PROTOCOL

Study ID: 213376

Official Title of Study A Two-Part First Time in Human (FTIH) Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeat Oral Doses of GSK3884464 in a Randomized, Double Blind, Placebo-Controlled, Dose Escalation Study in Healthy Participants

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TITLE PAGE

Protocol Title: A Two-Part First Time in Human (FTIH) Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeat Oral Doses of GSK3884464 in a Randomized, Double Blind, Placebo-Controlled, Dose Escalation Study in Healthy Participants

Protocol Number: 213376/ Amendment 04

Compound Number: GSK3884464

Study Phase: Phase 1

Short Title: A FTIH study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeat doses of GSK3884464 in healthy participants

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**TMF Number**
Amendment 04	06 Apr 2022	*TMF- 14577739*
Amendment 03	*17-FEB-2022*	*TMF- 14464572*
Amendment 02	*04-JAN-2022*	*TMF-14366164*
Amendment 01	*19-AUG-2021*	*TMF-13947787*
Original Protocol	*09-JUN-2021*	*TMF-13810865*

Amendment 04 06 Apr 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it impacts the safety of participants.

Overall Rationale for the Amendment: This Protocol Amendment 04 is being implemented to update safety monitoring and to correct typographical errors.

Where the Amendment Applies:

This Protocol Amendment 04 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis: Overall Design, Disclosure Statement and Intervention Groups and Duration	**Previous:** There will be three cohorts with 9 participants in each cohort, each cohort will have 3 time periods. **Revised:** There will be up to three cohorts with 9 participants in each cohort, each cohort will have up to 3 time periods.	The change was made to allow flexibility of up to 3 cohorts in each Part and up to 3 dose levels in each cohort, and extension of duration of each cohort.
	Previous: **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and 21-days (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants. It will consist of 3 ascending dose cohorts with 8 participants per cohort. **Revised:** **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and up to 21-days (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants (See Section 4.4). It will consist of up to 3 dose cohorts with 8 participants per cohort.	This change was made to the dosing schedule to permit closer safety monitoring of LFTs for participants in Part 2 of the study.
	Previous: This is a First Time in Human Study. Sentinel dosing will be incorporated in each Part of the study and at each dose level. For Part 1, only 2 to 3 participants will be dosed at a time, and their LFTs will be monitored until Day 6 before the next participants in the cohort are dosed. **Revised:** This is a First Time in Human Study. Sentinel dosing will be incorporated in each Part of the study and at each dose level. For Part 1, up to 3 participants will be dosed at a time, and their LFTs will be monitored until Day 6 or until resolution (whichever is later) before the next participants in the cohort are dosed. For Part 2, up to 3 participants will be dosed at a time and will be monitored for a minimum of 5 days prior to dosing the rest of the cohort.	The change was made to allow flexibility of up to 3 participants in each Part (1 and 2), up to 3 dose levels in each cohort, and in length of duration of Cohort 6.
	Previous: Part 1 will consist of three cohorts. Each cohort will include 3 intervention periods. These will each be a single dose,	

Section # and Name	Description of Change	Brief Rationale
	crossover design. Part 2 will consist of three cohorts. Cohorts 4 and 5 (14-day) and Cohort 6 (21-day) will be a sequential group, repeat dose with one intervention period. **Revised:** Part 1 will consist of up to three cohorts. Each cohort could include up to 3 intervention periods. These will each be a single dose, crossover design. Part 2 will consist of up to three cohorts. Cohorts 4 and 5 (14-day) and Cohort 6 (up to 21-days) will be a sequential group, repeat dose with one intervention period (See Section 4.4). **Previous:** Part 1: Each of the 3 cohorts will be approximately 70 days. Part 2: Cohorts 4 and 5 will be approximately 61 days and Cohort 6 will be approximately 68 days. **Revised:** Part 1: Each of the 3 cohorts will be approximately 76 days. Part 2: Cohorts 4 and 5 will be approximately 72 days and Cohort 6 will be approximately 80 days.	This change was made to the length of the study Parts as a result of the closer safety monitoring of LFTs for study participants. Update of length of study due to additional and updated safety measures.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema Figure 1 Overall Study Design Figure 2 Part 1 Design and Cohort Dosing Figure 3: Part 2 Design	**Previous:** Within a cohort, participants will be randomized to one of 3 treatment sequences such that each participant receives 2 active doses and 1 placebo dose resulting in each active dose being administered to 6 participants and placebo to 3 participants. **Revised:** Within a cohort, participants will be randomized to one of 3 treatment sequences such that each participant receives up to 2 active doses and 1 placebo dose resulting in each active dose being administered to up to 6 participants and placebo to up to 3 participants. **Previous:** Part 2, Cohorts 4 and 5 will be 14 days and Cohort 6 will be 21 days **Revised:** Part 2, Cohorts 4 and 5 will be 14 days and Cohort 6 will be up to 21 days **Previous:** Final Dose Escalation Meeting: Dose escalations will be determined by PK and full safety data **Revised:** Final Dose Escalation Meeting: Dose escalations will be determined by full safety data, PK data and PD data (if available). **Previous:** Dose escalations will be determined by PK and Safety data **Revised**: Dose escalations will be determined by Safety data, PK data and PD data (if available). **Previous:** Subsequent dose escalations will be determined based on safety and PK data **Revised**: Subsequent dose escalations will be determined based on safety, PK data and PD data (if available).	This change was made to the length of the study Parts as a result of the closer safety monitoring of LFTs for study participants. Added in review of PD data for Dose escalation decisions.

Section # and Name	Description of Change	Brief Rationale
Figure 4 Part 2 Cohorts 4 and 5 Dosing Figure 5 Part 2 Cohort 6 Dosing	**Previous:** Dose escalations will be determined by PK and Safety data **Revised**: Dose escalations will be determined by Safety data, PK data and PD data (if available) **Previous:** Cohorts 4 and 5 will be approximately 61 days. **Revised:** Cohorts 4 and 5 will be approximately 72 days. **Previous:** Cohort 6 will be approximately 68 days. **Revised:** Cohort 6 will be approximately 80 days. Study treatment may be less than 21 days.	Update of length of study due to additional and updated safety measures.
Section 1.3 Schedule of Activities	**Previous:** The Ethics Committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). **Revised**: The UK ethics board, the MHRA and investigator will be informed of any significant safety issues, including those that require amendment of the Patient Information Sheet and Consent Form (PICF).	Clarification on who (and under what circumstance) to inform (UK ethics, MHRA and the investigator) when changes are required to the Patient Information Sheet and Consent Form (PICF). Language aligns with Section 8 Study Assessments and procedures.
Section 1.3.1 Part 1: Single Dose Administration in Healthy Participants (Cohorts 1, 2 and 3) Clinical laboratory assessments (heme/chem/ urinalysis-including liver chemistries) Plasma NT-proBNP	**Revised:** Added X in SOA Gamma-glutamyl transferase (GGT) added in SOA to Days 4, 6, and Follow up **Revised: Text Added** *EW and Follow up Visit or until resolution (whichever is later). **Previous**: *Serum and renal chemistries only pre-dose on D1. **Revised:** Daily serum chemistries D4 through D6	Additional chemistry blood draws added in Part 1 to monitor for liver chemistry changes.

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	and EW as required. Follow up until resolution as required. **Previous:** Pre-dose and 24hr on D2 and at follow up visit. **Revised:** Pre-dose,24hr on D2, Day 6 prior to discharge, and at follow up visit.	
Section 1.3.2: Part 2 (Cohorts 4 and 5): Multiple Dose Administration to Healthy Participants for 14 days of Treatment Clinical laboratory assessments (heme/chem/ urinalysis-including liver chemistries)	**Revised: Added text** *Gamma-GT on days 7-14, D19, Follow up and Early Withdrawal Visit or until resolution (whichever is later). **Previous:** *D1, D4, D11 and D18 (serum and renal chemistries only). **Revised:** Daily serum chemistries and urinalysis from D3 through 24hrs after last day of dosing, at D19 and Follow up Visit or until resolution (whichever is later)	Additional chemistry blood draws and Urine Albumin to Creatine ratio (UACR) added in Part 2 to monitor for liver and renal chemistry changes.
Core Urine Safety monitoring assessments	**Previous:** *D4 and D11 only. **Revised** *Daily UACR from day 4 through 24hrs after last day of dosing and D19. Additional testing as required until resolution.	
Continuous cardiac telemetry	**Previous**: Continuous cardiac monitoring should be started approximately 90min before dosing on D1 through D14 after the Holter Monitor is applied. **Revised:** Continuous cardiac monitoring should be started approximately 90min before dosing on D1 through D15 after CCI CCI is removed.	Correction of telemetry notes.
Entero-Tracker or Entero-Test (bile sample collection Entero-Tracker or Entero-Test	**Previous:** Only in either Cohort 5 or 6 (depending	Updated notes to include Cohort 4 as part of the

Section # and Name	Description of Change	Brief Rationale
food cue	on PK from Cohort 1) **Revised:** Only in either Cohort 5 or 6 (depending on PK from Part 1, and Cohort 4).	decision making for Entero-Tracker timing.
Section 1.3.3: Part 2 (Cohort 6): Multiple Dose Administration to Healthy Participants for 21 days of Treatment	**Previous** Part 2 (Cohort 6): Multiple Dose Administration to Healthy Participants for 21 days of Treatment **Revised** Part 2 (Cohort 6): Multiple Dose Administration to Healthy Participants for up to 21 days of Treatment.	The change was made to allow flexibility of dosing in Cohort 6
Clinical laboratory assessments (heme/chem/ urinalysis-including liver chemistries)	**Revised:** *Gamma-GT on day 7-14, D21, Follow up and Early Withdrawal Visit or until resolution (whichever is later). **Previous:** *D1, D4, D11 and D18 (serum and renal chemistries only). **Revised:** *Daily chemistries and urinalysis from D3 through last day of dosing, at D26 and Follow up Visit or until resolution (whichever is later).	Additional chemistry blood draws and Urine Albumin to Creatine ratio (UACR) added in Part 2 to monitor for liver and renal chemistry changes
Core Urine Safety monitoring assessments	**Previous:** *Days 4, 11 and 18 only. **Revised** *Daily UACR from day 4 through 24hrs after last day of dosing and D26. Additional testing as required until resolution.	
Continuous cardiac telemetry	**Previous**: Continuous cardiac monitoring should be started approximately 90min before dosing on D1 through D21 after the Holter Monitor is applied. **Revised:** Continuous cardiac monitoring should be started approximately 90min before dosing on D1 through D22 after CCI CCI is removed.	Correction of telemetry notes.
Entero-Tracker or Entero-Test (bile sample collection Entero-Tracker or Entero-Test food cue	**Previous:** Only in either Cohort 5 or 6 (depending on PK from Cohort 1)	Updated notes to include Cohort 4 as part of the decision making for Entero-Tracker timing.

Section # and Name	Description of Change	Brief Rationale
	Revised: Only in either Cohort 5 or 6 (depending on PK from Part 1 and Cohort 4).	
Section 2.2 Background	**Previous:** The preclinical findings to date (described in detail in the Investigator's Brochure) suggest GSK3884464 acts through a novel mechanism of action for the treatment of HFrEF [GlaxoSmithKline Document Number RPS-CLIN-000167] **Revised:** The preclinical findings to date (described in detail in the Investigator's Brochure) suggest GSK3884464 acts through a novel mechanism of action for the treatment of HFrEF [GlaxoSmithKline Document Number RPS-CLIN-000167]	Updated IB number of IB Supplement.
Section 2.3 Benefit/Risk Assessment	**Previous:** Summaries of findings from these pre-clinical studies can be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-000167]. **Revised:** Summaries of findings from these pre-clinical studies can be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-000167]. **Previous:** IB [GlaxoSmithKline Document Number RPS-CLIN-000167]. **Revised:** IB [GlaxoSmithKline Document Number RPS-CLIN-000167031946].	Updated IB number of IB Supplement.
Section 2.3.1 Risk Assessment Exclusion Criteria	**Previous:** Screening urine albumin:creatinine ratio ≥30 mg/gm (>3 mg/mmol). **Revised:** Screening urine albumin:creatinine ratio ≥30 mg/gm (≥3 mg/mmol).	Corrected symbol > to ≥.
Study Stopping criteria Renal	**Previous**: Renal stopping criteria: Participants (all parts) **Revised** Renal stopping criteria: Individual (all	Section updated and renal stopping criteria was further defined to better monitor potential safety signals.

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	parts) **Previous:** New onset of any clinically significant and persistent (within 48 hrs) hematuria as confirmed by microscopy. **Revised:** New onset of any clinically significant and persistent (for 48 hrs) hematuria as confirmed by microscopy (in the absence of any other clinical cause). **Previous:** New onset of clinically significant and persistent (within 48 hrs) proteinuria (Spot Urine Albumin Creatinine ratio [ACR] ≥3mg/mmol) in the absence of another clinical explanation e.g. calculus/infection **Revised:** New onset of clinically significant and persistent (for 48 hours from the dosing day in the SAD part and at any point in the MAD) proteinuria (Spot Urine Albumin Creatinine ratio [ACR] ≥30mg/mmol) in the absence of another clinical explanation e.g. calculus/infection **Previous:** Change in serum creatinine >26 µmol/L (0.3 mg/dl) from baseline or > 25 % from baseline. If change in serum creatinine measures >26 µmol/L (0.3 mg/dl) or > 25 %, repeat within 24 hrs. If confirmed, the participant will be withdrawn. If a participant meets the withdrawal criteria for serum creatinine, then further investigations will be performed. **Revised:** If there is any increase in serum creatinine >26µmol/L (≥0.3mg/dl), repeat within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed. Increase in serum creatinine (ΔsCr) of >25% from baseline on 2 consecutive assessments within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will	
Study Stopping criteria Hepatoxicity		

Section # and Name	Description of Change	Brief Rationale
	be performed. **Previous:** The study will be temporarily halted if 2 or more participants across all study parts develop any of the above withdrawal criteria when considered related to study treatment. **Revised** If 2 or more participants in a given dose cohort develop any of the above withdrawal criteria, when considered related to study drug, then that cohort will be temporarily halted. **Previous:** Liver enzymes and bilirubin assessments. **Revised:** Liver enzymes and bilirubin assessments D4 through D6 in SAD and daily (from day 3 through 24hrs after last day of dosing, and at D19) in the MAD part of the study. **Revised: Added Text** Careful LFT monitoring will be implemented in the Part 2 of the study to minimise the risk of exposing the participants to additional study drug in the case of an elevation of ALT/AST above the individual stopping criteria. **Revised: Text added** In the ongoing study 213376, three cases of transient LFT increase have been observed in the 110mg single dose level with no concurrent symptoms. **Previous:** Liver Stopping Criteria **Revised:** Individual Liver Stopping Criteria	Clarified study stopping criteria based on study drug not placebo. Clarification of liver stopping criteria. Section updated and liver stopping criteria was further defined to better monitor potential safety signals.
Section 4.1 Overall Design	**Previous:** Each participant will participate in 3 dosing periods and will receive 2 doses of GSK3884464 and 1 dose of placebo in a randomized fashion. **Revised:** Each participant will participate in up to 3 dosing periods and will receive up to 2	These changes were made to the dosing criteria to clarify that the dose may be adjusted between dosing periods and to describe how to proceed with dosing and the minimum number of participants required in case stopping criteria are met.

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	doses of GSK3884464 and 1 dose of placebo in a randomized fashion. **Previous** A minimum of 3 cohorts is anticipated. If a participant is withdrawn from the study, the participant may be replaced as necessary with another participant assigned to the same treatment sequence with respect to active and placebo doses to ensure that at least 4 participants receive each active dose and 1 participant receives placebo and must complete the safety and PK assessments through at least the 120hr post-dose (or 5 half-lives, whichever is longer). **Revised:** A minimum of 3 cohorts is anticipated. If a participant is withdrawn from the study, the participant may be replaced as necessary with another participant assigned to the same treatment sequence with respect to active and placebo doses to ensure that at least 3 participants receive each active dose and 1 participant receives placebo and must complete the safety and PK assessments through at least the 120hr post-dose (or 5 half-lives, whichever is longer). **Previous:** **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and a 21-day (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants. **Revised:** **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and up to a 21-day (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants (See Section 4.4). **Previous**: Participants will report to the Clinical Research Unit on Day –1 and will remain in the unit until completion of the assessments on Day 19 (Cohorts 4 and 5) or Day 26 (Cohort 6). Participants will be randomly assigned to receive GSK3884464 or placebo (approximately 6 study intervention and 2 placebo). Plasma and urine PK, PD, and biomarker samples will be collected through the 19-	Update to language to permit at least 3 participants on active dose with safety and PK through 120 hours may be used dosing decisions. Update to language in Part 2 to provide flexibility in Cohort 6.

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	day or 26-day in-patient stay. **Revised:** Participants will report to the Clinical Research Unit on Day –1 and will remain in the unit until completion of the assessments on Day 19 (Cohorts 4 and 5) or Day 26 at the latest (Cohort 6). Participants will be randomly assigned to receive GSK3884464 or placebo (approximately 6 study intervention and 2 placebo). Plasma and urine PK, PD, and biomarker samples will be collected through the 19-day or up to 26-day in-patient stay. **Previous:** Safety, tolerability, and PK data will be reviewed in a minimum of 4 participants receiving active treatment upon completion of assessments at the end of their cohort (before initiation of dosing in the next cohort). Participants will be replaced as required to maintain the minimum number on treatment. The dose of GSK3884464 may be adjusted (lower or higher) based on the data from Part 1 and for cohorts going forward based upon the safety, tolerability, PK, and preliminary PD data from the previous cohort if available. See Section, 4.4 for information on the decision to proceed to the next dose level **Revised:** In both Part 1 and 2, the dose and/or frequency of GSK3884464 may be adjusted (lower or higher) based upon the safety, tolerability, PK, and PD data (if available) from previous Cohorts and dose levels. Safety, tolerability, and PK data will be reviewed in a minimum of 3 participants receiving active treatment upon completion of assessments at the end of their cohort (before initiation of dosing in the next cohort); participants will be replaced as required to maintain the minimum number on treatment. This requirement will be superseded in case stopping criteria (see Section 7.1) are met and it is not deemed safe to proceed with dosing at a certain GSK3884464 dose level: in this scenario, the dose might be de-escalated and its level may be selected based on safety, tolerability, PK and PD	This update permits change in dose levels based on active 3 participants and this change may be superseded by stopping criteria in Section 7.1

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	data (as available) in less than 3 participants receiving active treatment. See Section, 4.4 for information on the decision to proceed to the next dose level	
Section 4.2 Scientific Rationale for Study Design	**Previous:** As sufficient data from the Entero-Tracker or Entero-Test string is expected following one dose of the study drug, this assessment will be restricted to only one cohort in Part 2 (anticipated to be the second or third dose level depending on PK results in Part 1) during a participants' steady state. **Revised:** As sufficient data from the Entero-Tracker or Entero-Test string is expected following one dose of the study drug, this assessment will be restricted to only one cohort in Part 2 (anticipated to be the second or third dose level depending on PK results in Part 1 and Cohort 4) during a participants' steady state.	
Section 4.3.1 Prediction of Human PK and Safety Cover	**Previous:** Methodological details of the dose prediction are described in GlaxoSmithKline Document Number RPS-CLIN-000167, 2021 **Revised:** Methodological details of the dose prediction are described in GlaxoSmithKline Document Number RPS-CLIN-000167, 2022 **Previous:** Dose escalation in each part of the study will be guided by the review of emerging PK, safety and tolerability data; the exposure increments will be approximately 2-3 fold. **Revised:** Dose escalation in each part of the study will be guided by the review of emerging PK, safety, tolerability data and PD data if available; the exposure increments will be approximately 2-3 fold.	Updated IB number of IB Supplement Addition of PD data for review at Dose escalation meeting (if available) to help in dose selection.
Section 4.3.2 Prediction of Dose Levels for Part 1	**Previous:** The selection of the subsequent doses may deviate from those in the table, based on emerging available safety, tolerability,	Addition of PD data for dose selection if it is available for Part 1.

Section # and Name	Description of Change	Brief Rationale
	and PK data from previous dose levels. **Revised:** The selection of the subsequent doses may deviate from those in the table, based on emerging available safety, tolerability, PK data and PD data if available from previous dose levels.	
Section 4.3.3 Prediction of Dose Levels for Part 2	**Previous:** The decision to progress to Part 2 and the selection of the actual dose levels, of the repeat dose regimen and of the number of cohorts will be made by the DEC, based on safety, tolerability and PK data from Part 1 (Section 4.4, Section 10.1.5). The predicted doses to be explored in Part 2 may be adjusted to the new start and maximum doses pending data obtained in Part 1. **Revised:** The decision to progress to Part 2 and the selection of the actual dose levels, of the repeat dose regimen and of the number of cohorts will be made by the DEC, based on all available safety, tolerability, PK and PD data from Part 1 (Section 4.4, Section 10.1.5). The predicted doses to be explored in Part 2 may be adjusted to the new starting and maximum doses pending data obtained in Part 1. **Previous:** Three dose levels are planned in Part 2; their expected steady-state Cmax and AUC will have been shown to be safe after a single dose in Part 1. **Revised:** Up to three dose levels are planned in Part 2; their expected steady-state Cmax and AUC will have been shown to be safe after a single dose in Part 1.	Addition of PD data for dose selection if it is available for Part 2. These changes were made to the dosing criteria to clarify dose may be adjusted between dosing periods.
Section 4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study.	**Previous:** The decision to proceed to the next dose level, to progress through each Part/Cohort, and to include an additional cohort/dose level (if necessary) will be made by the DEC. The anticipated mean plasma exposure (C_{max} and AUC) for any dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study	These changes were made to the dosing criteria to clarify dose may be adjusted between dosing periods. This update permits change in dose levels based on 3 active participants and this change may be superseded by stopping criteria in Section 7.1 Lastly this section has updated dose

Section # and Name	Description of Change	Brief Rationale
	(Section 4.3.1). **Revised:** The decision to proceed to the next dose level, to progress through each Part/Cohort, and to include an additional cohort/dose level (if necessary) will be made by the DEC. In addition, the DEC may review data from Cohort 5 and determine duration of treatment in Cohort 6. The anticipated mean plasma exposure (C_{max} and AUC) for any dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study (Section 4.3.1). **Previous:** Each meeting will be scheduled to occur at the end of each cohort and / or treatment period on data obtained after each dose level. Dose escalation decisions will be based on data obtained from 4 or more participants on active treatment at the prior dose level. The review data set will consist at minimum AE listings, safety labs, electrocardiograms (ECG), vital signs (VS), and PK results derived from at least 24-hour plasma profiles. Pharmacodynamic (PD) data will be reviewed as available but will not be required for an escalation decision. **Revised:** Each meeting will be scheduled to occur at the end of each cohort and/or treatment period to review data obtained after each dose level. Dose escalation decisions will be based on data obtained from 3 or more participants on active treatment at the prior dose level, unless stopping criteria (see Section 7.1) are met at the prior dose level and the subsequent dose is de-escalated. The review data set will consist at minimum AE listings, safety labs, electrocardiograms (ECG), vital signs (VS), and PK results derived from at least 24-hour plasma profiles. Pharmacodynamic (PD) data will be reviewed as available for Part 1 and may be used with the rest of the data in dose selection to start and progress Part 2. PD data may not be required for an escalation decision	escalation criteria. .

