing potential[3] | | | |
| Other Screening Tests | • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)<br>• Alcohol urine test<br>• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines; may require urine creatinine analyses) | | | |

| Laboratory Assessments | Parameters |
|---|---|
| | • Serology (HIV antibody, HBsAg, anti- hepatitis B core antibodies (IgM) and hepatitis C virus antibody)<br>• COVID-19 testing will be in line with site procedure |

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

# 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.<br><br>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. |

| **Definition of Unsolicited and Solicited AE** |
|---|
| • An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.<br>• Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.<br>• Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.<br>• Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary. |
| **Events Meeting the AE Definition** |
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. |

- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

**Events NOT Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:**

**a. Results in death**

**b. Is life threatening**

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

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

### 10.3.3. Definition of Cardiovascular Events

**Cardiovascular Events (CV) Definition:**

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism

| **Cardiovascular Events (CV) Definition:** |
|---|
| • Deep venous thrombosis/pulmonary embolism<br>• Revascularization |

### 10.3.4. Recording and Follow-Up of AE and SAE

| **AE and SAE Recording** |
|---|
| • When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant AE/SAE information.<br>• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.<br>• There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.<br>• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. |
| **Assessment of Intensity** |
| The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:<br><br>• Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.<br>• Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.<br>• Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Selfcare ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. |
| **Assessment of Causality** |
| • The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. |

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

### 10.3.5. Reporting of SAE to GSK

**SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.

| **SAE Reporting to GSK via Electronic Data Collection Tool** |
|---|
| • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.<br>• The site will enter the SAE data into the electronic system as soon as it becomes available.<br>• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.<br>• Contacts for SAE reporting can be found in the SRM. |

| **SAE Reporting to GSK via Paper Data Collection Tool** |
|---|
| • Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor**.<br>• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.<br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.<br>• Contacts for SAE reporting can be found in the SRM. |

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Definitions:

**Woman of Childbearing Potential (WOCBP)**

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

**Notes**:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

**Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

**Woman of Nonchildbearing Potential (WONCBP)**

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

**Note**: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.2. Contraception Guidance:

Male participants have no restrictions as outlined in Section 5.1.

Female partners of childbearing potential who are not currently pregnant must use an additional highly effective contraceptive method with a failure rate of < 1 % per year, as outlined in the se below:

| **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **Highly Effective Methods[b] That Have Low User Dependency** |
| Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] |
| IUD |
| IUS[c] |
| Bilateral tubal occlusion |
| Azoospermic partner (vasectomized or due to a medical cause)<br>*Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*<br>Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. |

| **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **Highly Effective Methods[b] That Are User Dependent** |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]<br>• oral<br>• intravaginal<br>• transdermal<br>• injectable |
| Progestogen-only hormone contraception associated with inhibition of ovulation[c]<br>• oral<br>• injectable |
| Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* |
| a. Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.<br>b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.<br>c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.<br><br>Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction) |

### 10.4.3. Collection of Pregnancy Information

Female participants who become pregnant:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Section 10.3 (Appendix 3). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting

Any female participant who becomes pregnant while participating:

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

## 10.5. Appendix 5: Genetics

**USE/ANALYSIS OF DNA**

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK3923868. They may also be used to develop tests/assays including diagnostic tests) related to GSK3923868. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3923868 (or study interventions of this class) continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

## 10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria and required follow up assessments. In applying the liver chemistry stopping criteria, the investigator should consider that intensive muscular exercise can also cause asymptomatic elevations of liver function tests such as ALT and AST [Pettersson, 2007].