Section # and Name	Description of Change	Brief Rationale
	Previous: Progression to the next higher dose level will be halted if: **Revised:** Progression to the next higher dose level <u>in a given cohort</u> will be halted if: **Previous:** The dose escalation will stop, and no further participants will be dosed at that dose level or any higher level. Revised: The dose escalation will stop <u>after completing the dose level</u>, and no further participants will be dosed at that dose level or any higher level. **Previous:** At a minimum, Multiple Ascending Dose (MAD) Cohort dose levels will be defined based upon Dose Escalation Committee (DEC) review of the first five Single Ascending Dose (SAD) dose levels. Additional MAD cohorts will be based on DEC review of subsequent SAD dose levels and the previous MAD. **Revised:** At a minimum, Multiple Ascending Dose (MAD) Cohort dose levels will be defined based upon Dose Escalation Committee (DEC) review of <u>up to the first</u> five Single Ascending Dose (SAD) dose levels. Additional MAD cohorts will be based on DEC review of subsequent SAD dose levels and the previous MAD.	
Section 5.2 Exclusion Criteria	**Previous:** Screening urine albumin:creatinine ratio >30 mg/gm (>3 mg/mmol). **Revised:** Screening urine albumin:creatinine ratio <u>≥</u>30 mg/gm (<u>≥</u>3 mg/mmol).	Correction of typographical error.
Section 6.3.2 Blinding	**Previous:** In addition, the sponsor will be blinded to treatment allocations, except for roles required to be “unblind” in order to manage study conduct, oversight and safety. This will be documented and maintained in the electronic Trial Master	Addition of GSK unblinded personnel.

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	File (eTMF). **Revised:** In addition, the sponsor will be blinded to treatment allocations, except for roles required to be "unblind" in order to manage study conduct, oversight and safety. Additional internal GSK safety representatives may be consulted and unblinded as deemed necessary by the DEC. This will be documented and maintained in the electronic Trial Master File (eTMF).	
Section 6.5 Dose Modification	**Previous:** The dosing schedule may be modified to expand a dosing cohort to further evaluate safety, PK and/or PD at a given dose level or to add cohorts to evaluate additional dose regimens. **Revised:** The dosing schedule may be modified to expand a dosing cohort to further evaluate safety, PK and/or PD at a given dose level.	This part of the sentence was removed to be in line with text in previous Sections detailed above.
Section 7.1.1.3 Dose Expansion Criteria	**Previous:** Four additional subjects on active and 2 additional subjects on placebo will be recruited at the same dose level. Any cohort expansion will be contingent on approval of an amended protocol by the UK ethics board and the MHRA. **Revised:** Up to four additional participants on active and 2 additional participants on placebo may be recruited at the same dose level. Any further cohort expansion will be contingent on approval of an amended protocol by the UK ethics board and the MHRA.	Clarification that less than 4 additional participants may be recruited at a dose level.
Section 7.1.5 Renal Section 7.1.5 Renal Stopping Criteria	**Previous:** New onset of any clinically significant and persistent (for 48 hours) hematuria as confirmed by microscopy (with no other identifiable clinical cause). **Revised:** New onset of any clinically significant and persistent (for 48 hours) hematuria as confirmed by microscopy (in the absence of any other clinical cause). **Previous:**	Updated and further defined renal stopping criteria to better monitor any potential safety signals. Clarified renal monitoring

Section # and Name	Description of Change	Brief Rationale
	New onset of clinically significant and persistent (within 48 hours) proteinuria (Spot Urine ACR ratio ≥3 mg/mmol) in absence of another clinical explanation e.g. calculus/infection. **Revised:** New onset of clinically significant and persistent (for 48 hours <u>from the dosing day in the SAD part and at any point in the MAD</u>) proteinuria (Spot Urine <u>Albumin Creatinine ratio</u> [ACR] ≥<u>3</u>0 mg/mmol) in absence of another clinical explanation e.g. calculus/infection. **Previous** If there is any change in serum creatinine > 26µmol/L (0.3 mg/dl), repeat within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed **Revised:** If there is any change in serum creatinine > 26µmol/L (<u>≥</u>0.3 mg/dl), repeat within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed **Revised: Added text** <u>If 2 or more participants in a given dose cohort develop any of the above withdrawal criteria, when considered related to study drug, then that cohort will be temporarily halted.</u>	criteria for hematuria and increased ACR to greater than ≥ 30mg/mmol from≥ 3mg/mmol to measure albuminuria (as required) not microalbuminuria. Updated renal stopping criteria.
Section 8 Study Assessments And procedures	**Previous:** The UK ethics board, the MHRA and investigator will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Patient Information Sheet and Consent Form (PICF). **Revised:** The UK ethics board, the MHRA and investigator will be informed of any <u>significant</u> safety issues, <u>including those</u> that require amendment of the Patient Information Sheet and Consent Form (PICF).	Updated guidance on informing Ethics, Regulatory and the investigator of significant safety issues.
Section 8.2.3.3 Continuous Cardiac Telemetry	**Revised: Added Text** <u>In addition, participants are permitted to be off telemetry during the 3D</u>	Updated guidance on removal of telemetry during an 3D echocardiogram.

Section # and Name	Description of Change	Brief Rationale
	echocardiogram procedure in Cohorts 4, 5 and 6.	
Section 8.4.1 Plasma Sample Collection	**Previous**: Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. **Revised**: Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the cohort/study Part has been unblinded.	Language has been updated to provide flexibility in reporting data.
Section 8.4.3 Bile Sample Collection	**Previous:** Bile samples for analysis of metabolites will be collected via the Entero-Tracker or Entero-Test in either the second cohort (Day 14) or third cohort (Day 21) in Part 2 (depending on PK results in Part 1). **Revised:** Bile samples for analysis of metabolites will be collected via the Entero-Tracker or Entero-Test in either the second cohort (Day 14) or third cohort (Day 21) in Part 2 (depending on PK results in Part 1 and Cohort 4).	Updated notes to include Cohort 4 as part of the decision making for Entero-Tracker timing.
Section 8.4.4 Sample Analysis	**Previous**: Drug concentration information will not be reported to investigative sites or blinded personnel until the study has been unblinded. **Revised**: Drug concentration information will not be reported to investigative sites or blinded personnel until the cohort / study Part has been unblinded.	Language has been updated to provide flexibility in reporting data.
Section 8.4.6: Adverse Events of Special Interest	**Previous:** No AE's of special interest will be collected in this study. **Revised:** Adverse Events of Special Interest (AESI) are selected AEs that must be reported to the Sponsor's Medical Monitor within 24 hours regardless of relationship to study treatment.	Addition of language to define Adverse Events of Special Interest.

Section # and Name	Description of Change	Brief Rationale
	For this study the AESI represent moderate or severe increases in liver function analyses.	
Section 9.5 Interim analyses	**Previous:** No formal interim analysis is planned. Safety and pharmacokinetic data will be reviewed by the DEC before dose escalation in each study Part, and between study Parts. **Revised:** Data may be analyzed at the end of each completed cohort/study Part. Safety and pharmacokinetic data (and PD data if available) will be reviewed by the DEC before dose escalation in each study Part, and between study Parts.	Language has been updated to provide flexibility in reporting data.
Section 10.2 Appendix 2: Clinical Laboratory Tests: Table 7	Previous: Gamma-glutamyl transferase (GGT) removed from Other Assessments Revised Gamma-glutamyl transferase (GGT) moved from Other Safety Assessments **Previous:** If trace protein or blood in urine is detected, a repeat test will be performed within 48hrs, except if the repeat test is required at Screening the site should repeat as soon as possible within the screening period. **Revised:** If trace protein or blood in urine is detected, a repeat test will be performed within 24hrs, except if the repeat test is required at Screening the site should repeat as soon as possible within the screening period.	Additional Gamma-glutamyl transferase (GGT) monitoring is now part of the safety update Updated trace protein or blood in urine test to shorter time period to repeat test.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Two-Part First Time in Human (FTIH) Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Repeat Oral Doses of GSK3884464 in a Randomized, Double Blind, Placebo-Controlled, Dose Escalation Study in Healthy Participants

Brief Title: A FTIH study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeat doses of GSK3884464 in healthy participants

Rationale: This study will be the first in human and the primary objective is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and repeat doses of GSK3884464 administered to healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
• To characterize the safety and tolerability profile of GSK3884464 in healthy participants.	• Number and percentage of healthy participants with adverse events. • Clinically significant changes from baseline in laboratory values, vital signs, continuous telemetry, 12-lead electrocardiogram (ECG), and echocardiograms (in Part 2 only) up to and including the follow up visit (7-10 days post final dose).
• To characterize the plasma PK of GSK3884464 in healthy participants.	• Plasma pharmacokinetic parameters following single oral doses including $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{½}$). • Plasma pharmacokinetic parameters following repeat oral doses including AUC_{τ}, C_{max}, trough plasma concentration ($C\tau$), time to maximum observed plasma drug concentration (t_{max}), terminal half-life ($t½$), accumulation ratios based on AUC_{τ} (R_{AUC}), on C_{max} (R_{Cmax}), and on C_{τ} ($R_{C\tau}$).

Objectives	Endpoints
Secondary	**Secondary**
• To evaluate target engagement following single and repeat oral doses of GSK3884464 in healthy participants.	• Maximum changes from baseline in NQO1 mRNA in whole blood post treatment with GSK3884464 in all parts of the study.

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Overall Design: This First Time in Human (FTIH) study 213376 will be a randomized, double-blind placebo-controlled study of the oral administration of GSK3884464 in healthy participants. As this will be the first time GSK3884464 will be given to humans, the study design may change based on emerging data as the study progresses.

The study is planned to have two Parts and will be conducted at a single center.

1. **Part 1** will be a 3-period crossover design, single dose (SD), dose escalation study in healthy participants. Participants will receive GSK3884464 or matching placebo as an oral dose. There will be up to three cohorts with 9 participants in each cohort, each cohort will have up to 3 time periods.
2. **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and up to 21-days (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants (See Section 4.4). It will consist of up to 3 dose cohorts with 8 participants per cohort. Participants in each cohort will receive GSK3884464 or matching placebo; not all participants will receive placebo.

Disclosure Statement: This is a First Time in Human Study. Sentinel dosing will be incorporated in each Part of the study and at each dose level. For Part 1, up to 3 participants will be dosed at a time, and their LFTs will be monitored until Day 6 or until resolution (whichever is later) before the next participants in the cohort are dosed. For Part 2, up to 3 participants will be dosed at a time and will be monitored for a minimum of 5 days prior to dosing the rest of the cohort.

The dose escalation committee will review data after each cohort and Part to assess safety. In addition, data from each Cohort will be evaluated to establish whether a switch to a gastro-resistant capsule will be used for the subsequent doses. Details of these criteria and switch are in Section 10.5. The participants, investigator, and study site staff will all be blinded. The sponsor will be blinded to treatment allocations, except for roles required to be “unblind” in order to manage study conduct, oversight and safety. GSK staff analyzing samples derived from this study will be unblinded. The schematics for each Part are provided in Section 1.2 and refer to Section 4.1 for Study Design.

Number of Participants:

A sufficient number of participants will be screened and randomly assigned to study drug (active or placebo) to achieve approximately 51 evaluable participants. It is estimated that Part 1 will have three cohorts for a total of 27 evaluable participants and Part 2 will have 24 evaluable participants. Additional participants/cohorts may be enrolled to allow for evaluation of additional dosing regimens levels as required.

Intervention Groups and Duration:

Screening	All screening assessments listed in the Schedule of Activities (SoA) will be completed within 28 days prior to first dose.
Intervention Period	Part 1 will consist of up to three cohorts. Each cohort could include up to 3 intervention periods. These will each be a single dose, crossover design. Part 2 will consist of up to three cohorts. Cohorts 4 and 5 (14-day) and Cohort 6 (up to 21-days) will be a sequential group, repeat dose with one intervention period (See Section 4.4).
Washout Period	In Part 1, a washout period of a minimum of 7 days or 5 half-lives (whichever is the longer) between each dose for an individual participant.
Follow-up	Each cohort will have a follow up visit 7-10 days after the last study treatment.
Total duration of study Parts (approximate)	Part 1: Each of the 3 cohorts will be approximately 76 days. Part 2: Cohorts 4 and 5 will be approximately 72 days and Cohort 6 will be approximately 80 days.

Dose Escalation Committee: A Dose Escalation Committee (DEC) will be used to ensure data integrity in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions for this study. The Committee will review emerging data and recommend changes to the study, and review safety parameters during the study. The details and composition of the DEC will be included in the Dose Escalation Plan (DEP), to be completed prior to commencement of study enrolment.

1.2. Schema

Figure 1 Overall Study Design

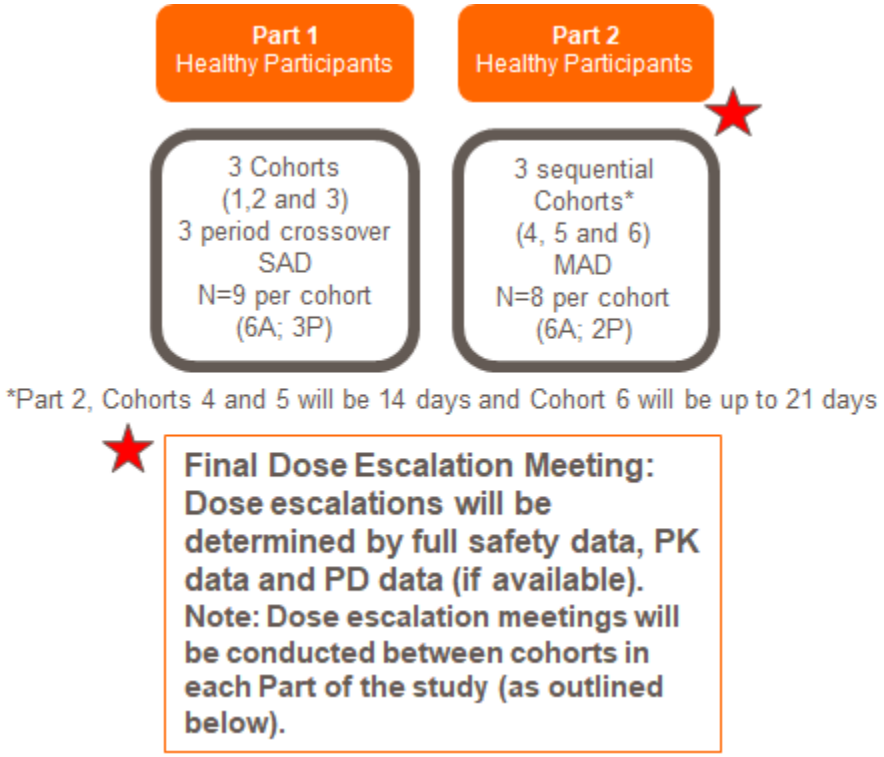
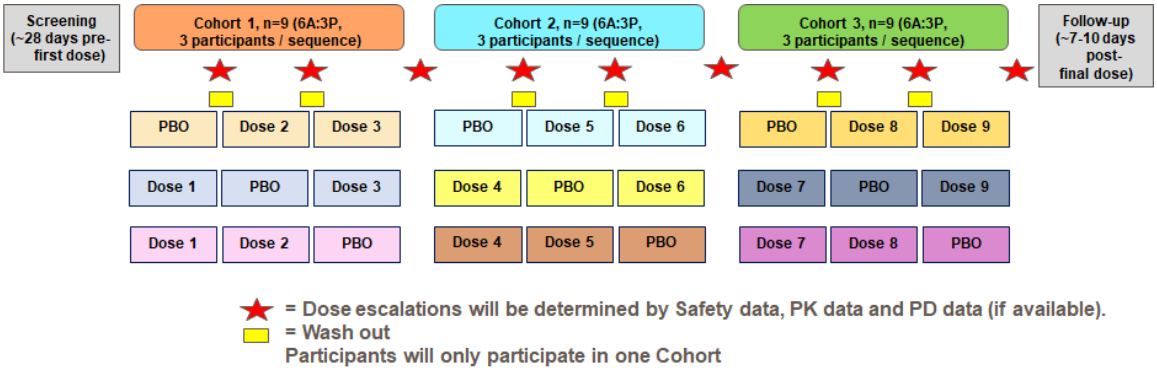


Figure 2 Part 1 Design and Cohort Dosing



Initial dosing for each dose level will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo (see Section 4.1). Within a cohort, participants will be randomized to one of 3 treatment sequences such that each participant receives up to 2 active doses and 1 placebo dose resulting in each active dose being administered to up to 6 participants and placebo to up to 3 participants.

Starting dose (Dose 1) = 1 mg

Subsequent dose escalations will be determined based on safety, PK data and PD data (if available).

Maximum predicted dose = 550 mg

Washout = minimum 7 days or 5 half-lives, whichever is longer
See Section 1.3.1, Section 4.1 and refer to SRM

Figure 3 Part 2 Design

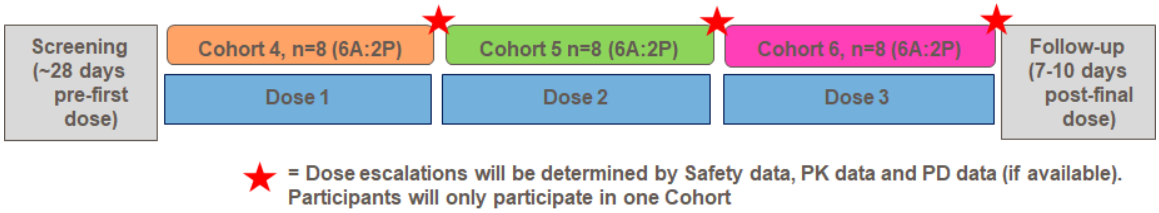


Figure 4 Part 2 Cohorts 4 and 5 Dosing

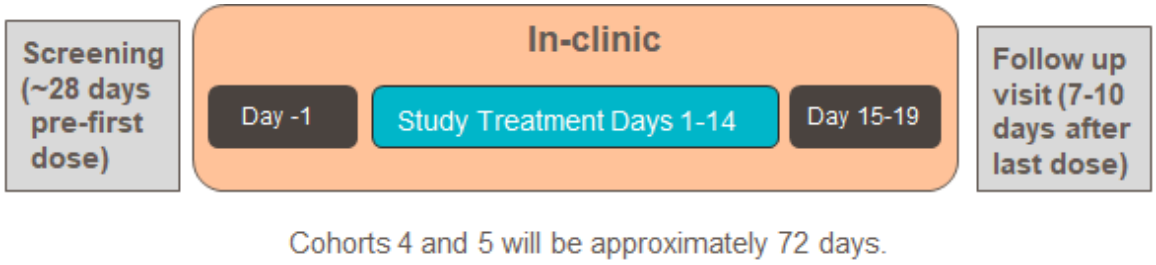
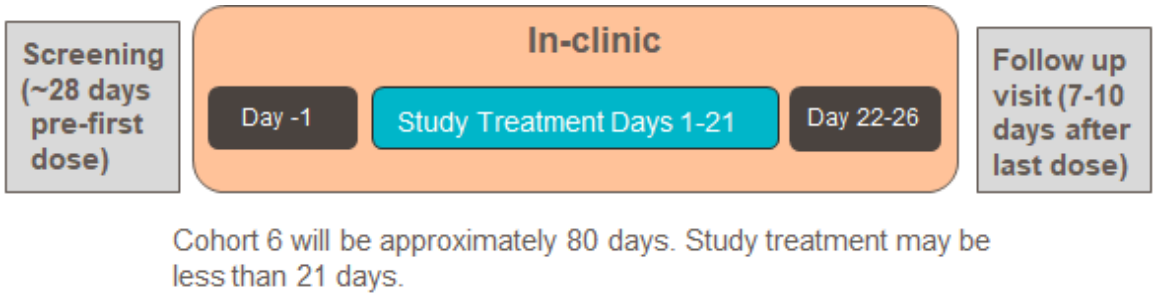


Figure 5 Part 2 Cohort 6 Dosing

Initial dosing for each dose level will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo. See Section 1.3.2 and Section 4.1.



1.3. Schedule of Activities

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic and biomarkers, may be altered during the course of the study based on emerging data or in-stream analyses (e.g., to obtain data closer to the time of peak plasma concentrations) to better characterize safety, PK, or PD.