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN<br>If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.<br>See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment<br>• Report the event to GSK within 24 hours<br>• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]<br>• Perform liver event follow up assessments<br>• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)<br>MONITORING:<br>If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs<br>• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline<br>• A specialist or hepatology consultation is recommended<br>If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72</td><td>• Viral hepatitis serology[3]<br>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend<br>• Obtain blood sample for PK analysis, within 48 hours of last dose[4]<br>• Serum CPK and LDH.<br>• Fractionate bilirubin, if total bilirubin≥2xULN<br>• Obtain complete blood count with differential to assess eosinophilia<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form<br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.<br>• Record alcohol use on the liver event alcohol intake case report form<br>If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.</td></tr>
</table>

| **Liver Chemistry Stopping Criteria** | |
|---|---|
| **hrs**<br>• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. |

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

## 10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

### 10.7.1. Definition of Medical Device AE and ADE

| **Medical Device AE and ADE Definition** |
|---|
| • A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.<br>• An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |

### 10.7.2. Definition of Medical Device SAE, SADE and USADE

| **A Medical Device SAE is** any serious adverse event **that:** | |
|---|---|
| a. | Led to death |
| b. | Led to serious deterioration in the health of the participant, that either resulted in:<br>• A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.<br>• A permanent impairment of a body structure or a body function.<br>• Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.<br>• Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function |
| c. | Led to fetal distress, fetal death or a congenital abnormality or birth defect |
| d. | Is a suspected transmission of any infectious agent via a medicinal product |

| **SADE definition** |
|---|
| • A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.<br>• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. |
| **Unanticipated SADE (USADE) definition** |
| • An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3). |

### 10.7.3. Definition of Device Deficiency

| **Device Deficiency Definition** |
|---|
| • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer. |

### 10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

| **AE, SAE and Device Deficiency Recording** |
|---|
| • When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.<br>• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE/device deficiency form.<br>• There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. |

**AE, SAE and Device Deficiency Recording**

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

**Assessment of Intensity**

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

| **AE, SAE and Device Deficiency Recording** |
|---|
| • The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.<br>• For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.<br>• There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.<br>• The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.<br>• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |
| **Follow-up of AE/SAE/device deficiency** |
| • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.<br>• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.<br>• New or updated information will be recorded in the originally completed form.<br>• The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information. |

### 10.7.5. Reporting of SAEs

| **SAE Reporting to GSK via an Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.<br>• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours.<br>• The site will enter the SAE data into the electronic system as soon as it becomes available. |

| **SAE Reporting to GSK via an Electronic Data Collection Tool** |
|---|
| • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK medical monitor by telephone.<br>• Contacts for SAE reporting can be found in the SRM. |
| **SAE Reporting to GSK via Paper Data CollectionTool** |
| • Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK medical monitor.<br>• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.<br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.<br>• Contacts for SAE reporting can be found in the SRM. |

### 10.7.6. Reporting of SADEs

| **SADE Reporting to GSK** |
|---|
| NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.<br>• Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.<br>• GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.<br>• Refer to the paper medical device deficiency report form for details on transmission of this information to the sponsor. |

## 10.8. Appendix 8: Country-specific Requirements

None

## 10.9. Appendix 9: COVID-19

### 10.9.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

### 10.9.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

### 10.9.3. Data Management/Monitoring

If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote SDV/SDR where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

eCRF/CRF Final or Interim Sign off Process: The PI is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the

study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the DoR Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

## 10.10. Appendix 10: Protocol Amendment History

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE.

| **DOCUMENT HISTORY** | | |
|---|---|---|
| **Document** | **Date** | **Document Identifier** |
| Amendment 01 | 27 October 2022 | TMF-15074949 |
| Original Protocol 00 | 08 July 2022 | TMF-14593236 |

**Amendment 01:** 27 October 2022

**Overall Rationale for the Amendment:** This amendment has been made in response to a request from the Federal Institute of Drugs and Medical Devices (BfArM).

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Section 6.5.1.2: Study specific dose escalation stopping criteria | "study" and "if one or more of the following criteria are met" were added to the first paragraph as follows.<br>"Dose escalation and **study** will be temporarily halted and no further participants will be dosed until completion of a full safety review **if one or more of the following criteria are met**" | These edits were made to clarify the study stopping criteria. |
| Section 10.1.9: Study and Site Start and Closure | The following sentence has been removed, and reasons for study termination have been expanded.<br>"GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK" | This section was amended per a request from BfArM CTA review. |