Any changes in the timing or addition of time points for any planned study assessments will 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 UK ethics board, the MHRA and investigator will be informed of any significant safety issues, including those that require amendment of the Patient Information Sheet and Consent Form (PICF). The changes will be approved by the IRB/IEC before implementation as required. Allowed time windows will be specified in the Study Reference Manual (SRM).

1.3.1. Part 1: Single Dose Administration in Healthy Participants (Cohorts 1, 2 and 3)

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
Outpatient Visit	X								X	X	*As needed for additional safety evaluation between each study treatment (minimum 10 days).*
COVID-19 Testing[1]	X							X		X*	*Screening: in accordance with site procedures.* *Day 1 to 5: Ad hoc testing based on clinical presentations and site procedures.* *D6: Sample collected upon discharge.* **Early withdrawal only*
Admission to the Clinical Unit		X									
Inpatient Stay in the Clinical Unit		X	X	X	X	X	X	X			
Informed consent	X										

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
Inclusion and exclusion criteria	X	X									*Recheck clinical status before randomization and/or 1st dose of study intervention.*
Demography	X										
Randomization			X								
Study intervention			X								
Full physical examination including height	X									X*	*Height is collected at Screening only.* *Refer to Section 8.2.1* **Early withdrawal only*
Weight	X							X			*Weight must be collected in the morning after urination, before drinking or eating.*
Brief physical		X		X				X		X	*Refer to Section 8.2.1*

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
Medical/Medication/Drug/Alcohol/ CV disease history	X	X									*Review and update on D-1. Refer to Section 5.3.2* *Refer to SRM for testing*
FSH test	X										*If indicated in women, Refer to Section 10.4.1*
Urine Drug and Alcohol Breath Test	X	X									
Gamma-glutamyl transferase (GGT)	X					X		X		X*	**EW and Follow up Visit or until resolution (whichever is later).*
HIV, Hepatitis B and Hepatitis C screening	X										
Smokelyzer test	X	X									

		Treatment Period Study Period (Days)							Wash[2]-out		Notes
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] /**Early withdrawal**	
Clinical laboratory assessments (hema/chem/urinalysis-including liver chemistries)	X	X	X	X	X	X*	X*	X*		X*	*Refer to Section 10.2* **Daily serum chemistries D4 through D6 and EW as required. Follow up until resolution as required.* *For urinalysis, first void, when possible.*
Fasting HbA1c	X										
CCI [redacted]											

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
Vital signs and Temperature	X	X	X	X	X	X	X	X		X	*Vital signs to include HR, BP, and respiration rate.* *BP and HR will be assessed in a semi-supine position.* *Triplicate readings to be conducted for all BP readings.* *Vital Signs to be conducted on D -1 and pre-dose on D1 and then at the subsequent time points post-dose:15min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr, 96hr, 120hr (morning of D6).* *(Refer to Section 8.2.2).* *Daily temperature.*

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
12-lead ECG	X	X	X	X	X	X	X	X		X	*ECGs scheduled at the same time as a PK draw should be performed before PK draw.* *Single 12-Lead ECGs to be conducted in a semi-supine position daily and on Day 1 predose and then at the subsequent time points post-dose: 15 min, 1 hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr, 96hr, 120hr (morning of D6) (Refer to Section 8.2.3.1).* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *If any abnormal ECG reading is recorded, refer to Section 7.1.2 for appropriate action.*

		Treatment Period Study Period (Days)							Wash[2]-out		Notes
Procedure	Screening (up to 28 days before Day 1)	-1	1	2	3	4	5	6		Follow-Up (7-10 days post last dose)[1] /Early withdrawal	
CCI [redacted]											

		Treatment Period **Study Period (Days)**							**Wash[2]-out**		**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
Continuous cardiac telemetry			X	X	X						*Continuous cardiac monitoring should be started approximately 90min before dosing on D1. Full disclosures will be reviewed in detail in real-time.* *Remove D3 approximately 60hrs after dosing.*
3D Echocardiogram	X										

		Treatment Period Study Period (Days)							Wash[2]-out		Notes
Procedure	**Screening (up to 28 days before Day 1)**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**Follow-Up** (7-10 days post last dose)[1] **/Early withdrawal**	
CCI [redacted]											
Plasma hs Troponin			X	X						X	*Pre-dose and 24hr on D2 and at follow up visit.*

Procedure	Screening (up to 28 days before Day 1)	Treatment Period Study Period (Days) -1	1	2	3	4	5	6	Wash[2]-out	Follow-Up (7-10 days post last dose)[1] /Early withdrawal	Notes
Plasma NT-proBNP			X	X				X		X	*Pre-dose,24hr on D2, Day 6 prior to discharge, and at follow up visit.*
PD Whole Blood PAXgene samples (including NQO1 mRNA)			X	X							*For NQO1 CCI analyses:* *Pre-dose and 2hr, 6hr, 12hr, 24hr (D2) post-dose.* *Refer to SRM.*
CCI											
Meals		X	X	X	X	X	X	X			*No breakfast on D1.* *For participants taking the study intervention in gastro-resistant capsule form, fasting must be for 2hr post-dose.*
AE review		X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
SAE review	X	X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
Concomitant medication review		X	X	X	X	X	X	X	X	X	*Refer to Section 6.8*

Procedure	Screening (up to 28 days before Day 1)	Treatment Period Study Period (Days) -1	1	2	3	4	5	6	Wash[2]-out	Follow-Up (7-10 days post last dose)[1] /Early withdrawal	Notes
Discharge from the clinical unit								X			*Following completion of all assessments.*

1. Follow-Up visit: If a participant meets the criteria of a participant with known COVID-19 positive contacts in the past 14 days or is determined to have a high clinical index of suspicion for COVID-19 or has a positive laboratory confirmation of COVID-19 infection the follow-up visit may be deferred beyond 14 days after the last dose and scheduled/rescheduled at a timepoint as deemed appropriate by the Investigator.
2. Washout period is defined as a minimum 7 days or 5 half-lives, whichever is longer. Each patient will do three washouts.

CCI [redacted]

1.3.2. Part 2 (Cohorts 4 and 5): Multiple Dose Administration to Healthy Participants for 14 days of Treatment

	Screening and Baseline Period		**Treatment Period Study Period (Days)**						**Follow Up** (7-10 days post last dose)[1]	**Early With-drawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Outpatient Visit	X								X	X	
COVID-19 Testing[1]	X							X*			*Screening: in accordance with site procedures.* ***Days -1 to 18: Ad hoc testing based on clinical presentations and site procedures**.* **D19 only: Sample collected upon discharge.*
Admission to Clinical Unit		X									
Inpatient stay at Clinical Unit		X	X	X	X	X	X	X			
Informed consent	X										
Inclusion and exclusion criteria	X	X									*Recheck clinical status before randomization and/or 1st dose of study intervention.*
Demography	X										
Full physical examination including height	X									X	*Height is collected at Screening only. Refer to Section 8.2.1*
Randomization			X								
Weight	X		X				X				*Weight must be collected in the morning after urination, before drinking or eating.*

	Screening and Baseline Period		**Treatment Period Study Period (Days)**						**Follow Up** (7-10 days post last dose)[1]	**Early With-drawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Brief physical		X	X	X*			X	X*	X		*Refer to Section 8.2.1* **D2 and D15 only.*
Medical/Medication/Drug/Alcohol/CV disease history	X	X									*Review and update on D -1.* *Refer to Section 5.3.2.* *Refer to SRM for testing.*
FSH test	X										*If indicated in women, Refer to Section 10.4.1.*
Urine Drug & Alcohol Breath Test	X	X									*Refer to Section 10.2.*
Gamma-glutamyl transferase (GGT)	X				X	X	X	X*	X	X	**Gamma-GT on days 7-14, D19, Follow up and Early Withdrawal Visit or until resolution (whichever is later).*
HIV, Hepatitis B and Hepatitis C screening	X										
Fasting HbA1c	X										
Fasting Serum Insulin			X	X*		X*	X				**D4 and D11 only*
Adrenocorticotropic hormone (ACTH) and Cortisol		X*	X*				X*	X*		X	**Collect midnight D-1 and D14 and at 8am before dosing on D1 and 8am on D15.* *Samples should be collected at same time of day (i.e. no more than ±1hr of the collection time).* *If labs are abnormal, follow up should also be included after at least 7 days off treatment,*

	Screening and Baseline Period		Treatment Period Study Period (Days)						Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Aldosterone		X	X	X*		X*			X	X	*D4 and D11 only *Collect all samples at first AM draw.*
Smokelyzer test	X	X									
CCI [redacted]											

	Screening and Baseline Period		**Treatment Period Study Period (Days)**						**Follow Up** (7-10 days post last dose)[1]	**Early With-drawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Vital signs and Temperature	X	X	X	X	X	X	X	X	X	X	*Vital signs to include HR, BP, and respiration rate.* *BP and HR will be assessed in a semi-supine position.* *Triplicate readings to be conducted for all BP readings.* *Vital Signs to be conducted on Day -1 and pre-dose every day.* *In addition, the following timepoints should be obtained on Days 1 and 14 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr, 96hr, 120hr.* *(Refer to Section 8.2.2).* *Daily temperature.*
Columbia Suicide Severity Rating Scale (C-SSRS)		X			X		X		X	X	*Refer to SRM*
Cognitive Assessment (6-CIT)		X			X		X		X	X	*Refer to SRM*
12-lead ECG	X	X	X	X	X	X	X	X	X	X	*ECGs scheduled at the same time as a PK draw should be performed before PK draw.* *Single 12-Lead ECGs to be conducted on Day -1 and pre-dose every day.* *In addition, the following timepoints should be obtained on; D1 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr.* *Days 2-13 daily.* *D14 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr,*

	Screening and Baseline Period		Treatment Period Study Period (Days)						Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
											96hr, 120 hr. *Refer to Section 8.2.3.1.* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *If any abnormal ECG reading is recorded, refer to Section 7.1.2 for appropriate action.*
CCI [redacted]											

	Screening and Baseline Period		**Treatment Period Study Period (Days)**						**Follow Up** (7-10 days post last dose)[1]	**Early Withdrawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
3D Echocardiogram	X						X*				**May be performed within 24hrs pre- or post-dosing.*
CCI [redacted]											
Entero-Tracker or Entero-Test (bile sample collection							X				*Only in either Cohort 5 or 6 (depending on PK from Part 1 and Cohort 4).* *Entero-Tracker capsule to be swallowed ~2hr after dosing* *Details are in the SRM.*

	Screening and Baseline Period		Treatment Period Study Period (Days)						Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Entero-Tracker or Entero-Test food cue							X				*Only in either Cohort 5 or 6 (depending on PK from Part 1 and Cohort 4).* *Food cue will be given ~6hr post-dose.* *Details are in the SRM.*
Plasma hsTroponin			X		X		X		X	X*	*Pre-dose samples* **Collect when decision to withdrawal is made.*
Plasma NT-proBNP			X		X		X		X	X*	*Pre-dose samples* **Collect when decision to withdrawal is made.*
PD[3] Whole Blood PAXgene samples (including NQO1 mRNA)			X		X		X				*For NQO1 CCI [redacted] analyses:* *Pre-dose and 6hr, and 12hr post-dose.* *Refer to SRM*
PD[3] serum samples			X		X		X				*For oxidative stress biomarkers.* *Pre-dose samples. Refer to SRM*
CCI [redacted]											

	Screening and Baseline Period		Treatment Period Study Period (Days)						Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-19**			
Meals		X	X	X	X	X	X	X			*No breakfast on D1 and D14, serial PK days.* *For participants taking the study intervention in gastro-resistant capsule form, fasting must be for 2hr post-dose.*
Study intervention			X	X	X	X	X				
CCI [redacted]											
AE review		X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
SAE review	X	X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
Concomitant medication review		X	X	X	X	X	X	X	X	X	*Refer to Section 6.8*
Discharge from the clinical unit								X*			**Discharge on D19 following completion of all assessments.*

1. Follow-Up visit: If a participant meets the criteria of a participant with known COVID-19 positive contacts in the past 14 days, or is determined to have a high clinical index of suspicion for COVID-19, or has a positive laboratory confirmation of COVID-19 infection the follow-up visit may be deferred beyond 14 days after the last dose and scheduled/rescheduled at a timepoint as deemed appropriate by the Investigator

CCI [redacted]

3. PD= Pharmacodynamic

1.3.3. Part 2 (Cohort 6): Multiple Dose Administration to Healthy Participants for up to 21 days of Treatment

	Screening and Baseline Period		**Treatment Period Study Period (Days)**								**Follow Up** (7-10 days post last dose)[1]	**Early Withdrawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
Outpatient Visit	X										X	X	
COVID-19 Testing[1]	X									X*			*Screening: in accordance with site procedures.* ***D1 through D25: Ad hoc testing based on clinical presentations and site procedures.*** **D26 only: Sample collected upon discharge.*
Admission to Clinical Unit		X											.
Inpatient stay at Clinical Unit		X	X	X	X	X	X	X	X	X			
Informed consent	X												
Inclusion and exclusion criteria	X	X											*Recheck clinical status before randomization and/or 1st dose of study intervention.*
Demography	X												
Full physical examination including height	X											X	*Height is collected at Screening only. Refer to Section 8.2.1*
Randomization			X										
Weight	X		X				X		X				*Weight must be collected in the morning after urination, before drinking or eating.*

	Screening and Baseline Period		**Treatment Period Study Period (Days)**								**Follow Up** (7-10 days post last dose)[1]	**Early Withdrawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
Brief physical		X		X*			X	X*		X*	X		**D2, D15 and D22 only.* *Refer to Section 8.2.1*
Medical/Medication/Drug/Alcohol/ CV disease history	X	X											*Review and update on Day -1.* *Refer to Section 5.3.2.* *Refer to SRM for testing.*
FSH test	X												*If indicated for women. Refer to Section 10.4.1*
Urine Drug & Alcohol Breath Test	X	X											*Refer to Section 10.2.*
Gamma-glutamyl transferase (GGT)	X				X	X	X		X		X	X*	**Gamma-GT on days 7-14, D21, Follow up, and Early Withdrawal Visit or until resolution (whichever is later)..*
HIV, Hepatitis B and Hepatitis C screening	X												
Fasting HbA1c	X												
Adrenocorticotropic hormone (ACTH) and Cortisol		X*	X*						X*	X*	X		**Collect midnight D-1 and D21 and at 8am before dosing on D1 and 8am on D22.* *Samples should be collected at same time of day (i.e. no more than ±1hr of the collection time).* *If labs are abnormal, follow up should also be*

	Screening and Baseline Period		Treatment Period Study Period (Days)								Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
													included after at least 7 days off treatment,
Aldosterone		X	X	X*		X*		X*			X	X	**D4, D11, and D18 only* *Collect all samples at first AM draw.*
Fasting Serum Insulin			X	X*		X*		X*	X				**D4, D11 and D18 only*
Smokelyzer test	X	X											
CCI [redacted]													

	Screening and Baseline Period		Treatment Period Study Period (Days)								Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
CCI													
Vital signs and Temperature	X	X	X	X	X	X	X	X	X	X	X	X	*Vital signs to include HR, BP, and respiration rate.* *BP and HR will be assessed in a semi-supine position.* *Triplicate readings to be conducted for all BP readings.* *Vital Signs to be conducted on D -1 and pre-dose every day.* *In addition, the following timepoints should be obtained on D1 and D21 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr, 96hr, 120hr.* *(Refer to Section 8.2.2).*
Columbia Suicide Severity Rating Scale (C- SSRS))		X			X		X		X		X	X	*Refer to SRM*

	Screening and Baseline Period		Treatment Period Study Period (Days)								Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
Cognitive Assessment (6-CIT)		X			X		X		X		X	X	*Refer to SRM*
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	*ECGs scheduled at the same time as a PK draw should be performed before PK draw.* *Single 12-Lead ECGs to be conducted on Day -1 and pre-dose every day.* *In addition, the following timepoints should be obtained on D1 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr.* *Days 2-20 daily.* *D21 post-dose: 15 min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 72hr, 96hr, 120hr.* *Refer to Section 8.2.3.1.* *Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.* *If any abnormal ECG reading is recorded, refer to Section 7.1.2 for appropriate action.*
CCI [redacted]													

	Screening and Baseline Period		Treatment Period Study Period (Days)								Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
CCI [redacted]													
3D Echocardiogram	X						X*		X*				*May be performed within 24hrs pre- or post-dosing.
CCI [redacted]													

	Screening and Baseline Period		**Treatment Period Study Period (Days)**								**Follow Up** (7-10 days post last dose)[1]	**Early Withdrawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
													D1: pre-dose, post dose: 30min, 1hr, 1.5hr, 2hr, 3hr, 4hr, 6hr, 8hr, 12hr; 18hr, 24hr. *D7: collect at the following timepoints: pre-dose, 6hr and 12hr* **Draw only on D4, D11 and D18 and collect only pre-dose samples.* *D21 through D26: pre-dose, post dose: 30min, 1hr, 1.5hr, 2hr, 3hr, 4hr, 6hr, 8hr, 12hr; 18hr, 24hr, 36hr, 48hr, 72hr, 96hr, 120hr* *The PK sampling time points stated may be modified depending on emerging PK information as appropriate.* ***Metabolite plasma samples only on D1, D21 and D22 (to collect 24 hr sample only) with same timepoints as described for PK plasma sample above (See Section 8.4.1and SRM).*
Entero-Tracker or Entero-Tes (bile sample collection									X				*Only in either Cohort 5 or 6 (depending on PK from Part 1 and Cohort 4).* *Entero-Tracker capsule to be swallowed ~2hr after dosing* *Details are in the SRM.*

	Screening and Baseline Period		**Treatment Period Study Period (Days)**								**Follow Up** (7-10 days post last dose)[1]	**Early Withdrawal**	**Notes**
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
Entero-Tracker or Entero-Test food cue									X				*Only in either Cohort 5 or 6 (depending on PK from Part 1 and Cohort 4).* *Food cue will be given ~6hr post-dose.*
Plasma hsTroponin			X		X				X		X	X*	*Pre-dose samples.* **Collect when decision to withdrawal is made.*
Plasma NT-proBNP			X		X				X		X	X*	*Pre-dose samples.* **Collect when decision to withdrawal is made.*
PD[3] Whole Blood PAXgene samples (including NQO1 mRNA)			X		X				X				*For NQO1 (and other gene expression) analyses:* *Pre-dose and 6hr, 12hr post-dose. Refer to SRM.*
PD[3] serum samples			X		X				X				*For oxidative stress biomarkers.* *Pre-dose samples. Refer to SRM*
CCI [redacted]													
Meals		X	X	X	X	X	X	X	X	X			*No breakfast on D1 and D21, serial PK days.*

	Screening and Baseline Period		Treatment Period Study Period (Days)								Follow Up (7-10 days post last dose)[1]	Early Withdrawal	Notes
Procedure	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Days 2-6**	**Day 7**	**Days 8-13**	**Day 14**	**Days 15-20**	**Day 21**	**Days 22-26**			
													For participants taking the study intervention in gastro-resistant capsule form, fasting must be for 2hr post-dose.
Study intervention			X	X	X	X	X	X	X				
AE review		X	X	X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
SAE review	X	X	X	X	X	X	X	X	X	X	X	X	*Refer to Section 8.3*
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	*Refer to Section 6.8*
CCI [redacted]													
Discharge from the clinical unit										X*			**Discharge on D26 following completion of all assessments*

1. Follow-Up visit: If a participant meets the criteria of a participant with known COVID-19 positive contacts in the past 14 days, or is determined to have a high clinical index of suspicion for COVID-19, or has a positive laboratory confirmation of COVID-19 infection the follow-up visit may be deferred beyond 14 days after the last dose and scheduled/rescheduled at a timepoint as deemed appropriate by the Investigator

CCI [redacted]

3. PD= Pharmacodynamic

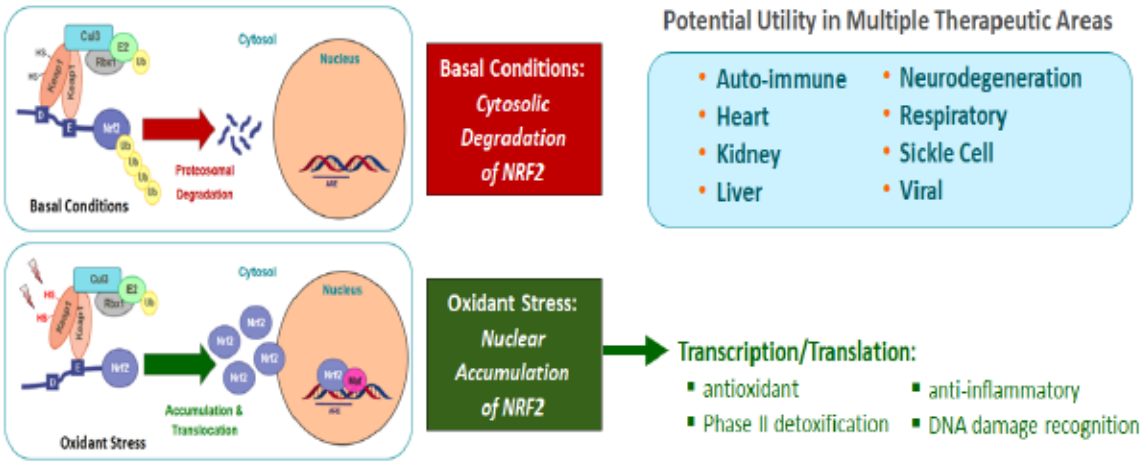
2. INTRODUCTION

GSK3884464 is a selective oral KEAP1 blocker/NRF2 activator that is being investigated as a once daily, first in class treatment for heart failure. GSK3884464 fully restored cardiac function without altering heart rate or blood pressure in a preclinical model of non-ischemic heart failure (HF), and also improved oxidation impaired contractility in human iPSC cardiomyocytes (iPSC-CMs). These findings suggest KEAP1 blockade/NRF2 activation may represent a novel mechanism for the treatment of heart failure.

There are currently an estimated 40 million heart failure (HF) patients worldwide, half of whom have heart failure with reduced ejection fraction (HFrEF). In the US alone the number of HF patients is projected to exceed 8 million by 2030 [Shah, 2017]. HF has a complex etiology driven by a spectrum of cardiac stressors of which the most common are hypertension, ischemic injury, vascular disease, or genetic predispositions to cardiac dysfunction. The progression of HF is characterized by structural and molecular remodeling of the heart, which may include ventricular hypertrophy, dilation, deranged myocardial metabolism, oxidant stress, inflammation, fibrosis and cell death [Shimizu, 2016]. The net effect of this maladaptive remodeling is reduced cardiac performance which progresses inexorably to pump failure [Drazner, 2011]. The current standard of care, including renin-angiotensin-aldosterone system inhibitors, neprilysin inhibitors, β-blockers, and cardiac resynchronization therapy all report decreased left ventricular (LV) dilation and end systolic dimensions with significant improvements in contractile function. However, despite the benefits of current therapies the 5-year HF mortality rate remains over 75%, with a mean survival of 2.1 years, in patients hospitalized for HF [Shah, 2017]

GSK3884464 is an orally active, non-covalent KEAP1-NRF2 competitive inhibitor that selectively targets the Kelch domain of KEAP1. The compound blocks the incorporation of NRF2 into the KEAP1 E3-ligase ubiquitin complex and thereby impairs the constitutive proteasomal degradation of NRF2. The net effect is the liberation and nuclear translocation of NRF2 and subsequent activation of NRF2 regulated gene transcription. KEAP1 is a ubiquitously expressed cytosolic redox sensor and substrate adapter protein for the Cullin-3 E3 ubiquitin ligase complex. The canonical regulation of KEAP1 is through its redox sensing domain (BTB domain), where reactive oxygen species modify cysteine residues resulting in a destabilized KEAP1 E3 ligase complex and subsequent liberation of substrate transacting proteins such as NRF2 (Figure 6).

Figure 6 NRF2 is regulated by KEAP1



NRF2 is regulated by KEAP1, a ubiquitously expressed cytosolic redox sensor and substrate adapter protein for the Cullin-3, E3 ubiquitin ligase complex. When oxidant stress is low, KEAP1 keeps NRF2 complexed with Cullin-3, E3 ubiquitin ligase to induce proteasomal degradation and prevent NRF2 nuclear accumulation. When oxidant stress is high, E3 ligase is disrupted and NRF2 is not degraded and can translocate into the nucleus.

The most well characterized substrate and pathway of KEAP1 relates to the transcription factor NRF2, where redox stress results in NRF2 nuclear translocation and NRF2 mediated transcriptional activation of phase II xenobiotic metabolism genes [Dinkova-Kostova, 2017]. However, GSK3884464 does not function through the redox sensing mechanism but instead selectively binds to the KEAP1-kelch domain which has been shown to result in redox independent liberation of NRF2 activity. Importantly, GSK3884464 is mechanistically distinct and pharmacologically differentiated from covalent, non-selective competitor assets that target the BTB domain of KEAP1. In addition, the chemical and physicochemical properties of GSK3884464 are favorable for the development of a medicine.

GSK3884464 has demonstrated potent disruption of the KEAP1-NRF2 protein-protein interaction in biochemical assays and potent activation of the NRF2 pathway in multiple human cell types. In addition, GSK3884464 has demonstrated robust target engagement in multiple rodent and non-rodent species following repeat oral dosing, CCI

CCI

In a series of preclinical rodent heart failure related studies, KEAP1 blockers and NRF2 activators have shown benefit. Furthermore, GSK3884464 has demonstrated the capacity to protect the viability and contractile function of human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) exposed to a severe oxidation and cytotoxicity challenge, which may be relevant considering that human HF patients carry a significant oxidant burden. In addition, in a mouse HF model of severe hemodynamic stress, administration of GSK3884464 and other KEAP1 blocker/NRF2 activator were shown to normalize left ventricular (LV) ejection fraction assessed by transthoracic

echocardiography. Importantly, the ejection fraction increase did not appear to occur by changing afterload (i.e. lowering blood pressure) or heart rate, the mechanisms by which many established HF therapies (i.e. Angiotensin-converting enzyme inhibitor (ACE) inhibitors/Angiotensin II receptor blockers (ARBs)/β-blockers) improve cardiac function. The findings in the mouse HF model have been highly reproducible, and the magnitude of benefit is exceptional in the context of non-hemodynamic mechanisms.

There are other aspects of the KEAP1-NRF2 protein that may provide a beneficial effect on metabolic disease. In addition to the cardioprotection demonstrated with GSK3884464 and other similar KEAP1 blockers/NRF2 activators, which suggests a novel mechanism for treating heart failure with reduced ejection fraction, the KEAP1/NRF2 pathway has also been reported to play a role in metabolic homeostasis. Pharmacological activation of NRF2 by the covalent NRF2 activators TBE-31 or Sulforaphane in mice with diet-induced type 2 diabetes mellitus (T2DM) resulted in improved glucose disposal [Sharma, 2018, Axelsson, 2017], while treatment with Sulforaphane reduced fasting blood glucose and glycated hemoglobin (HbA1c) in obese patients with T2DM [Axelsson, 2017]. Additionally, pharmacological activation of NRF2 with TBE-31 in mice with diet-induced obesity and insulin resistance reversed insulin resistance, suppressed hepatic steatosis and ameliorated both nonalcoholic steatohepatitis (NASH) and liver fibrosis [Sharma, 2018]. These preclinical findings support potential utilization in additional patient populations (i.e. diabetes, NASH, obesity, etc.), including patients with HF with preserved ejection fraction (HFpEF) where insulin sensitivity (signalling for glucose/fat utilization) contributes to the underlying pathophysiology. Other exploratory biomarkers are being collected to inform these alternative indications.

2.1. Study Rationale

This will be a first in human study and the main objective is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and repeat oral doses of GSK3884464 administered to healthy participants.

2.2. Background

Despite the relatively large number of approved therapies on the market for HFrEF, significant unmet need still exists for these patients as the 5-year mortality remains around 50%. Therefore, there is a significant need for novel therapies to treat HFrEF. The current SoC for HFrEF generally provides benefit by affecting loading conditions or supraphysiologically increasing cardiomyocyte cytosolic calcium levels, creating the potential for hypotension and proarrhythmogenesis, respectively, which limits dose and therapeutic potential. Novel investigative drugs that target other mechanisms that do not affect blood pressure or heart rate, such as GSK3884464, have the potential to fill this large unmet need for HFrEF patients.

GSK3884464 protects the viability and contractile function of human iPSC-CMs exposed to severe oxidative stress (relevant as HFrEF patients demonstrate a significant oxidant burden) and normalizes LV ejection fraction in a murine model of non-ischemic heart failure. The preclinical findings to date (described in detail in the Investigator's Brochure) suggest GSK3884464 acts through a novel mechanism of action for the treatment of HFrEF [GlaxoSmithKline Document Number RPS-CLIN-000167]

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK3884464 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

There is no expected benefit to participants taking part in this study.

To date, GSK3884464 has not been administered to human participants; therefore, no clinical data are available. This is the first single and multiple dose study proposed in human participants with GSK3884464.

The risk assessment of GSK3884464 is based on the pre-clinical studies conducted to date and data in the published literature. Summaries of findings from these pre-clinical studies can be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-000167]. -

Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Section 2.3.1. In this study, safety will be monitored closely both by subjective reporting and by objective means, i.e. serial assessments of vital signs, clinical laboratory information and cardiac monitoring. This study will be run in a clinical unit with immediate access to hospital facilities for the treatment of medical emergencies.

In light of the coronavirus 2019 (COVID-19) pandemic, all participants will be screened for COVID-19 prior to, during, and at the end of the study period(s).

More detailed information about the known and expected benefits and risks and reasonable expected adverse events for GSK3884464 may be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-000167].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention	
Renal	In rats given ≥0.3 mg/kg/day, dose- and time-dependent increased kidney weight, tubular degeneration/regeneration and mononuclear cell inflammation were observed. The effects contributed to the moribund condition in female rats given 1 mg/kg/day for 10 days. Following a 4 week off-treatment period, effects were largely reversible. CCI [redacted] CCI were increased on Day 7 of dosing when measured in an affected rat given 0.3 mg/kg/day. Similar kidney weight and microscopic findings were observed in mice but were of minimal severity, not considered adverse, but persisted following a 4 week off-pretreatment period. In monkeys, effects were limited to increased kidney weight at all doses. The rat is considered to be sensitive to renal effects versus other species (including human) due to species differences in pharmacology. There is approximately 0.01- fold, 0.19- fold, and 2.7- fold margins from the predicted human exposure (AUC) at the highest proposed repeat dose of 210 mg/day to the NOAEL in rats, mice,	**The following inclusion and exclusion criteria have been included to further mitigate this risk:** **Inclusion criteria:** Urinary analysis at screening to be free of blood and protein. If trace protein or blood is found, a repeat test will be performed within 24 hrs, or as soon as possible within screening period. If trace blood or protein is still seen on repeat analysis, the patient is ineligible. **Exclusion criteria:** • History of current or past significant renal diseases to be excluded, e.g. Acute Kidney Injury, parenchymal kidney disease. Not to exclude past history of renal calculi. • Screening estimated glomerular filtration rate (eGFR) (CKD-EPI) ≤ 90 ml/min/1.73m^2. • Screening urine albumin:creatinine ratio ≥30 mg/gm (≥3 mg/mmol).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and monkeys, respectively.	**Monitoring (all Parts):** • Monitoring serum potassium. • Serum renal function and urinary analysis monitoring (first void if possible). • Urine albumin:creatinine ratio (first void if possible). • Urine glucose by dipstick, if dipstick is positive then send for laboratory urine glucose with contemporaneous serum glucose. • By observing the PK safety margin for renal findings by targeting up to the total plasma AUC and Cmax to be below the monkey plasma NOAEL ($AUC_{0\text{-}24h}$ of 316000 ng.h/mL and a mean plasma Cmax of 48300 ng/mL). • Monitor for clinical symptoms of polyuria and polydipsia; if symptoms are suggestive, then exclude endocrine causes and quantify urine output (Refer to SRM). **Renal stopping criteria**: **Individual** (all parts) • Relevant renal safety data from the current and any previous cohort will be considered

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		as part of dose escalation decisions. • New onset of any clinically significant and persistent (for 48 hrs) hematuria as confirmed by microscopy (in the absence of any other clinical cause). • New onset of clinically significant and persistent (for 48 hours from the dosing day in the SAD part and at any point in the MAD) proteinuria (Spot Urine Albumin Creatinine ratio [ACR] ≥30mg/mmol) in the absence of another clinical explanation e.g. calculus/infection • If there is any increase in serum creatinine >26 µmol/L (>0.3mg/dl) repeat within 24 hours. If confirmed, the participant will be withdrawn. and further investigations will be performed. • Increase in serum creatinine (ΔsCr) of >25% from baseline on 2 consecutive assessments within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed. • Reduction in eGFR from baseline > 25 % from baseline. If reduction in eGFR is > 25 %, repeat within 24 hrs. If confirmed, the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		participant will be withdrawn. If a participant meets the withdrawal criteria for eGFR, then further investigations will be performed **Study Stopping criteria** If 2 or more participants in a given dose cohort develop any of the above withdrawal criteria, when considered related to study drug, then that cohort will be temporarily halted. CCI [redacted]
Hepatotoxicity	In rats, dose-dependent adverse effects in the liver (increases liver weight and/or hepatocellular hypertrophy, serum liver enzymes and total bilirubin, hepatocellular cytoplasmic rarefaction, and mixed cell inflammation) were observed, which occurred at doses below estimated efficacious clinical exposures but were largely reversible. The rat is considered to be sensitive to adverse liver effects versus other species (including human) due to species differences in pharmacology.	**The following exclusion criteria have been included to further mitigate this risk**: • Current or chronic history of liver disease or known hepatic or biliary abnormalities. • Alanine transaminase (ALT) ≥ ULN. • Bilirubin ≥ ULN. • Positive Hepatitis C and/or Hepatitis B antibody test result.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In mice, hepatocellular hypertrophy was observed at ≥5 mg/kg/day and was associated with increased liver weight. Following an off-treatment period, similar effects were observed but were lesser in severity. In monkeys, increased liver weight, decreased total cholesterol and bilirubin were observed at ≥ 5mg/kg/day. At ≥ 25mg/kg/day, decreased ALP was observed. There is approximately 0.01- fold, 0.19- fold, and 2.7- fold margins from the predicted human exposure (AUC) at the highest proposed repeat dose of 210 mg/day to the NOAEL in rats, mice, and monkeys, respectively. In the ongoing study 213376, three cases of transient LFT increase have been observed in the 110mg single dose level with no concurrent symptoms.	• Regular alcohol consumption within recommended limit within the past six months prior to the study. **Monitoring:** • Liver enzymes and bilirubin assessments daily D4 through D6 in SAD and from day 3 through 24hrs after last day of dosing, and at D19) in the MAD part of the study • Bile samples for analysis of GSK3884464 and any metabolites in one of the cohorts only (Entero-Tracker). • Careful LFT monitoring will be implemented in the Part 2 of the study to minimise the risk of exposing the participants to additional study drug in the case of an elevation of ALT/AST above the individual stopping criteria. **Individual Liver stopping criteria**: • ALT ≥ 3xULN. Relevant liver safety data from the current and any previous cohort will be considered as part of dose escalation decisions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GI effects	In mice and rats, dose-dependent, reversible hyperplasia/hyperkeratosis and/or mixed cell inflammation in the esophagus, stomach (nonglandular and glandular), and (in mice only) tongue were observed. In mice, these effects contributed to morbidity. The rodent GI effects were reversible following an off-treatment period. While the rodent gastrointestinal effects occurred below estimated efficacious exposures, the weight of evidence supports that these effects are pharmacologically mediated, rodent-specific, and not relevant to human. In monkey, decreased body weight, emesis and reduced eating/salivation were observed at 100, ≥ 30 and ≥ 10 mg/kg/day, respectively, in the absence of microscopic findings. There is approximately 0.01- fold, 0.19- fold, and 2.7- fold margins from the predicted human exposure (AUC) at the highest proposed repeat dose of 210 mg/day to the NOAEL in rats, mice, and monkeys, respectively.	**The following exclusion criteria have been included to reduce this risk further**: • History or presence of significant gastrointestinal disorders (GERD, nausea, vomiting or dysphagia). Participant monitoring will be done using a daily CCI [redacted] In the event of clinically significant toxicity, the participant will be withdrawn, and supportive therapy provided according to standard medical practice. Relevant GI safety data from the current and any previous cohort will be considered as part of dose escalation decisions with an option to switch to gastro-resistant capsules if the incidence of GI symptoms exceeds the placebo arm / historical placebo effects.
NRF-2 activation-dependent tumour progression and/or increased tumour chemoresistance (based on data in literature)	A potential class risk exists for NRF2 activators, with respect to providing a growth advantage to established cancers/and or chemoresistance in patients. However, antioxidants and NRF2 activators have been available as dietary supplements or	Participants will be exposed to study medication for a short duration in the current study (maximum 21 days dosing). **The following exclusion criteria have been included to reduce this risk further:**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	medicinal products for decades. For instance, the NRF2 activator Tecfidera (dimethyl fumarate) has been administered to at least 300,000 multiple sclerosis patients since launch. Currently, no excess malignancies are reported in the literature or in the Tecfidera prescribing information. Data from genotoxicity assessments suggest that GSK3884464 does not present a genotoxic hazard to humans.	• Lymphoma, leukaemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years. • Breast cancer within the past 10 years.
Reproductive toxicity	Animal reproductive studies have not been conducted with GSK3884464.	The following inclusion criteria have been included to reduce this risk further: • Male or females of non-childbearing potential (Section 5.1 and Section 10.4). For male subjects that are with female partners of childbearing potential, contraception must be used (Appendix 4).
Potential effects on CNS	KEAP1/NRF2 are ubiquitously expressed in human organs; including high amounts in the brain. Animal studies showed that GSK3884464 concentration was low in the brain, with tissue to plasma ratios of 0.061 and 0.026 for brain in rats and monkeys respectively. In vitro CNS multielectrode array toxicity assay showed no substantial effect with GSK3884464	• Participants with a history or current evidence of depression, bipolar disorder, suicidal ideation and behavior, or a lifetime history of suicide attempt will be excluded. Participants will be closely monitored. • Sentinel dosing approach will be utilized. • In line with FDA guidance, assessment of suicidal ideation and behaviour occurrence will be conducted in participants who receive repeated doses.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	on CNS activity up to 10 µM. No behavioural signs were noted during 6-week studies in rats at dose up to 30mg/kg and monkeys at dose up to 50 mg/kg, and no effects were observed in the IRWIN test at doses up to 30 mg/kg.	• Assessments of cognitive safety will be performed in participants with repeated doses. • Stopping criteria based on assessments of suicidal ideation and behaviour, and cognitive safety.
Study Procedures		
Bile Sampling (Entero-Tracker or Entero-Test)	The use of the Entero-Test has been approved by the European regulatory authorities (ISO 9001 and CE Mark Certification; European Union Medical Devices Directive (MDD)). • Streaks of blood on the string due to local irritation have been infrequently noted. • Rarely, a patient will be unable to swallow the capsule because of gagging or will vomit after doing so. • Gagging upon retrieval of the string can occur. • On a few occasions, an entire string has been swallowed without ill effects and passes out from the body in the faeces.	• The string will be securely taped in place (to the cheek of each participant) during the collection time to minimize risk of swallowing the entire string. • Any participant incapable of swallowing the string will be allowed to continue in the study without CCI [redacted] collection. • Participants undergoing bile sampling should not be exposed to magnetic resonance imaging (MRI) for at least 72 hrs post swallowing of the capsule device – such time will allow the stainless-steel ball to be expelled into the stool.
Other		
COVID-19	Participation within a clinic setting may increase the risk of contracting COVID-19.	**The following inclusion criteria have been included to reduce this risk further:**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Exposure to other participants and staff may increase the risk of exposure.	18 to 50 years of age inclusive. COVID-19 screening prior to study and testing during the study. Monitoring for clinical presentation of COVID-19 signs/symptoms. Conduct study at a site(s) which have the appropriate mitigation strategies in place. **The following exclusion criteria have been included to reduce this risk further:** • Participants with signs and symptoms suggestive of COVID-19 within 14 days of admission. • Participants with known COVID-19 positive contacts in the past 14 days.
Immunocompromization potential	In placebo-controlled trials, 6% of patients taking Tecfidera (dimethyl fumarate, DMF), a non-specific NRF2 activator, experienced lymphocyte counts of <0.5x10^9/L (lower limit of normal 0.91x10^9/L). No difference in infection rates was seen between patients taking Tecfidera and those taking placebo (Tecfidera, 2020 Prescribing Information, Revised 2020). GSK3884464 In mice, rats and monkeys, dose-dependent decreased thymic weight and cellularity were observed, reversible in rats and were considered	**The following criteria have been included to reduce this risk further:** • Clinical laboratory hematological assessments conducted at screening and at baseline. • Participants monitored throughout the study dosing cohorts. **The following exclusion criteria have been included to reduce this risk further:** • History or presence of significant hematological disorder capable of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	secondary to stress. In rodents, decreased lymphocyte count and marginal zone lymphocytes and/or increased absolute platelet count were observed at non-tolerated doses and/or attributable to stress. Additionally, immunophenotyping of monkey blood following 6 weeks of dosing did not demonstrate any effects.	constituting a risk when taking the study treatment; or interfering with the interpretation of data. • Any clinically relevant abnormality on the screening laboratory examination and at any time during the study per Medical Monitor review.
Cardiovascular Effects	In toxicology studies, which were conducted for up to six weeks with daily oral dosing and in single dose safety pharmacology studies, there have been no cardiovascular effects observed in animals given GSK3884464. Specifically, there were no organ weight, macroscopic or microscopic effects observed in heart and/or the vasculature, nor were there any electrocardiography effects observed. In vitro, effects were limited to partial hERG inhibition at concentrations far exceeding the estimated clinical exposure range. In preclinical efficacy studies, upregulation of CCI [redacted] in the myocardium was seen as early as day three after the initiation of treatment. No effect on myocardial function was noted in healthy rodents, and improvements in ejection fraction (remodelling) were noted after approximately two weeks of treatment in a mouse model of pressure-overload heart failure.	**The following exclusion criteria have been included to reduce this risk further:** • Clinically significant high blood pressure and/or history of hypertension as determined by the investigator. • Serum troponin I or troponin-T greater than the upper limit of normal. • QTcF ≥450 msec; • Screening 12-lead ECG with any of the following: • Second- or third- degree atrioventricular block (AVB). o Two or more significant pathological Q-waves (defined as Q-wave ≥ 40 msec or depth greater than 0.4-0.5 mV) in a pattern consistent with a prior myocardial infarction.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		○ Ventricular pre-excitation. ○ Bradycardia as defined by sinus rate ≤ 30 beats per minute (BPM) ○ Complete left bundle branch block (LBBB) ○ History of QTc prolongation, symptomatic cardiac arrhythmias or cardiac arrest. • Screening Holter (24 hours) with any of the following: ○ Sinus bradycardia ≤ 30 BPM ○ Non-sustained ventricular tachycardia (NSVT) or more than 30 Ventricular Premature Depolarisations (VPD) during an hour. ○ Atrial arrhythmia ≥ 100 BPM for 3 seconds or longer or more than 40 Atrial Premature Depolarisation (APD) during an hour. During the trial period, telemetry and ECG monitoring will be performed. Additionally, regular measurements of high-sensitivity troponin and NT-pro BNP will be reviewed during the study.

2.3.2. Benefit Assessment

No clinical benefit is expected for participants in this FTIH study.