## 10.11. Appendix 11: Abbreviations and Definitions and Trademarks

| | |
|---|---|
| ADE | Adverse devise effect |
| ADL | Activities of Daily Living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| AUC | area under the concentration-time curve |
| AUC(0-∞) | area under the concentration-time curve from time 0 (predose) extrapolated to infinite time |
| AUC(0-24) | area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose |
| AUC(0-t) | area under the concentration-time curve from time 0 to the time of the last quantifiable concentration |
| AUC(0-τ) | area under the concentration-time curve from time 0 (predose) to time tau |
| BMI | body mass index |
| CA | Competent Authorities |
| CIOMS | Council for International Organizations of Medical Sciences |
| CI | confidence interval |
| Cmax | maximum observed concentration |
| COVID | Coronavirus disease |
| COPD | Chronic obstructive pulmonary disease |
| CPK | creatine phosphokinase |
| CPMS | Clinical Pharmacokinetics Modelling and Simulation |
| CRO | Contract research organization |
| CRF | Case report form |
| CSR | Clinical Study Report |
| CTFG | Clinical Trial Facilitation Group |
| CV | Cardiovascular |
| CYP | cytochrome P450 |
| DEC | Dose escalation committee |
| DMPK | Drug metabolism and Pharmacokinetics |
| DoR | Delegation of Responsibilities |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| ERS | European Respiratory Society |
| FEV1 | forced expiratory volume in 1 second |
| FPFV | First Participant First Visit |
| FSH | follicle-stimulating hormone |
| FTIH | First time in human |
| FVC | forced vital capacity |
| G | Gram |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GSK | GlaxoSmithKline |
| HBsAg | hepatitis B surface antigen |
| HDPE | high-density polyethylene |
| HIV | human immunodeficiency virus |
| HRT | hormone replacement therapy |
| HRV | Human rhinovirus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IH | Inhaled |
| IMP | Investigational Medicinal Product |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | Intravenous |
| Kg | kilogram |
| LDH | lactate dehydrogenase |
| LAM | lactational amenorrhea method |
| $m^2$ | square meter |
| Mcg | Microgram |
| MCH | mean corpuscular hemoglobin |
| MCV | mean corpuscular volume |
| MDR | Medical Device Regulation |
| Mg | Milligram |
| mL | Milliliter |
| MSDS | Material Safety Data Sheet |
| MedDRA | Medical dictionary for regulatory activities |
| Msec | Millisecond |
| NIMP | Non Investigational Medicinal Product |
| NOAEL | No Observed Adverse Effect Level |
| NQ | Non-quantifiable |
| OPS | Output and programming specifications |
| PBPK | Physiologically-based pharmacokinetics |
| PCI | Potential clinical interest |
| PEF | Peak Expiratory Flow |
| PI | Principle investigator |
| PK | pharmacokinetic(s) |
| PKPD | pharmacokinetic/pharmacodynamic modelling |
| PopPK | population PK |
| PT | Prothrombin time |
| QC | Quality check |

| | |
|---|---|
| QTc | corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave |
| QTcF | corrected QT interval using the Fridericia formula |
| QTL | quality tolerance limit |
| RBC | Red blood cell count |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SADE | serious adverse device effects |
| SAP | Statistical Analysis Plan |
| SGOT | Serum Glutamic-Pyruvic Transaminase |
| SGPT | Serum Glutamic-Pyruvic Transaminase |
| SoA | schedule of activities |
| SD | single dose |
| SDR | Source document review |
| SDS | Safety Data Sheet |
| SDV | Source document verification |
| SOP | Standard operating procedures |
| SRM | Study reference manual |
| SUSAR | suspected unexpected serious adverse reactions |
| t1/2 | terminal phase half-life |
| TE | Target engagement |
| Tmax | time to reach maximum observed plasma concentration |
| ULN | upper limit of normal |
| USADE | Unanticipated serious adverse device event |
| WBC | White blood cell count |
| WONCBP | Wome(a)n of nonchildbearing potential |
| WOCBP | Woman of childbearing potential |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| None |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| GastroPlus |
| MedDRA |
| CCI [redacted] |
| WinNonlin |

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