This study will provide initial safety, tolerability, pharmacokinetic, and pharmacodynamic data to better inform dose selection and safety monitoring in the subsequent studies in the clinical development program.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to the participants in this study, the potential risks identified in association with study intervention and procedures are considered minimal and justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
• To characterize the safety and tolerability profile of GSK3884464 in healthy participants.	• Number and percentage of healthy participants (single and repeat doses) with adverse events. • Clinically significant changes from baseline in laboratory values, vital signs, continuous telemetry, 12-lead electrocardiogram (ECG), and echocardiograms (in Part 2 only) up to and including the follow up visit (7-10 days post final dose).
• To characterize the plasma PK of GSK3884464 in healthy participants (single and repeat dosing).	• Plasma pharmacokinetic parameters following single oral doses including $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{½}$). • Plasma pharmacokinetic parameters following repeat oral doses including AUC_{τ}, C_{max}, trough plasma concentration ($C\tau$), time to maximum observed plasma drug concentration (t_{max}), terminal half-life ($t½$), accumulation ratios based on AUC_{τ} (R_{AUC}), on C_{max} (R_{Cmax}), and on C_{τ} ($R_{C\tau}$).

Objectives	Endpoints
Secondary	**Secondary**
• To evaluate target engagement following single and repeat oral doses in healthy participants.	• Maximum changes from baseline in NQO1 mRNA in whole blood post treatment with GSK3884464 in all parts of the study.
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[redacted]

4. STUDY DESIGN

4.1. Overall Design

This First Time in Human (FTIH) study 213376 will be a randomized, double-blind, placebo-controlled study of the oral administration of GSK3884464 in healthy participants. As this will be the first time GSK3884464 is given to humans, the study design may change based on emerging data as the study progresses.

The study is planned to have two Parts (Parts 1, and 2) and will be conducted at one center.

1. **Part 1** will be a 3-period crossover design, single dose (SD), dose escalation study with 3 participants per sequence in healthy participants. Each participant will participate in up to 3 dosing periods and will receive up to 2 doses of GSK3884464 and 1 dose of placebo in a randomized fashion. There will be a minimum of 7 days (or 5 half-lives, whichever is longer) washout period between dosing in each session.

Approximately 9 participants will be enrolled in each cohort. Participants will be admitted to the Clinical Research Unit on Day –1 and will remain in the unit until completion of the assessments on Day 6 as outlined in the SoA. Participants will be discharged from the clinical unit for the washout period between dosing sessions and will return approximately 7-10 days after their last dosing session for a follow-up visit.

Participants will be randomized to treatment sequences such that in each period up to 6 participants will receive active dose and up to 3 participants will receive placebo. Up to 2 to 3 participants will be dosed at a time, and their LFTs will be closely monitored before the next participants receive study treatment. A minimum of 3 cohorts is anticipated. If a participant is withdrawn from the study, the participant may be replaced as necessary with another participant assigned to the same treatment sequence with respect to active and placebo doses to ensure that at least 3 participants receive each active dose and 1 participant receives placebo, and must complete the safety and PK assessments through at least the 120hr post-dose (or 5 half-lives, whichever is longer). Additional participants may be dosed at a given level if additional data are necessary to establish safety, tolerability, or PK parameters prior to dose escalation.

2. **Part 2** will be a sequential design, 14-day (Cohorts 4 and 5) and up to a 21-day (Cohort 6) repeat-dose (RD), dose escalation study in healthy participants (See Section 4.4). Each cohort will consist of approximately 8 participants. Participants in each cohort will receive GSK3884464 or matching placebo according to a randomization schedule prepared prior to the start of the study. The study will be conducted sequentially starting with Dose 1. Participants will receive repeat daily doses of the study intervention or placebo based on PK data obtained in Part 1 and ongoing PK data in Part 2.

Participants will report to the Clinical Research Unit on Day –1 and will remain in the unit until completion of the assessments on Day 19 (Cohorts 4 and 5) or Day 26 at the latest (Cohort 6). Participants will be randomly assigned to receive GSK3884464 or placebo (approximately 6 study intervention and 2 placebo). Plasma and urine PK, PD, and biomarker samples will be collected through the 19-day or up to 26-day in-patient stay. All participants will return to the Clinical Research Unit for a follow up visit approximately 7-10 days after their last dose of study treatment.

In both Part 1 and 2, the dose and/or frequency of GSK3884464 may be adjusted (lower or higher) based upon the safety, tolerability, PK, and PD data (as available) from previous Cohorts and dose levels. Safety, tolerability, and PK data will be reviewed in a minimum of 3 participants receiving active treatment upon completion of assessments at the end of their cohort (before initiation of dosing in the next cohort); participants will be replaced as required to maintain the minimum number on treatment. This requirement will be superseded in case stopping criteria (see Section 7.1) are met and it is not deemed safe to proceed with dosing at a certain GSK3884464 dose level: in this scenario, the dose might be de-escalated and its level may be selected based on safety, tolerability, PK and PD data (if available) in less than 3 participants receiving active treatment. See Sections 4.4 for information on the decision to proceed to the next dose level

Disclosure Statement: This is a First Time in Human Study. Each active dose level will be administered initially to a smaller group of sentinel participants (1 on active and 1 on placebo) to evaluate safety at each dose level. In Part 1, sentinel participants will be followed clinically for 6 days (predicted half-life for GSK3884464 is approximately 12hrs) to allow for adequate observation of safety. In Part 2, sentinel participants will be followed clinically for 14 days to allow for adequate observation of safety to monitor for emergence of adverse events. If no acute safety issues are observed in this smaller group of sentinel participants (including review of the safety laboratory results), then the remaining participants will receive the same dose prior to dose escalation (Section 4.4).

4.2. Scientific Rationale for Study Design

The study design is based on well-established and published methods to evaluate the first single and repeat dose administration of experimental drugs, including the use of sentinels. This study is placebo-controlled to allow for a valid evaluation of adverse events attributable to treatment versus those independent of treatment.

Participants in Part 2 will be enrolled into the study with a BMI range from 22-30. This selected range will bias towards heavier participants who are more likely to have insulin resistance to determine if GSK 3884464 has an impact on fasting glucose and insulin levels.

This FTIH study will include evaluation of PD markers to assess target engagement (i.e. NQO1 mRNA in whole blood). Additional exploratory biomarkers of oxidative stress, inflammation, and renal toxicity may be assessed to understand effects of GSK3884464 in healthy participants.

In order to characterize potential biliary elimination pathways, this study will also employ the Entero-Tracker or Entero-Test for sampling of [redacted] to conduct qualitative assessment of drug metabolites in this matrix. The Entero-Tracker or Entero-Test is a recent replacement device for a similar device, Entero-Test, an FDA 510k exempt device which has been shown to be an easy-to-use and minimally-invasive method for sampling bile from the duodenum [Guiney, 2011].

Information on the biliary disposition of drug-related material derived in the current study may avoid the need for invasive methods of bile collection in future studies. As sufficient data from the Entero-Tracker or Entero-Test string is expected following one dose of the

study drug, this assessment will be restricted to only one cohort in Part 2 (anticipated to be the second or third dose level depending on PK results in Part 1 and Cohort 4) during a participants' steady state. The Entero-Tracker or Entero-Test bile sample collected from placebo-dosed subjects will be considered as the control.

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4.2.1. Participant Input into Design

There was no participant input into the study design of the Protocol.

4.3. Justification for Dose

4.3.1. Prediction of Human PK and Safety Cover

Pharmacokinetics of GSK3884464 in human was predicted by allometric scaling of data from rat, dog, and monkey [GlaxoSmithKline Document Number 2020N459103_01, 2021]. Ex vivo target engagement, in terms of NQO1 mRNA induction in human blood, was modelled as a function of drug concentration and time. The in vivo time course of NQO1 mRNA level after a single dose and during repeated dosing were then simulated according to the predicted PK profiles. CCI

. Methodological details of the dose prediction are described in GlaxoSmithKline Document Number RPS-CLIN-000167, 2022 [GlaxoSmithKline Document Number 2021N467036_00, 2021].

The starting dose for Part 1 will be 1 mg. This dose is predicted to produce approximately 15% NQO1 mRNA induction at peak which is considered as the minimal anticipated biological effect level (MABEL). The predicted therapeutic dose is up to approximately 100 mg/day. Dose escalation in each part of the study will be guided by the review of emerging PK, safety, tolerability data and PD data if available; the exposure increments will be approximately 2-3 fold. To account for the high uncertainty in therapeutic dose prediction and the likely increased variability (in dosing adherence, PK, PD, safety and

tolerability) in future large outpatient trials in diverse populations, the planned top dose will aim to achieve exposure close to parity with exposure at the NOAEL dose in the most relevant toxicology species to adequately assess the safety and tolerability to protect patients in future trials.

Among the toxicology species, the plasma exposure at the NOAEL is in the order of monkey > mouse > rat. Because the dose limiting gastrointestinal toxicity in the mouse and renal toxicity in the rat are considered rodent-specific, the monkey is considered as the most sensitive relevant species.

The predicted human PK and exposure margin to the NOAEL in the monkey at the proposed doses for each part of the study are shown in the following sections (Section 4.3.2 and Section 4.3.3 for Part 1 and 2 respectively). For all Parts of the study, the mean plasma drug exposure at the top dose, predicted by emerging PK data, will not exceed the corresponding steady-state value at the NOAEL of 50 mg/kg/day in the six-week toxicology study in the monkey (Day 42 AUC = 316000 ng.h/mL and Cmax = 48300 ng/mL).

4.3.2. Prediction of Dose Levels for Part 1

The predicted exposure and the safety cover of the doses planned for Part 1 are shown in Table 1. The starting dose will be 1 mg (expected MABEL). The selection of the subsequent doses may deviate from those in the table, based on emerging available safety, tolerability, PK data and PD data if available from previous dose levels.

The decision on progression to the next dose level will be made by the Dose Escalation Committee (DEC); (see Section 4.4 and Section 10.1.5). The top dose will be aimed to cover the exposure that is anticipated to be produced during repeat (due to accumulation) in subsequent parts of the study.

In the event the observed exposure at the starting dose (1 mg) is lower than the corresponding predicted exposure, the next dose will target the exposure at the MABEL. In this case the escalation increment can be greater than 3-fold. In the event the observed exposure at the starting dose (1 mg) is substantially higher than the corresponding predicted exposure, the next dose will be revised to produce a 2-3-fold increment in exposure, consistent and no greater than the currently planned increments, if the dose escalation stopping criteria are not met.

Table 1 Projected plasma GSK3884464 exposure and safety cover following single oral doses of GSK3884464.

Dose Level	Dose [mg]	Predicted plasma exposures[1]		Fold safety cover[2]	
		C_{max} [ng/mL]	AUC [ng/mL × h]	C_{max}[ng/mL]	AUC [ng/mL × h]
1	1	84.337	557.14	572.7	567.2
2	3	253.01	1671.4	190.9	189.1
3	9	759.03	5014.3	63.6	63.0
4	20	1686.6	11143	28.6	28.4
5	40	3373.2	22286	14.3	14.2
6	80	6746.4	44572	7.2	7.1
7	160	13493	89144	3.6	3.5
8	300	25299	167142	1.9	1.9
9	550	46382	306427	1.0	1.0

1. Total plasma exposure predicted via allometry (C_{max} is maximum concentration achieved after single dose, and AUC is area under concentration extrapolated to infinity).
2. Ratio of steady-state plasma drug exposure at the 6-week monkey toxicity study NOAEL dose of 50 mg/kg/day (Day 42 AUC and Cmax of 316000 ng.h/mL and 48300 ng/mL, respectively) to predicted plasma AUC and Cmax in human after a single dose.

4.3.3. Prediction of Dose Levels for Part 2

The decision to progress to Part 2 and the selection of the actual dose levels, of the repeat dose regimen and of the number of cohorts will be made by the DEC, based on all available safety, tolerability, PK and available PD data from Part 1 (Section 4.4, Section 10.1.5). The predicted doses to be explored in Part 2 may be adjusted to the new starting and maximum doses pending data obtained in Part 1.

A once daily (QD) regimen is currently planned for repeat dosing; twice-daily (BID) dosing might be considered depending on PK data from Part 1, if QD dosing is predicted to produce high fluctuations in PK ($C_{max}/C\tau$ > 5-fold).

Up to three dose levels are planned in Part 2; their expected steady-state Cmax and AUC will have been shown to be safe after a single dose in Part 1. The exposure at the top dose will not exceed the monkey NOAEL. The predicted exposure and related safety cover for the planned QD doses are shown in Table 2.

The possibility to include additional cohort(s), to investigate higher dosing levels (with exposure capped at monkey NOAEL), might be considered in the event that no safety signals are observed in the three planned cohorts. In the event the observed exposure at the starting dose (1 mg) is substantially higher than the corresponding predicted exposure, the next dose will be revised to produce a 2-3-fold increment in exposure,

consistent and no greater than the currently planned increments, if the dose escalation stopping criteria are not met.

Table 2 Projected plasma GSK3884464 exposure and safety cover following multiple oral doses of GSK3884464.

Dose Level	Dose [mg/day]	Predicted plasma exposures[1]		Fold safety cover[2]	
		$C_{max,SS}$ [ng/mL]	AUCτ [ng/mL × h]	$C_{max,SS}$ [ng/mL]	AUCτ [ng/mL × h]
1	20	1858.7	11143	26.0	28.4
2	70	6505.5	39001	7.4	8.1
3	210	19516	117002	2.5	2.7

1. Total plasma exposure predicted via allometry (C_{max_SS} is maximum concentration at steady state, and AUCτ is area under concentration over dosing Interval=24 hours).
2. Ratio of steady-state plasma drug exposure at the 6-week monkey toxicity study NOAEL dose of 50 mg/kg/day (Day 42 AUC and Cmax of 316000 ng.h/mL and 48300 ng/mL, respectively) to predicted plasma AUC and Cmax in human.

4.4. Criteria for Dose Escalation and for Progressing Between Parts of the Study

The decision to proceed to the next dose level, to progress through each Part/Cohort, and to include an additional cohort/dose level (if necessary) will be made by the DEC. In addition, the DEC may review data from Cohort 5 and determine duration of treatment in Cohort 6 The anticipated mean plasma exposure (C_{max} and AUC) for any dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study (Section 4.3.1).

GSK will conduct regular dose escalation meetings throughout the course of Part 1 and Part 2. Each meeting will be scheduled to occur at the end of each cohort and / or treatment period to review data obtained after each dose level. Dose escalation decisions will be based on data obtained from 3 or more participants on active treatment at the prior dose level, unless stopping criteria (see Section 7.1) are met at the prior dose level and the subsequent dose is de-escalated. The review data set will consist at minimum AE listings, safety labs, electrocardiograms (ECG), vital signs (VS), and PK results derived from at least 24-hour plasma profiles. Pharmacodynamic (PD) data will be reviewed as available for Part 1 and may be used with the rest of the data in dose selection to start and progress Part 2. PD data may not be required for an escalation decision. Flagged vital signs, cardiac monitoring (telemetry), ECG and laboratory findings will also be reviewed. The decision to switch to the gastro resistant capsules will be made by the DEC after review of the AE listings and will be based on clinical judgement.

Progression to the next higher dose level in a given cohort will be halted if:

- Two or more participants in the same cohort experience severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as at least possibly related to the administration of GSK3884464), independent of within or not within

the same system-organ-class; and independent of whether it is related to study intervention or not.

- Any participant experiences a serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the administration of GSK3884464).
- Three or more participants in a cohort experience the same adverse event of moderate severity that can be reasonably attributed to dosing with GSK3884464.

The dose escalation will stop after completing the dose level, and no further participants will be dosed at that dose level or any higher level. Lower doses and progression to Part 2 may occur. If after consultation the Sponsor deems that dosing can resume at that level or higher, the Sponsor will submit an application for a substantial amendment to the Regulatory Agency.

The decision to progress from Part 1 to Part 2 of the will be made by the DEC in consultation with the Nephrology and other safety panels, if required. The final dose-escalation decision and rationale for each cohort will be discussed with the investigator(s) during teleconferences(s) and documented in writing, with copies maintained at each study site and in the study master file.

Progression to the next part of the study will be halted if:

- Stopping criteria will be mean exposure exceeding or predicted to exceed the exposure observed at plasma NOAEL in the 6-week GLP monkey toxicity study (50 mg/kg/day), corresponding to Day 42 monkey plasma AUC of 316000ng.mL×h and C_{max} of 48300 ng/mL.
- Three or more participants in the same part experience severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as at least possibly related to the administration of GSK3884464), independent of within or not within the same system-organ-class; or four or more participants in the same part experience the same adverse event of moderate severity that can be reasonably attributed to dosing with GSK3884464.
- Any participant experiences a serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the administration of GSK3884464).

The dose levels in Part 2 will only be started after the same or higher dose cohorts are complete in Part 1 with no dose escalation stopping criteria having been met, therefore, Part 2 may start before the completion of Part 1. At a minimum, Multiple Ascending Dose (MAD) Cohort dose levels will be defined based upon Dose Escalation Committee (DEC) review of up to the first five Single Ascending Dose (SAD) dose levels. Additional MAD cohorts will be based on DEC review of subsequent SAD dose levels and the previous MAD. Lastly, the maximum dose for Part 2 cannot exceed the maximum dose in Part 1.

4.5. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases in the particular part of the study they participated in, including the last scheduled procedure shown in the Schedule of Activities (see Section 1.3.1).

The end of the study is defined as the date of the last visit of the last participant in the study or if the Sponsor decides not to move to the next cohort.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment 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 the following criteria apply:

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
1. Healthy as determined by the experienced investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring/assessment. **NOTE**: A participant with a clinical abnormality, clinical history or laboratory parameter(s), which is/are not specifically listed in the inclusion or exclusion criteria, that are outside the reference range for the population being studied may be included only if the investigator and the Medical Monitor (as required) agree and document that the finding is unlikely to introduce additional risks and will not interfere with the study procedures. Screened participants with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator.

WEIGHT
2. **Part 1:** Body weight ≥ 50kg, body mass index (BMI) ≥18 and ≤ 30 kg/m^2 (inclusive). **Part 2:** Body weight ≥ 50kg, BMI ≥ 22 and ≤ 30 kg/m^2 (inclusive).

AGE
3. 18 to 50 years of age inclusive at the time of signing the informed consent.

RELEVANT HABITS
4. Non-smokers only (defined as a non-smoker during the last 3 months prior to screening).

SEX

5. Male or females of non-childbearing potential.

Contraceptive use by men and male participants' childbearing potential partners or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Participants with same sex partners (abstinence from penile-vaginal intercourse) are eligible.

a. Male Participants:

No reproductive exposure precautions (i.e., condom or other contraceptive) are required for male participants with a female of nonreproductive potential or male partner, when this is their preferred and usual lifestyle. Male participants with a female partner of reproductive potential are eligible to participate if they agree to the following during the dosing period and for at least 60 hrs after last dose plus:

- Refrain from donating sperm.

PLUS either:

- Are currently abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Have had a vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview.

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom;
  - Additionally, female partner to use a highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female Participants:

- A female participant is eligible to participate if she is a woman of nonchildbearing potential (WONCBP), as defined in Appendix 4.

INFORMED CONSENT

6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS

- History or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal (Gastroesophageal reflux disease (GERD), nausea, vomiting or dysphagia), endocrine, hematological or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
- History of current or past significant renal diseases (e.g. Acute Kidney Injury, parenchymal kidney disease).
- Clinically significant high blood pressure and/or history of hypertension as determined by the investigator.
- Serum troponin I or troponin-T greater than the upper limit of normal (ULN).
- Lymphoma, leukaemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
- Breast cancer within the past 10 years.
- QTcF >450 msec;
  - Screening 12-lead ECG with any of the following:
    - Second- or third- degree atrioventricular block (AVB).
    - Two or more significant pathological Q-waves (defined as Q-wave > 40 msec or depth greater than 0.4-0.5 mV) in a pattern consistent with a prior myocardial infarction.
    - Ventricular pre-excitation.
    - Bradycardia as defined by sinus rate ≤ 35 beats per minute (BPM)
    - Complete left bundle branch block (LBBB)
  - History of QTc prolongation, symptomatic cardiac arrhythmias or cardiac arrest.
- Screening Holter (24 hours) with any of the following:
    - Sinus bradycardia ≤ 30 BPM
    - Non-sustained ventricular tachycardia (NSVT) or more than 30 Ventricular Premature Depolarisations (VPD) during an hour.
    - Atrial arrhythmia > 100 BPM for 3 seconds or longer or more than 40 Atrial Premature Depolarisation (APD) during an hour.
- Any clinically relevant abnormality on the screening medical assessments.
- Alanine transaminase (ALT) > ULN.

- Bilirubin > ULN.
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

PRIOR/CONCOMITANT THERAPY

- Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer [eg. Rifampin, St John's Wort extract]) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety. By exception, all participants may take Paracetamol (≤ 2 grams/day) up to 48 hours prior to the first dose of study drug.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

- Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period.
- Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
- Current enrollment or past participation in a clinical trial within the last 30 days before signing of the consent in this or any other clinical study involving an investigational drug or any other type of medical research.

DIAGNOSTIC ASSESSMENTS

- A positive laboratory confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19.

  NOTE: High clinical index of suspicion: Participants with signs/symptoms suggestive of COVID-19 (i.e. fever, cough, etc) w/in 14 days and /or with known COVID-19 positive contacts in the past 14 days.
- Participants with an HbA1c > 48 mmol/mol at screening.
- Presence of Hepatitis B surface antigen at screening.
- Positive Hepatitis C antibody test result at screening.

  NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained.
- Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

  NOTE: Test is optional and participants with negative Hepatitis C antibody test

DIAGNOSTIC ASSESSMENTS
are not required to also undergo Hepatitis C RNA testing. • Positive pre-study drug/alcohol screen. • Positive human immunodeficiency virus (HIV) antibody test. • Estimated glomerular filtration rate (eGFR) ≤ 90 ml/minute/1.73m^2 calculated by the CKD-EPI equation as below: eGFR = 141 x min (SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black] • Screening urine albumin:creatinine ratio ≥30 mg/gm (≥3 mg/mmol) • Regular use of known drugs of abuse.

OTHER EXCLUSIONS
• Regular alcohol consumption within six months prior to the study defined as: • An average weekly intake of ≥14 units for males ≥14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. • Smokelyzer test levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 3 months prior to screening. • Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study. • Subjects with a history or current evidence of depression, bipolar disorder, suicidal ideation and behavior, or a lifetime history of suicide attempt will be excluded.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study drug dosing until after the final dose.
- Participants taking study intervention in gastro-resistant capsule form will be fasted for at least 2 hrs post dose. Participants must fast from all food and drink (except water) for at least 8 hours prior to any fasting clinical laboratory evaluations.
- Participants will not receive breakfast on days when serial planned PK samples are collected.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Participants will refrain from smoking or using tobacco or nicotine-containing products from at least 3 months prior to the Screening Visit through the last blood sample collected.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (e.g., watching television, reading).

All participants must be resting in a semi-supine position for 10 minutes prior to and 5 minutes after each ECG/VS/and PK draw while on the continuous cardiac monitoring. Participants must be in a semi-supine resting position that must be maintained 60 minutes prior to dosing.

It is recommended that participants should self-quarantine when outside of the clinical unit from the time of COVID-19 testing on first admission through the follow up visit and should be encouraged to wear a mask or facial covering when moving between home and the clinic. Participants should monitor body temperature daily while not in the clinical unit and report an elevation above 100.4F (38 C). In addition, participants should report a lack of smell to the clinical site staff.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently 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, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened and retested, but only after consultation and agreement with the GSK Medical Monitor.

6. STUDY INTERVENTION AND CONCOMITANT MEDICATION

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

ARM Name	Experimental	Control	Experimental	Control
Intervention Name	GSK3884464	Placebo	GSK3884464	Placebo
Type	Drug	Drug	Drug	Drug
Dose Formulation	Solution	Solution	Capsule	Capsule
Unit Dose Strength(s)	0.1 mg/mL	Volume to match Study Drug	Flexible dosing from 3mg – 100 mg per capsule.	Excipient fill weight and capsule count to match Study Drug.
Dosage Level(s)	1 – 3 mg	To match study drug	Up to 550 mg QD using multiple capsules	To match study drug
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP and NIMP	IMP	NIMP	IMP	NIMP
Sourcing	Pharmaceutical ingredient provided centrally by the Sponsor with solution prepared by CUC, Cambridge, UK	Solution prepared by CUC, Cambridge, UK	Pharmaceutical ingredient provided centrally by the Sponsor with capsules prepared by CUC, Cambridge, UK	Capsules provided centrally by prepared by CUC, Cambridge, UK

ARM Name	Experimental	Control	Experimental	Control
Packaging and Labelling	Solutions will be prepared in amber type-1 glass bottles with child resistant closures and labelled as required per country requirement.	Solutions will be prepared in amber type-1 glass bottles with child resistant closures and labelled as required per country requirement	Capsules are packaged in round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures and labelled as required per country requirement.	Capsules are packaged in round, opaque white, high density polyethylene (HDPE) bottles with child resistant closures and labelled as required per country requirement.
			The active pharmaceutical ingredient (API) will be weighed into hydroxypropyl methylcellulose (HPMC) capsules for oral administration. If deemed necessary as the study progresses, gastro-resistant capsules (composed of hydroxypropyl methylcellulose acetate succinate (HPMC-AS) may be substituted.	

6.2. Preparation/Handling/Storage/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.
- 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 (SRM).
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the

investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.2.1. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics (GSK), prior to the start of the study, using validated software.

Doses of GSK3884464 will be compounded at CUC Pharmacy United Kingdom. For doses ≥3 mg, the active pharmaceutical ingredient (API) will be weighed into Hydroxypropyl methylcellulose (HPMC) capsules for oral administration. If deemed necessary as the study progresses, gastro-resistant capsules (composed of HPMC/ Hydroxypropyl methylcellulose Acetate Succinate (HPMC-AS) may be substituted.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Participants will be randomised to a treatment or treatment sequence at the start of each Part/Cohort in accordance with the randomisation schedule generated by Clinical Statistics, GSK.

Part 1: Each cohort will have approximately 9 participants and will be randomized to one of 3 treatment sequences, with 3 participants per sequence, (See Table 3, Table 4 and Table 5) in a 1:1:1 ratio. Within each period, allocation to GSK3884464 and placebo will be 2:1. Within each sequence, an increasing dose of GSK3884464 will be administered in each period.

Table 3 Part 1, Cohort 1

Sequence	Period 1	Period 2	Period 3
1.1	Placebo	SD2	SD3
1.2	SD1	Placebo	SD3
1.3	SD1	SD2	Placebo

Table 4 Part 1, Cohort 2

Sequence	Period 1	Period 2	Period 3
1.4	Placebo	SD5	SD6
1.5	SD4	Placebo	SD6
1.6	SD4	SD5	Placebo

Table 5 Part 1, Cohort 3

Sequence	Period 1	Period 2	Period 3
1.7	Placebo	SD8	SD9
1.8	SD7	Placebo	SD9
1.9	SD7	SD8	Placebo

Part 2: Each dose cohort will have approximately 8 participants and will be randomized to receive either GSK3884464 or placebo in sequential design using a 3:1 allocation ratio as illustrated in Table 6.

Table 6 Part 2

Dose Cohort	Regimen
Cohort 2.1	RD1 or Placebo
Cohort 2.2	RD2 or Placebo
Cohort 2.3	RD3 or Placebo

6.3.2. Blinding

This will be a double-blind study, which means that the participant, investigator and trial staff at the study site (apart from unblinded administrator(s) and pharmacy staff) will be blinded to the trial treatment allocated to each individual participant.

In addition, the sponsor will be blinded to treatment allocations, except for roles required to be "unblind" in order to manage study conduct, oversight and safety. Additional internal GSK safety representatives may be consulted and unblinded as deemed necessary by the DEC. This will be documented and maintained in the electronic Trial Master File (eTMF).

In the case of emergency unblinding, the following will apply:

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.
- It is preferred (but not required) that the investigator first contact the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.

The date and reason for the unblinding must be fully documented in the case report form (CRF).

A participant will be withdrawn if the participant's study drug code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

GSK's Global Clinical Safety and Pharmacovigilance (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 the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- 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. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.
- A record of the quantity of GSK3884464 or placebo capsules dispensed to and taken 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 some alterations from the currently outlined dosing schedule (Section 4.3.2 and Section 4.3.3), but the predicted mean plasma exposure (C_{max} and AUC) for any single or repeat dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study (Section 4.3.1).

The dosing schedule may be modified to expand a dosing cohort to further evaluate safety, PK and/or PD at a given dose level. The actual doses to be administered may involve either an increase or a decrease in the planned doses. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study participants. Any cohort expansion or addition will be contingent on approval of an amended protocol by the UK ethics board and the MHRA.

The details on the dose escalation committee can be found in Section 4.4 and Section 10.1.5. Discontinuation of study intervention and study progression stopping criteria are located in Section 7.

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

Participants will not receive any additional treatment from GSK after completion of the study because efficacy of the investigational product has not yet been determined.

6.7. Treatment of Overdose

For this study, study treatment will be administered by study staff.

Any dose of GSK3884464 greater than the planned dose within a 24-hour time period ± 6 hours will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for at least 72 hours.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention 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, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment 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 vitamins, recreational drugs, and dietary or herbal supplements such as St John's Wort) 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 drug until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen at doses of ≤2 grams/day or Ibuprofen ≤1200 mg/day, is permitted for use at any time during the study. Other concomitant medication may be considered on a case-by-case basis, in consideration of the recommendations as follows, by the investigator in consultation with the Medical Monitor if required.

In vitro incubations of GSK3884464 with recombinant human UGT enzymes and human liver microsomes indicated that the metabolism of GSK3884464 was dependent on UDPGA, a cofactor required for UGT enzyme activity, with contributions from UGT1A3 and UGT1A9. The overall victim drug-drug interaction (DDI) risk with single inhibition of these enzymes may be low due to the multiple clearance mechanisms. However, since glucuronidation was a predominant metabolic route in human hepatocytes, co-administration of a potent inducer, eg, phenytoin and rifampin, can result in decreased levels of GSK3884464. Contraindication or replacement thereof is recommended. The following classes of therapies and examples are prohibited for concomitant or prior use within 2 weeks:

Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone

Antimycobacterials: rifampin, rifapentine

Herbal product: St John's wort (Hypericum perforatum) extract

Estrogen containing oral contraceptive: ethinylestradiol/levonorgestrel

In vitro, GSK3884464 is an inducer of CYP3A4, UGT1A1 and UGT1A4 as well as an inhibitor of drug metabolising enzyme UGT2B15 and transporters Pgp, BCRP, OATP1B1, OAT1 and OAT3. Based on the intended clinical dose and predicted systemic plasma concentration of GSK3884464, preliminary SIMCYP^{TM} (Fit-for-Purpose PBPK) modelling suggested a low risk of perpetrator DDIs against these enzymes and transporters, at the predicted human dose up to 500 mg, QD [GlaxoSmithKline Document Number 2021N467036_00, 2021].

Notwithstanding the modelling and DDI risk prediction will be a continuous exercise of optimization and improvement as the human PK data become available during the current study and future clinical investigation. Consequently, the recommendations and criteria for concomitant medications will be reviewed and updated accordingly.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation or Early Withdrawal) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for final safety, PK, PD and follow up assessments. See the SOA in Section 1.3 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.

Discontinuation of study intervention and study progression stopping criteria are located in Section 7. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committee will then take place prior to any resumption of dosing.

7.1.1. Liver Chemistry Stopping Criteria

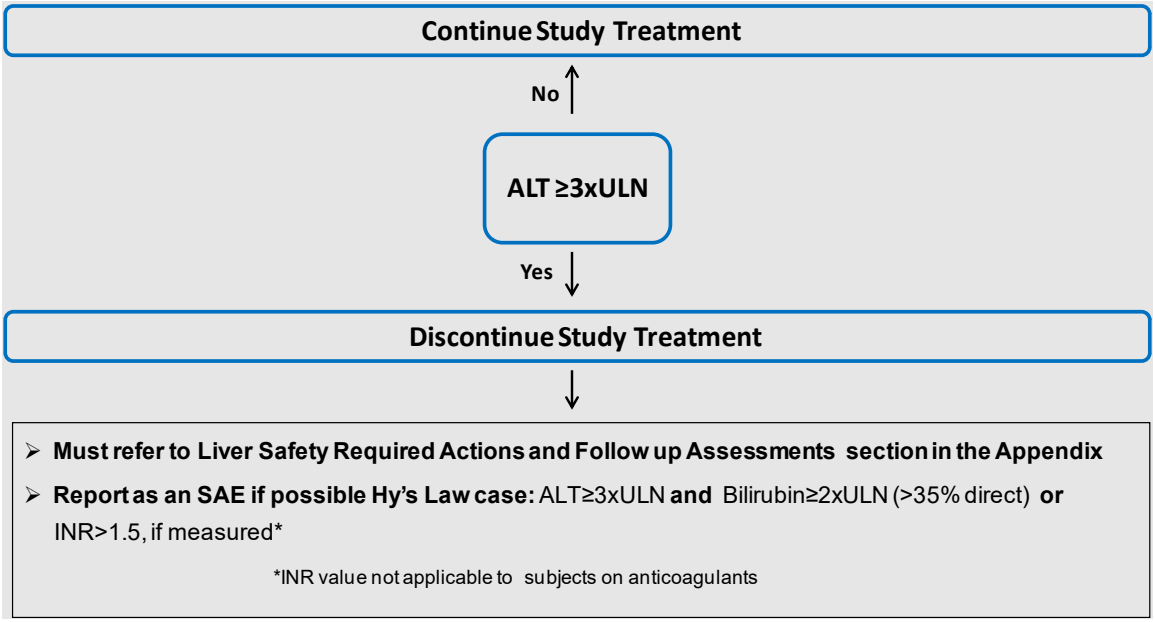
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

- a participant meets one of the conditions outlined in the algorithm or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the investigator considers that it is in the best interest of the participant.

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow-up Assessments Section can be found in Appendix 5.

7.1.1.1. Study intervention restart or rechallenge after liver stopping criteria are met

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

7.1.1.2. Study temporary halt criteria and potential study stopping criteria

If the following criteria are met in at least one subject, in any arm of the study, the study will be put on temporary halt:

- ALT≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) OR (International Normalized Ratio) INR >1.5.

7.1.1.3. Dose expansion criteria

If ≥ 2 subjects in any dose level experience an **isolated ALT≥3xULN** (on active treatment) then the following dose expansion criteria applies:

Up to four additional participants on active and 2 additional participants on placebo may be recruited at the same dose level. Any further cohort expansion will be contingent on approval of an amended protocol by the UK ethics board and the MHRA.

7.1.2. QTc Stopping Criteria

A subject that meets either bulleted criterion below based on the average of triplicate ECG readings will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline in healthy volunteer participants: QTcF >60 msec

7.1.3. Left Ventricular (LV) Ejection Fraction Stopping Criteria

A subject that meets the criteria below on any scheduled or unscheduled study echocardiogram will be withdrawn from the study:

LV ejection fraction is lower by 10% or more than the pre-dose baseline value and the investigator, in consultation with the Medical Monitor, think there is a reasonable chance the change in ejection fraction is attributable to the investigational product.

7.1.4. Cardiac Arrhythmia Stopping Criteria

A clinically concerning cardiac arrhythmia in this study is any type of arrhythmia or divergent QRS complex morphology that is deemed by the Investigator to be reasonably attributable to GSK3884464 - rather than within normal variation for each type of affected subject receiving repeat dose GSK3884464.

Furthermore, a clinically concerning arrhythmia is an adverse event which is deemed by the Investigator in consultation with the Medical Monitor to be of sufficient temporal duration and / or character to potentially affect subject safety.

All clinically concerning cardiac arrhythmias in individual participants will be reviewed by the Investigator in consultation with the Medical Monitor at the earliest possible opportunity after the event. In addition, cardiac arrhythmias will also be reviewed by a cardiologist where it is deemed appropriate to do so by the Investigator in consultation with the Medical Monitor on a case-by-case basis.

Detection of any of the following during baseline assessment or following administration of study intervention will lead to withdrawal:

a). Sustained monomorphic or polymorphic ventricular tachycardia (VT).

b). Non-sustained but symptomatic or hemodynamically significant monomorphic or polymorphic (VT).

c). High-grade or complete heart block.

d). Symptomatic bradycardia.

Additional clinically significant cardiac events could include, but are not restricted, to:

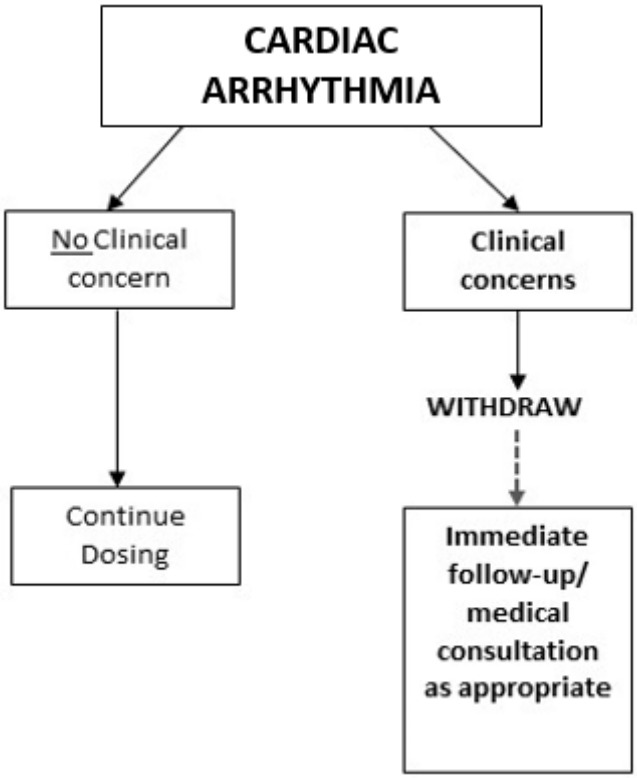
- A non-sustained wide-complex tachyarrhythmia ≥ 100 beats per minute (BPM) that is:
    - accompanied by symptoms, hemodynamic compromise, or other new ECG changes (e.g. new ST depression).
    - repetitive (e.g. repeated short salvos).
    - greater than 10 seconds in duration.

Participants who either have a clinically concerning arrhythmic event during the study, or where there is electrophysiological diagnostic uncertainty on cardiac telemetry / ECG,

must be withdrawn from the study and be appropriately followed up immediately. Medical consultation with a cardiologist should be obtained. The Medical Monitor should be informed as soon as possible. This includes participants who develop non-sustained but asymptomatic and hemodynamically tolerated monomorphic or polymorphic VT who will be evaluated to determine the cause of the VT.

A plasma sample for PK analysis should be obtained as soon as possible after detecting a clinically concerning or life-threatening cardiac arrhythmia, or within 48 hours of last dose.

Figure 7 Algorithm for Management of Participants having received one or more doses of study treatment based on Arrhythmia Characterization



7.1.5. Renal Stopping Criteria

Any of the following events which are reasonably attributable to GSK3884464 will be nominally categorized as a severe adverse event and will constitute individual stopping criteria for participants:

- New onset of any clinically significant and persistent (for 48 hours) hematuria as confirmed by microscopy (in the absence of any other clinical cause).
- New onset of clinically significant and persistent (for 48 hours from the dosing day in the SAD part and at any point in the MAD) proteinuria (Spot Urine Albumin Creatinine ratio [ACR] ratio ≥30 mg/mmol) in absence of another clinical explanation e.g. calculus/infection

- If there is any change in serum creatinine > 26µmol/L (>0.3 mg/dl), repeat within 24 hours. If confirmed, the participant will be withdrawn, and further investigations will be performed.
- Increase in serum creatinine (ΔsCr) of >25% from baseline on 2 consecutive assessments within 24 hours.
- A 25% decline in eGFR below baseline on two consecutive assessments within 24 hours. If confirmed, the participant will be withdrawn. If a participant meets the withdrawal criteria for eGFR, then further investigations will be performed.

All abnormal results that meet the above criteria should be discussed with the Medical Monitor as soon as possible to arrange for follow-up testing.

If 2 or more participants in a given dose cohort develop any of the above withdrawal criteria, when considered related to study drug, then that cohort will be temporarily halted.

7.1.6. Pharmacokinetic Stopping Criteria

The following dose adjustment / PK stopping criteria will apply:

- Stopping criteria will be mean exposure exceeding or predicted to exceed the exposure observed at plasma NOAEL in the 6-week GLP monkey toxicity study (50 mg/kg/day), corresponding to Day 42 monkey plasma AUC of 316000 ng.mL×h and C_{max} of 48300 ng/mL.
- Throughout all parts of the study, PK data from previous dose levels will be used to predict exposure to the next dose level or study Part. If the mean exposure at the next dose level is predicted to exceed the PK stopping criteria exposure, dose escalation will be stopped, or dose adjustment will be planned, as appropriate.

The GSK DEC team will decide based on safety, tolerability, and PK information whether to evaluate any lower doses or repeat doses already evaluated in remaining periods to collect additional safety and PK data.

7.1.7. Additional Stopping Criteria

7.1.7.1. Neuropsychiatric Issues

Suicidal Ideation and Behavior:

If Columbia Suicide Severity Rating Scale (C-SSRS) assessment indicate a clinically relevant increase in suicidal ideation or behavior or a subject shows new signs or symptoms during the study treatment period suggestive of an increase in suicidal ideation and behavior, psychiatric consultation will be obtained and the Sponsor's Medical Monitor should be contacted. Discontinuation of study intervention is mandated in case the participant scores "yes" on item four or item five of the Suicidal Ideation Section of the Columbia Suicide Severity Rating Scale (C-SSRS) or "yes" on any item of the Suicidal Behavior Section. In addition, study investigators may also decide to discontinue dosing based on their clinical judgment for observations that do not specifically meet these thresholds, if they feel this is appropriate for best ensuring the safety of study subjects. See SRM for additional information.

Cognitive Safety:

If cognitive test results of the 6-item cognitive impairment test (6-CIT) indicate a clinically significant effect of GSK3884464 on cognitive safety or the subject shows new signs or symptoms during the study treatment period suggestive of an effect on cognitive safety, psychiatric consultation should be obtained and the Sponsor's Medical Monitor should be contacted. If the increased risk can be confirmed the subject must be discontinued from the study.

In case there is objective evidence that a subject is in psychological distress, the subject will be immediately evaluated and the subject must be discontinued from the study if the investigators based on their clinical evaluation feel this is appropriate for best ensuring the safety of study subjects. Concerning symptoms might include:

Nervousness,

Anxiety, irritability

Sudden worsening of mood

Sudden outbursts of anger ("anger attacks")

Sudden panic or anxiety attacks

Agitation

Feeling unreal or detached

Confusion or trouble concentrating

Forgetfulness or problems with memory

Mood swings

Trouble sleeping, insomnia

Fatigue, tiredness

See SRM for additional information.

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 Section 1.3 (SoA). Refer to the SoA in Section 1.3 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- Every effort will be made to take a blood sample at the time of the event of discontinuation or study withdrawal for pharmacokinetic analysis.
- The participant will be permanently discontinued both from the study intervention and from the study at the same 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.
- Participants testing positive for COVID-19 will be discontinued from study treatment and appropriate contact tracing conducted within the unit will be done according to local legislation. Decisions to terminate all study participation and how to maintain adequate safety follow up will be agreed upon by the study investigator in consultation with the Medical Monitor.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants

randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study, as a whole, are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (See Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor 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 (Section 1.3), is essential and required for study conduct. Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact participant safety. The following points must be noted:

If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

- 12-lead ECG
- vital signs
- blood draws

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

The timing and number of planned study assessments, including safety, PK, PD/biomarker or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

The UK ethics board, the MHRA and investigator will be informed of any significant safety issues, including those that require amendment of the Patient Information Sheet and Consent Form (PICF).

- 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 time frame defined in the SoA (Section 1.3).
- 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.
- A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

8.1. Efficacy Assessments

Not Applicable.

8.2. Safety Assessments

Planned time points 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 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.
- Participants who report symptoms suggestive of COVID-19 while in the research unit should be isolated in the unit or at home and tested for COVID-19 infection using an approved molecular test.

8.2.2. Vital Signs

- 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.
- Blood pressure and pulse measurements will be assessed in a semi-supine position after at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure

readings will be recorded at intervals of at least 1 minute). The 3 blood pressure readings will be recorded in the CRF.

8.2.3. Cardiac Assessments

8.2.3.1. 12-lead safety ECGs

- Single 12-lead ECG will be measured in semi-supine position after 5 minutes rest as outlined in the SoA (Section 1.3.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.3 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- At each time point a single ECG is required. Triplicate ECGs will be performed only if an abnormality is detected. The 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.
- Safety ECGs will be printed and interpreted on-site by the Investigator to ensure subject safety. Safety ECGs may be printed from the Global Instrumentation Holter device (See Section 8.2.3.2).

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8.2.3.3. Continuous Cardiac Telemetry

Continuous cardiac telemetry will start in a supine position after at least 5 minutes rest at the time point indicated in the SoA (Section 1.3). Participants are not required to remain in a supine position during the remaining duration of collection of cardiac telemetry, as indicated in the SoA (Section 1.3). Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents. Participants in each Part are permitted up to a total of 30 minutes off monitoring per day in the evening to allow for showering without this being considered a deviation, except when they have serial PK days when the monitor should be continuous. In addition, participants are permitted to be off telemetry during the 3D echocardiogram procedure in Cohorts 4, 5 and 6. See SRM for additional details.

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8.2.3.5. Echocardiograms

Three-dimensional echocardiograms will be performed at screening and in Part 2 of the study according to the SoA (Section 1.3). This procedure uses sound waves to create pictures of the heart and will provide detailed information on how well (or how hard) the heart is working. An echocardiogram does not expose participants to radiation.

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8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event (AE) section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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, or within 6 days after the last dose of study intervention, 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 such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology of the abnormality should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 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. Suicidal Ideation and Behavior Risk Monitoring

Based on evidence of limited distribution to the brain in rats and monkeys, GSK considers it important to monitor for any increased risk of suicidal thinking or behavior when GSK3884464 is given to human participants before or during clinical studies with compounds such as this. Subjects being treated with GSK3884464 should be assessed and monitored appropriately for suicidality and unusual changes in behavior.

8.2.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

Baseline assessment of suicidal ideation and behaviour and treatment emergent suicidal ideation and behaviour will be assessed during this study using the Columbia Suicide Severity Rating Scale (C-SSRS). C-SSRS is a brief questionnaire designed to assess severity and change in suicidality by integrating both behavior and ideation. The C-SSRS was designed to address the need for a summary measure to track changes in the severity/intensity of suicidality across both clinical settings and treatment trials. It assesses intensity of ideation (a potentially important marker of severity), specifically asking about frequency, duration, intrusiveness, controllability and deterrents. In addition, both the modal and most severe forms of ideation are captured. This procedure should be performed in participants receiving repeat doses in Part 2 as listed in the SoA. The questionnaires should be completed by a health professional trained in this procedure following discussions with the subject at each visit. If additional information is provided by a caregiver, relative, friend etc then this information should also be taken into account when completing the questionnaire. Any suicide attempts or Investigator concerns about issues raised during the completion of this questionnaire should be discussed immediately (with 24hr) with the GlaxoSmithKline Medical Monitor. Refer to SRM for additional information.

8.2.6.2. Six-Item Cognitive Impairment Test (6-CIT)

The 6-CIT is a brief neuropsychological screening test for cognitive impairment taking less than 5 minutes (three orientation items, count backwards from 20, months of the year in reverse order, and learn an address).

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

The definitions of an adverse event (AE) or serious adverse events (SAEs) can be found in Appendix 3.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3, Section 10.3.

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 reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

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

- All SAEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3.1).
- However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- 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 Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3.1).
- 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.
- Investigators are not obligated to actively seek information on AEs or SAEs after the 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.

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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 Appendix 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, UK ethics board, the MHRA and investigators.
- An investigator who receives an investigator safety report describing a 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 Investigator's Brochure and will notify the UK ethics board, and the MHRA if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until time period for reporting pregnancies and should align with the time period for post-intervention contraception determined in Section 5.1 and Section 10.3.3.

The investigator will attempt to collect pregnancy information on any male participant's female partner becomes pregnant while participating in this study. This applies only to male participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (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.

8.4. Pharmacokinetics

8.4.1. Plasma Sample Collection

Blood samples of approximately 1 mL will be collected for plasma PK analysis of GSK3884464 at the timepoints indicated in the SoA, Section 1.3. The timing of the PK samples may be altered during the course of the study based on newly available data to ensure appropriate monitoring (e.g., to obtain samples closer to the time of peak plasma concentrations).

Additional volumes of blood (2 mL for all time-points from pre-dose to 8 hr and 5 mL for time-points 12hr to 24hr) will be collected in Part 1 (Cohort 2 and 3) and Part 2 (Days 1, 14 & 15 for Cohorts 4 and 5 and Days 1, 21 & 22 for Cohort 6) only, as specified in the SoA (Section 1.3) to assess for GSK3884464-related metabolites.

Instructions for the collection, handling, and shipping of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of GSK3884464 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Residual plasma samples may be used to assess for GSK3884464-related metabolites.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the cohort/study Part has been unblinded.

8.4.3. Bile Sample Collection

Bile samples for analysis of metabolites will be collected via the Entero-Tracker or Entero-Test in either the second cohort (Day 14) or third cohort (Day 21) in Part 2 (depending on PK results in Part 1 and Cohort 4).

The Entero-Tracker or Entero-Test comprises a gelatine capsule which contains 90 cm or 140 cm of nylon string attached to a 1 g steel weight. One end of the string is attached to the outside of the mouth before swallowing the capsule, so that it can still be retrieved. The gelatine capsule dissolves in the stomach whilst the string and weight continue to the

duodenum via peristalsis. Following a food cue to stimulate gall bladder emptying the string is withdrawn.

On withdrawal of the string through the mouth the steel weight separates from the string at the pyloric sphincter and is excreted in the faeces. Once the string has been removed from the participant it will be frozen and shipped for metabolite profiling (to be conducted in a separate study).

Full details of the Entero-Tracker or Entero-Test sample collection, processing, storage and shipping procedures are provided in the SRM.

8.4.4. Sample Analysis

Analysis of GSK3884464 in plasma and urine samples will be performed under the control of GSK BIB IVIVT. Concentrations of GSK3884464 will be determined using the currently approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. SRM, CLW, SOW) and raw data will be archived in the GSK R&D archives. Additional parameters may be analyzed if determined appropriate; more details will be provided in the Statistical Analysis Plan (SAP). Processing, storage and shipping procedures are provided in the SRM.

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Once the sample has been analyzed for GSK3884464 any remaining sample may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

Drug concentration information that may unblind the study will only be shared with the DMPK and Bioimaging Study Director and scientists who are conducting and reporting the GSK3884464 metabolism study which is separate from this protocol. This information is needed to differentiate active-dosed subjects from placebo to inform on the metabolite identification study conduct. Drug concentration information will not be reported to investigative sites or blinded personnel until the cohort/study Part has been unblinded.

8.4.5. Disease-Related Events (DRE) and/or Disease-Related Outcomes (DRO) Not Qualifying as SAEs

No DREs or DROs not qualifying as SAEs will be collected in this study.

8.4.6. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are selected AEs that must be reported to the Sponsor's Medical Monitor within 24 hours regardless of relationship to study treatment.

For this study the AESI represent moderate or severe increases in liver function analyses.

8.5. Genetics

Genetics are not evaluated in this study.

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8.6.1. Pharmacodynamics

Preclinical *in vivo* data has shown that GSK3884464 demonstrated robust target engagement as measured by increased expression/activity of NQO1, a target gene regulated by NRF2, in tissues and whole blood. Elevation of NQO1 mRNA, following treatment with GSK3884464, in whole blood samples being collected in the study would provide evidence of proximal target engagement and activation of NRF2. Therefore, this is a secondary endpoint for the study and will be used to characterize the relationship between PK and PD for GSK3884464.

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8.7. Medical Resource Utilization and Health Economic

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objectives of this study are to assess the safety and tolerability of single and repeat ascending doses and to characterize the PK and PD of GSK3884464 in healthy participants. No formal statistical hypotheses will be tested.

Descriptive statistics will be used to assess safety and tolerability objectives. Treatment comparisons with placebo will be based on review of descriptive statistics and individual participant data.

Intercurrent events, the estimand strategy to handle such events and the changes to the respective analysis to implement the strategies will be highlighted in the SAP.

9.2. Sample Size Determination

A sufficient number of participants will be screened to achieve up to 51 randomly assigned to study intervention and up to 51 evaluable participants. It is estimated that Part 1 will have 27 evaluable participants; Part 2 will have 24 evaluable participants (6 for each of the three repeat doses levels and 6 for placebo). Additional participants/cohorts may be enrolled to allow for evaluation of additional dose levels. If participants prematurely discontinue during the study, additional replacement participants may be enrolled at the discretion of the Sponsor. These replacement participants will be assigned to the same treatment/treatment sequence as the corresponding participant who prematurely discontinued from the study.

The sample size has been assessed based on the evaluation of fold change from baseline (FCFB) of NQO1 expression, a secondary endpoint in the study to the end of repeated dosing. Assuming the within subject CV of 50% and based on 6 participants each in GSK3884464 and placebo treatment arms,

- If the true ratio of FCFB between GSK3884464 and placebo is 5-fold, then there is 69% probability that the observed ratio is greater than 4.2 -fold; if the true ratio is 6-fold, then the probability is 83%; if the true ratio is greater than 7-fold then the probability is greater than 90%. This provides high confidence of observing a clinical meaningful effect in the expected range (>5-fold) of target engagement in NOQ1.
- If the true ratio of FCFB between GSK3884464 and placebo is 1-fold, then the false positive rate that the observed ratio is greater than 4.2-fold is <0.1%.

9.3. Analysis Sets

For the purpose of analysis, he following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who were randomly assigned to treatment in the study. This population will be based on the treatment the participant was randomized to.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK	All participants in the Safety population who had at least one non-missing PK assessment (Non-quantifiable [NQ] values will be considered as valid PK assessment). This population will be based on the treatment the participant actually received.
PD	Participants in the Safety population with baseline and at least one post baseline PD measure (e.g. NQO1 mRNA)

9.4. Statistical Analyses

The SAP will be finalized prior to the first subject first visit 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 most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

9.4.1.1. Primary Endpoint(s)

- The primary objectives of the study are the characterization of the adverse event profile and safety and tolerability. The primary endpoints: adverse events and serious adverse events, and significant changes from baseline in laboratory values, ECG, vital signs, continuous telemetry, echocardiograms, etc., will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.
- For primary PK endpoints in this study, no formal hypotheses will be tested. All pharmacokinetic analyses will be performed on the PK Population and will follow the following rules:
    - Plasma concentration-time data of GSK3884464 will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study.

- From the plasma concentration-time data following single dose administration, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$), and apparent terminal phase half-life ($t_{1/2}$). Other parameters may be derived as appropriate; additional details will be provided in the SAP.
- From the plasma concentration-time data following repeat dose administration, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), trough concentrations (C_τ), area under the plasma concentration-time curve (AUC_τ) and apparent terminal phase half-life ($t_{1/2}$). Other parameters may be derived as appropriate; additional details will be provided in the SAP.
- Dose proportionality for single dose administration will be assessed by visual inspection of dose normalised $AUC_{(0-\infty)}$ and C_{max} values versus dose. Analysis of $\log_e$-transformed parameters may be carried out, using the power model. Dose proportionality for repeat dose administration may be assessed using similar methods to the single dose.
- The extent of accumulation after repeat dosing will be determined via computation of accumulation ratios based on AUC_τ (R_{AUC}), on C_{max} (R_{Cmax}), and on C_τ ($R_{C\tau}$). An assessment of time to achieve steady state will be made based on inspection of the trough concentrations.

9.4.1.2. Secondary Endpoint(s)

NQO1 mRNA: The normalized mRNA expression data will be analysed with a mixed effect model with subject as random effect, and treatment, visit and treatment by visit as fixed effect. The ratio to baseline at each post treatment visit will be estimated with 95% confidence interval.

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9.5. Interim Analyses

Data may be analyzed at the end of each completed cohort/study Part. Safety and pharmacokinetic data (and PD data if available) will be reviewed by the DEC before dose escalation in each study Part, and between study Parts. Data for these reviews will be cumulative and can include individual participant data, summaries by treatment group, and graphical displays. Dose escalation decisions will be made as outlined in Section 4.4, Section 6.5, and in the DEP.

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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and 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), 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 to the participant or their legally authorized representative (LAR) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

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 the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study intervention approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

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. Dose Escalation Committee

Participant safety will be continuously monitored by the Sponsor's DEC which includes safety signal detection at any time during the study.

The DEC consists of the Principal Investigator (or appropriate designee), Site Senior Clinical Development Manager, Medical Monitor, GSK Clinical Science Lead, GSK Study Delivery Lead, GSK Clinical Pharmacology Modelling and Simulation (CPMS) representative, GSK Drug Metabolism and Pharmacokinetics Lead, a GSK Global Clinical Safety and Pharmacovigilance (GCSP) Lead, GSK Clinical Biomarker Lead, GSK Study Data Manager, and a GSK Statistician**.** The GSK Medical Monitor and the GSK CPMS representative will remain unblinded for the dose escalation review throughout the course of the study. Additional internal GSK safety representatives may be consulted and included in the dose escalation decision making, in a blinded or unblinded manner as deemed necessary by the DEC.

The DEC will be used to ensure data integrity in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions for this study. The Committee will review emerging data and recommend changes to the study, and review safety parameters during the study.

The DEC will also review the data to determine if participants are experiencing higher than expected adverse GI symptoms based on responses the review of adverse events. Further details are in the DEP.

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 the investigators who were involved with the study with the full summary of the study results. 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 trial 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 trial 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 trial 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 trial 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 CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and 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 Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.

- 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 final Clinical Study Report (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 site open and will be the study start date.

Study/Site Termination

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. 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

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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

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 participant and should assure appropriate subject 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

All protocol required laboratory assessments, as defined in Table 7, must be conducted in accordance with the Laboratory Manual, and Protocol SoA (Section 1.3.1). Laboratory requisition forms must be completed, and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

- The clinical safety tests detailed in Table 7 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, which may require an unscheduled visit.

Table 7 Protocol-Required Safety Laboratory Assessments.

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count WBC Count (absolute) Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic	Total Protein

Laboratory Assessments	**Parameters**			
			Transaminase (SGPT)	
	Glucose[2]	Calcium	Alkaline phosphatase	Chloride
	Bicarbonate	Albumin	Uric Acid	Phosphate
	Creatinine Phosphokinase			
	LDL	Triglycerides		
Other Safety Assessments	• N-terminal -proBNP • hs Troponin • eGFR • Gamma-glutamyl transferase (GGT)			
Routine Urinalysis[3]	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal) • Urine albumin:creatinine ratio • Urine creatinine • Urine phosphate (only in the event a participant has persistent serum hypophosphataemia)[4]			
Core Urine Monitoring Assessments	• Spot urine protein: creatinine (UPC) ratio • Urine phosphate			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula • COVID-19 testing[5] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed on the same sample to confirm the result) The results of each test must be entered into the CRF			
Other assessments	• Fasting Serum Insulin • Aldosterone[6], Cortisol[6] and ACTH[6] • HbA1c			

Laboratory Assessments	Parameters

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 7.1.1and Section 10.5 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. Glucose will be fasting for all assessments. For Part 2 Cohort 4 and 5 collect on D1, D4, D11 and D14. For Part 2 Cohort 6, collect D1, D4, D11, D18, and D21.
3. If trace protein or blood in urine is detected, a repeat test will be performed within 24 hrs, except if the repeat test is required at Screening the site should repeat as soon as possible within the screening period. If results are considered abnormal (guidance in SRM), further quantification is required at the investigator's discretion. If glucose is positive by dipstick, send for laboratory urine glucose with contemporaneous serum glucose.
4. If persistent serum hypophosphatemia (less than 2 mg/dL) confirm by repeat testing.
5. Two consecutive approved molecular tests (PCR or antigen test) separated by > 24 hours. The second test ideally should be within 72 hours of admission to the unit. If the second test is > 72 hours prior to unit admission, subjects should be advised to self -quarantine until entrance to the unit while awaiting final testing clearance. Ad hoc testing may be done based on clinical presentation and site procedure. Note: A SARS-CoV2 Ag test was recently approved and may be an alternative to PCR testing once the operating characteristics are understood. Other molecular tests for active infection are in development and may be used when approved by regulatory bodies.
6. See SoA for timing of tests.

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.
- 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/participant's parent(s)/LAR(s)] who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The [participants/ participant's parent(s)/LAR(s)] 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/ parental /LAR's] concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by [participant/participant's parent(s)/LAR(s)] will be collected during interview with the [participants/participant's parent(s)/LAR(s)] and by review of available medical records at the next visit.
- Solicited AEs are predefined local [at the injection site] 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).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

Events Meeting the AE Definition
• New conditions 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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 serious adverse event that, at any dose:
• Results in death
• 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.
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 fulfils 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.
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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Is a suspected transmission of any infectious agent via an authorised medicinal product
Other situations: • 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 or convulsions that do not result in hospitalization, 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 • Deep venous thrombosis/pulmonary embolism • 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. • The investigator will then record all relevant AE/SAE information in the CRF. • 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. • 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. • 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 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- 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.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 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. • New or updated information will be recorded in the originally completed CRF. • 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. • 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. • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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' • 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. • 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. • 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.** • 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. • 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. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

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 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 must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

• **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]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner 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.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable

• Sexual abstinence   • *Note: 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 men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception 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. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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 with friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

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

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • 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. 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 or non-GSK comparator treatments. Record the date/time of the PK sample draw and the date/time of the last dose of study treatment prior to PK 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.

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviations

Δ	Change from baseline
ΔΔ	Placebo-corrected change-from-baseline
6-CIT	6-item cognitive impairment test
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
ACR	Albumin Creatinine ratio
CCI	[redacted]
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
APD	Atrial Premature Depolarisation
ARB	Angiotensin II receptor blockers
AST	Aspartate transaminase
AUC	Area under the curve
$AUC_{(0-\infty)}$	Area under curve to infinity
$AUC_{(0-t)}$	Area under the curve to last quantifiable concentration
AVB	Atrioventricular block
β	Beta
BBB	Bundle branch block
BIB	Bioanalysis, Immunogenicity and Biomarkers
BMI	Body mass index

BPM	Beats per minute
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CCI	[redacted]
C_{max}	Maximum observed plasma concentration
C_{τ}	Plasma trough concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
Cr	Creatinine
CRF	Case report form
CSR	Clinical study report
CUC	Clinical Unit Cambridge
CV	Cardiovascular
DBL	Database lock
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
dL	Deciliter
DMPK	Drug Metabolism and Pharmacokinetics
DRE	Disease related events
DRO	Disease related outcome
ECG	Electrocardiogram

eCRF	Electronic case report form
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EW	Early withdrawal
CCI	[redacted]
FSH	Follicle stimulating hormone
FTIH	First time in human
gm	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GERD	Gastroesophageal reflux disease
CCI	[redacted]
GLP	Good laboratory practice
GR	Gastro-resistant
GSK	GlaxoSmithKline
h	Hour
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HDPE	High density polyethylene
HF	Heart failure
HFpEF	Heart failure preserved ejection fraction
HFrEF	Heart failure reduced ejection fraction
HIPAA	Health Insurance Portability and Accountability Act
HPMC-AS	Hydroxypropyl methylcellulose Acetate Succinate

HR	Heart rate
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
iPSC-CM	Induced Pluripotent Stem Cell-Derived cardiomyocyte
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IVIVT	In Vitro/In Vivo Translation
kg	kilogram
L	Liter
LAM	Lactational amenorrhoea method
LAR	Legally authorized representative
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
CCI [redacted]	
m^2	Square meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

MHRA	Medicines and Healthcare products Regulatory Agency
min	Minute
mL	Mililiter
mRNA	Messenger RNA
ms	Millisecond
MSDS	Material safety data sheet
mV	Millivolt
ng	Nanogram
NIMP	Non-Investigational Medicinal Product
NOAEL	No observed adverse effect level
NQ	Non-quantifiable
NQO1	NAD(P)H dehydrogenase (quinone 1)
NSVT	Non-sustained ventricular tachycardia
NTI	Narrow Therapeutic Index
NYHA	New York Heart Association
PD	Pharmacodynamic
pg	Picograms
PICF	Participant Information Sheet and Consent Form
PK	Pharmacokinetic
PR	PR interval of the ECG
QD	Once daily
QRS	QRS interval of the ECG
QT	QT Interval of the ECG
QTc	Corrected QT interval

QTcF	Corrected QT interval using Fridericia's formula
R_{AUC}	Accumulation ratios based on AUCτ
R_{Cmax}	Accumulation ratios based on C_{max}
$R_{C\tau}$	Accumulation ratio computed based on C_τ
RD	Repeat dose
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Single dose
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SoA	Schedule of Activities
SRM	Study Reference Manual
$t_{½}$	Terminal half-life
t_{max}	Time to maximum observed plasma drug concentration
TMF	Trial master file
CCI [redacted]	
ULN	Upper limit of normal
VPD	Ventricular Premature Depolarisation
VS	Vital Signs
VT	Ventricular tachycardia
WONCBP	Woman of Nonchildbearing Potential

Trademark Information

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10.7. Appendix 7: Protocol Amendment History

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order**.**		
Document	**Date**	**TMF Number**
Amendment 03	*17-FEB-2022*	*TMF- 14464572*
Amendment 02	*04-JAN-2022*	*TMF-14366164*
Amendment 01	*19-AUG-2021*	*TMF-13947787*
Original Protocol	*09-JUN-2021*	*TMF-13810865*

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Amendment 03 17-FEB-2022

This amendment is considered to be substantial.

Overall Rationale for the Amendment: This Protocol Amendment 03 is being implemented to provide additional safety monitoring.

Where the Amendment Applies:

This Protocol Amendment 03 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Previous: **Disclosure Statement**: This is a First Time in Human Study. Sentinel dosing will be incorporated in each Part of the study and at each dose level. Revised: **Disclosure Statement**: This is a First Time in Human Study. Sentinel dosing will be incorporated in each Part of the study and at each dose level. For Part 1, only 2 to 3 participants will be dosed at a time and their LFTs will be monitored until Day 6 before the next participants in the cohort are dosed.	This change was made to the dosing schedule to permit closer safety monitoring of LFTs for participants in Part 1 of the study.
Section 1.3.1 Part 1: Single Dose Administration in Healthy Participants (Cohorts 1, 2 and 3)	**Revised:** Clinical laboratory assessments (hema/chem/urinalysis-including liver chemistries) added to Day 4	Additional day chemistry blood draws added on Day 4 in Part 1 to monitor for liver chemistry changes. This is a safety update.
Section 4.1 Overall Design	Previous: Participants will be randomized to treatment sequences such that in each period up to 6 participants will receive active dose and up to 3 participants will receive placebo. Revised: Participants will be randomized to treatment sequences such that in each period up to 6 participants will receive active dose and up to 3 participants will receive placebo. Up to 2 to 3 participants will be dosed at a time, and their LFTs will be closely monitored before the next participants receive study treatment. Previous: In Part 1, sentinel participants will be followed clinically for 48 hrs (predicted half-life for GSK3884464 is approximately 12hrs) to allow for adequate observation of safety.	This change was made to the dosing schedule to permit closer safety monitoring of LFTs for participants in Part 1 of the study. The sentinel dosing regimen for the SAD portion of the study (Cohorts 2 and 3) was amended from 48 hours between doses to 6 days for safety monitoring for LFT changes.

Section # and Name	Description of Change	Brief Rationale
	Revised: In Part 1, sentinel participants will be followed clinically for 6 days to allow for adequate observation of safety. Previous: In Part 2, sentinel participants will be followed clinically for 60hrs (or 5 half-lives, whichever is longer) to allow for adequate observation of safety to monitor for emergence of adverse events Revised: In Part 2, sentinel participants will be followed clinically for 14 days to allow for adequate observation of safety to monitor for emergence of adverse events	Multiple Ascending Dose (MAD) phase of the study: observation period for sentinel dosing will be increased from 60 hours to 14 days for safety monitoring for LFT changes.
Section 6.8 Concomitant Therapy	Previous: Paracetamol/Acetaminophen at doses of ≤ 2 grams/day, is permitted for use at any time during the study. Revised: Paracetamol/Acetaminophen, at doses of ≤2 grams/day, or Ibuprofen ≤1200 mg/day, is permitted for use at any time during the study	The investigator is permitted an option to administer paracetamol or ibuprofen to participants if needed, in light of the potential impact of infrequent paracetamol use on LFT changes.

Amendment 02 04-JAN-2022

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment: This Protocol Amendment 02 is being implemented to update the timing of the PK sampling, to clarify the timing of the CCI [redacted] in Part 1, and to update information on the Dose Escalation and Study Progression. Typographical errors were also corrected.

Where the Amendment Applies:

This Protocol Amendment 02 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
1.0 Protocol Summary; Figure 1	PREVIOUS TEXT: (before progression to next Part) REVISED TEXT: Text and Star removed between Part 1 and Part 2	Figure 1 wording was updated to match removal of sentence from Section 4.4 as described below.
1.3. Schedule of Activities 1.3.1 Part 1 Single Dose Administration in Healthy Participants (Cohorts 1, 2 and 3) 1.3.2 Part 2 (Cohorts 4 and 5): Multiple Dose Administration to Healthy Participants for 14 days of Treatment and 1.3.3 Part 2 (Cohort 6): Multiple Dose Administration to Healthy Participants for 21 days of	PREVIOUS TEXT: PK plasma samples will be collected at the following time points: Pre-dose, post dose: 30min, 1hr, 1.5hr, 2hr, 3hr 4hr, 6hr, 8hr, 12hr; 18hr, 24hr, 36hr, 48hr,72hr, 96hr, 120hr (morning of D6). Metabolite plasma samples to be collected from Cohorts 2 and 3 only. REVISED TEXT: PK plasma samples will be collected at the following time points: Pre-dose, post dose: 15 min, 30min, 1hr, 1.5hr, 2hr, 4hr, 6hr, 8hr, 12hr; 18hr, 24hr, 36hr, 48hr,72hr, 96hr, 120hr (morning of D6). Metabolite plasma samples to be collected from Cohorts 2 and 3 only (See Section 8.4.1 and SRM). PREVIOUS TEXT: **Metabolite plasma samples only on D1, D14 and D15 (to collect 24 hr sample only) with same timepoints as described for PK plasma sample above. **Metabolite plasma samples only on D1, D21 and D22 (to collect 24 hr sample only) with same timepoints as described for PK plasma sample above. REVISED TEXT: **Metabolite plasma samples only on D1, D14 and D15 (to collect 24 hr sample only) with same timepoints as described for PK plasma sample above (See Section 8.4.1 and SRM).	The PK sampling time points were modified to better capture Tmax and Cmax, based on emerging PK information in Study Part 1. This is in-scope of the original protocol wording.

Section # and Name	Description of Change	Brief Rationale
Treatment	**Metabolite plasma samples only on D1, D21 and D22 (to collect 24 hr sample only) with same timepoints as described for PK plasma sample above (See Section 8.4.1 and SRM).	
CCI [redacted]		
Section 4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	PREVIOUS TEXT: It will be approximately 2 weeks between dose escalation in Part 1 and approximately 4 weeks between Parts 1 and 2. REVISED TEXT: Text was removed PREVIOUS TEXT: The dose levels in Part 2 will only be started after the same or higher dose cohorts are complete in Part 1 with no dose escalation stopping criteria having been met. In addition, the maximum dose for Part 2 cannot exceed the maximum dose in Part 1. REVISED TEXT: The dose levels in Part 2 will only be started after the same or higher dose cohorts are	As per protocol Section 4.3.3 and Section 4.4, and as confirmed by MHRA, dose levels in Part 2 will be tested only when same or higher dose levels will have been tested in Part 1 without meeting any dose escalation stopping criteria. This supersedes the need for separation of Part 1 and Part 2 by 4 weeks.

Section # and Name	Description of Change	Brief Rationale
	complete in Part 1 with no dose escalation stopping criteria having been met, therefore, Part 2 may start before the completion of Part 1. At a minimum, MAD Cohort dose levels will be defined based upon DEC review of the first five SAD dose levels. Additional MAD cohorts will be based on DEC review of subsequent SAD dose levels and the previous MAD. Lastly, the maximum dose for Part 2 cannot exceed the maximum dose in Part 1.	

Amendment 01 19-AUG-2021

Overall Rationale for the Amendment: This Protocol Amendment 01 is being implemented to correct typographical errors, to update information on the Dose Escalation Plan and Committee, Exclusion Criteria and provide information on Concomitant therapy.

Where the Amendment Applies:

This Protocol Amendment 01 applies to all countries and sites participating in the study.

Table of Specific Changes:

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Section # and Name	Description of Change	Brief Rationale
1 Protocol Summary	PREVIOUS: The Committee will review emerging data and recommend changes to the study, and review safety parameters during the study. The details and composition of the DEC will be included in a charter to be completed prior to commencement of study enrolment. REVISED: The Committee will review emerging data and recommend changes to the study, and review safety parameters during the study. The details and composition of the DEC will be included in the Dose Escalation Plan (DEP), to be completed prior to commencement of study enrolment.	Protocol was updated to refer to the Dose Escalation Plan which will replace the charter.
1.3. Schedule of Activities	Addition of missing X's to table, missing asterisks, and missing words. For example: Adrenocorticotropic hormone (ACTH) and Cortisol Plasma PK and metabolite sampling	To correct typographical errors.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Previous: The review of adverse events may trigger the switch to gastro-resistant capsules and the questionnaire will further capture tolerability information related to both capsules (Refer to Dose Escalation Plan [DEP] for switching criteria). REVISED: The review of adverse events may trigger the switch to gastro-resistant capsules and the questionnaire will further capture tolerability information related to both capsules (Refer to Section 4.4 for switching criteria)	Specific section in protocol was updated and referred to instead of separate plan.
4.3.2 Prediction of Dose Levels for Part 1	PREVIOUS: In the event the observed exposure at the starting dose (1 mg) is lower than the corresponding predicted exposure, the next dose will target the exposure at the MABEL. In this case the escalation increment can be greater than 3-fold. REVISED: In the event the observed exposure at the starting dose (1 mg) is lower than the corresponding predicted exposure, the next dose will target the exposure at the MABEL. In this case the escalation increment can be greater than 3-fold. In the event the observed exposure at the starting dose (1 mg) is substantially higher than the corresponding predicted exposure, the next dose will be revised to produce a 2-3-fold increment in exposure, consistent and no greater than the currently planned increments, if the dose escalation stopping criteria are not met.	This statement adds flexibility to adjust the predicted doses based on the data from Part 1.
4.3.3 Prediction of Dose Levels for Part 2	PREVIOUS: The decision to progress to Part 2 and the selection of the actual dose levels, of the repeat dose regimen and of the number of cohorts will be made by the DEC, based on safety, tolerability and PK data from Part 1 (see Section 4.4 and Section 10.1.5).	This statement adds flexibility to adjust the predicted doses based on the data from Part 1.
	REVISED: The decision to progress to Part 2 and the selection of the actual dose levels, of the repeat dose regimen and of the number of cohorts will be made by the DEC, based on safety, tolerability and PK data from Part 1 (Section 4.4, Section 10.1.5). The predicted doses to be explored in Part 2 may be adjusted to the new start and maximum doses pending data obtained in Part 1.	

Section # and Name	Description of Change	Brief Rationale
4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	PREVIOUS: The decision to proceed to the next dose level, to progress through each Part/Cohort, and to include an additional cohort/dose level (if necessary) will be made by the DEC. The anticipated mean plasma exposure (C_{max} and AUC) for any dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study (Section 4.3.1). The DEC consists of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Science Lead, GSK Study Delivery Lead, GSK Clinical Pharmacology Modelling and Simulation (CPMS) representative, a GSK Global Clinical Safety and Pharmacovigilance (GCSP) representative and a GSK Statistician. The GSK Medical Monitor and the GSK CPMS representative will remain unblinded for the dose escalation review throughout the course of the study. Additional internal GSK safety representatives may be consulted and included in the dose escalation decision making, in a blinded or unblinded manner as deemed necessary by the DEC. Details of the DEC membership, data to be reviewed, and stopping criteria will be outlined in the DEP (see also Section 10.1.5). REVISED The decision to proceed to the next dose level, to progress through each Part/Cohort, and to include an additional cohort/dose level (if necessary) will be made by the DEC. The anticipated mean plasma exposure (C_{max} and AUC) for any dose level to be administered will not exceed the limiting exposure criteria based on the plasma NOAEL dose from the monkey 6-week GLP tox study (Section 4.3.1)	This deleted text was moved to Section 10.1.5

Section # and Name	Description of Change	Brief Rationale
4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	PREVIOUS: The possibility to include additional cohort(s), to investigate higher dosing levels (with exposure capped at monkey NOAEL), might be considered in the event that no safety signals are observed in the three planned cohorts. REVISED: <u>In the event the observed exposure at the starting dose (1 mg) is substantially higher than the corresponding predicted exposure, the next dose will be revised to produce a 2-3-fold increment in exposure, consistent and no greater than the currently planned increments, if the dose escalation stopping criteria are not met.</u>	
4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	PREVIOUS: Dose escalation decisions will be based on data obtained from 4 or more participants on active treatment at the prior dose level and will be approximately 2 weeks between dose escalation; approximately 4 weeks between Parts 1 and 2 (Refer to DEP). The review data set will at minimum consist of AE listings, safety labs, electrocardiograms (ECG), vital signs (VS), and PK results derived from at least 24-hour plasma profiles Pharmacodynamic (PD) data will be reviewed as available but will not be required for an escalation decision. Flagged vital signs, cardiac monitoring (telemetry), ECG and laboratory findings will also be reviewed. The decision to switch to the GI resistant capsules will be made by the DEC after review of the AE listings.	Additional detail in protocol to describe dose level progression. References made to the Dose Escalation Plan and charter have been changed to reference Section 4 throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
	REVISED: GSK will conduct regular dose escalation meetings throughout the course of Part 1 and Part 2. Each meeting will be scheduled to occur at the end of each cohort and / or treatment period on data obtained after each dose level. Dose escalation decisions will be based on data obtained from 4 or more participants on active treatment at the prior dose level. It will be approximately 2 weeks between dose escalation in Part 1 and approximately 4 weeks between Parts 1 and 2. The review data set will consist at minimum AE listings, safety labs, electrocardiograms (ECG), vital signs (VS), and PK results derived from at least 24-hour plasma profiles Pharmacodynamic (PD) data will be reviewed as available but will not be required for an escalation decision. Flagged vital signs, cardiac monitoring (telemetry), ECG and laboratory findings will also be reviewed. The decision to switch to the gastro resistant capsules will be made by the DEC after review of the AE listings and will be based on clinical judgement.	
4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	Progression to the next higher dose level will be halted if: • Two or more participants in the same cohort experience severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as at least possibly related to the administration of GSK3884464), independent of within or not within the same system-organ-class; and independent of whether it is related to study intervention or not. • Any participant experiences a serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the administration of GSK3884464). • Three or more participants in a cohort experience the same adverse event of moderate severity that can be reasonably attributed to dosing with GSK3884464.	Additional detail in protocol to describe dose level progression based on Adverse Events.

Section # and Name	Description of Change	Brief Rationale
	The dose escalation will stop, and no further participants will be dosed at that dose level or any higher level. Lower doses and progression to Part 2 may occur. If after consultation the Sponsor deems that dosing can resume at that level or higher, the Sponsor will submit an application for a substantial amendment to the Regulatory Agency	
4.4 Criteria for Dose Escalation and for Progressing Between Parts of the Study	PREVIOUS: Criteria for progression from one part of the study to the next are further expanded upon in the dose escalation charter, to be completed prior to the commencement of the study. REVISED: The dose levels in Part 2 will only be started after the same or higher dose cohorts are complete in Part 1 with no dose escalation stopping criteria having been met. In addition, the maximum dose for Part 2 cannot exceed the maximum dose in Part 1	Expansion of criteria for dose expansion from Part 1 to Part 2.
5.2 Exclusion Criteria	PREVIOUS: Serum troponin I or troponin-T greater than 2x the upper limit of normal Alanine transaminase (ALT) > 1.5x upper limit of normal (ULN). Bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). REVISED: Serum troponin I or troponin-T greater than the upper limit of normal (ULN). Alanine transaminase (ALT) > ULN. Bilirubin > ULN. PREVIOUS: Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort)	1. Clarification of Exclusion criteria to match Risk table and meet Healthy Volunteer expectations. 2. Update exclusionary prescription and non-prescription medications 3. Update eGFR equation

Section # and Name	Description of Change	Brief Rationale
	REVISED: Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer [e.g. Rifampin, St John's Wort extract]) PREVIOUS: Estimated glomerular filtration rate (eGFR) ≤ 90 ml/minute/1.73m^2 calculated by the Cockroft-Gault equation as below: eGFR = [[140 - age(yr)] *weight(kg)] / [72*serum Cr(mg/dL)] (multiply by 0.85 for women). REVISED: Estimated glomerular filtration rate (eGFR) ≤ 90 ml/minute/1.73m^2 calculated by the CKD-EPI equation as below: eGFR = 141 x min (SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black]	
6.8 Concomitant Therapy	PREVIOUS: However, since glucuronidation was a predominant metabolic route in human hepatocytes, co-administration of a potent inducer, e.g., phenytoin and rifampin, can result in decreased levels of GSK3884464. Contraindication or replacement thereof is recommended. Please refer to the SRM for an exclusion criteria list of Prior and Concomitant medications. REVISED: However, since glucuronidation was a predominant metabolic route in human hepatocytes, co-administration of a potent inducer, e.g., phenytoin and rifampin, can result in decreased levels of GSK3884464. Contraindication or replacement thereof is recommended. The following classes of therapies and examples are prohibited for concomitant or prior use within 2 weeks: Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone Antimycobacterials: rifampin, rifapentine Estrogen containing oral contraceptive: ethinylestradiol/levonorgestrel	Additional detail in protocol to describe the excluded classes of prohibited concomitant medications.

Section # and Name	Description of Change	Brief Rationale
7.1.1.3 Dose Expansion Criteria	PREVIOUS: If ≥ 2 subjects in any dose level experience an **isolated ALT≥3xULN** (on active treatment) then the following dose expansion criteria applies: 4 additional subjects on active and 2 additional subjects on placebo will be recruited at the same dose level. REVISED: If ≥ 2 subjects in any dose level experience an **isolated ALT≥3xULN** (on active treatment) then the following dose expansion criteria applies: Four additional subjects on active and 2 additional subjects on placebo will be recruited at the same dose level. Any cohort expansion will be contingent on approval of an amended protocol by the UK ethics board and the MHRA.	MHRA requested cohort expansion result in protocol amendment to be approved by MHRA and UK ethics board.
7.1.8 Safety Stopping Criteria for Dose Escalation / Study Progression in Healthy Participants	Progression to the next higher dose level will be halted if: • Two or more participants in the same cohort experience severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as at least possibly related to the administration of GSK3884464), independent of within or not within the same system-organ-class; and independent of whether it is related to study intervention or not. • Any participant experiences a serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the administration of GSK3884464). • Three or more participants in a cohort experience the same adverse event of moderate severity that can be reasonably attributed to dosing with GSK3884464. The dose escalation will be temporarily halted, and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the GSK medical monitor, relevant GSK personnel, and with UK ethics board and the MHRA will then take place prior to any resumption of dosing, which may include the evaluation of lower doses.	This section was moved to Section 4.4

Section # and Name	Description of Change	Brief Rationale
8.4.4 Sample Analysis	PREVIOUS: Analysis of GSK3884464 in plasma and urine samples will be performed under the control of GSK BIB IVIVT. Concentrations of GSK3884464 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site for a specified portion of the retention period. Additional parameters may be analyzed if determined appropriate; more details will be provided in the Statistical Analysis Plan (SAP). Processing, storage and shipping procedures are provided in the SRM. REVISED: Analysis of GSK3884464 in plasma and urine samples will be performed under the control of GSK BIB IVIVT. Concentrations of GSK3884464 will be determined using the currently approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. SRM, CLW, SOW) and raw data will be archived in the GSK R&D archives.	Updated description of where documents and raw date will be archived.
10.1.5 Dose Escalation Committee	PREVIOUS: The DEC will also review the data to determine if participants are experiencing higher than expected adverse GI symptoms based on responses the review of adverse events. Further details are in the DEP. REVISED: The DEC consists of the Principal Investigator (or appropriate designee), Site Senior Clinical Development Manager, Medical Monitor, GSK Clinical Science Lead, GSK Study Delivery Lead, GSK Clinical Pharmacology Modelling and Simulation (CPMS) representative, GSK Drug Metabolism and Pharmacokinetics Lead, a GSK Global Clinical Safety and Pharmacovigilance (GCSP) Lead, GSK Clinical Biomarker Lead, GSK Study Data Manager, and a GSK Statistician. The GSK Medical Monitor and the GSK CPMS representative will remain unblinded for the dose escalation review throughout the course of the study.	Further description of the Dose Escalation Committee in the protocol and movement of committee description from Section 4.4.

Section # and Name	Description of Change	Brief Rationale
	Additional internal GSK safety representatives may be consulted and included in the dose escalation decision making, in a blinded or unblinded manner as deemed necessary by the DEC. The DEC will be used to ensure data integrity in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions for this study. The Committee will review emerging data and recommend changes to the study, and review safety parameters during the study. The DEC will also review the data to determine if participants are experiencing higher than expected adverse GI symptoms based on responses the review of adverse events. Further details are in the DEP.	
10.2 Appendix 2: Clinical Laboratory Tests	PREVIOUS: Other Screening Tests • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines5 • Urine cotinine level • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula • COVID-19 testing[6] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed on the same sample to confirm the result) REVISED: Other Screening Tests • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine cotinine level	Removal of Urine alcohol and drug screen as this is performed as a breath test and footnote.

Section # and Name	Description of Change	Brief Rationale
	• Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula • COVID-19 testing[6] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed on the same sample to confirm the result) PREVIOUS: The investigative site may screen for additional drugs of abuse as part of standard site practice and will be recorded in source documents. The study CRF will only collect drug screen results of those that are positive. PREVIOUS: Routine Urinalysis • Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal) • Urine albumin:creatinine ratio • Urine creatinine • Urine phosphate (only in the event a participant has persistent serum hypophosphataemia)[4] • eGFR REVISED: Other Safety Assessments • N-terminal -proBNP • hs Troponin • eGFR	Removal of incorrect placement of eGFR from Routine Urinalysis and added to Other Safety Assessments

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Signature Page for 213376 TMF-14577739 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 06-Apr-2022 14:58:29 GMT+0000

Signature Page for TMF-14577739 v2.0