TITLE PAGE

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Protocol Number: 207702

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Compound Number: GSK2798745

Development Phase: 2

Sponsor Name and Legal Registered Address:

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1. SYNOPSIS

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Rationale:

Chronic cough is a disease with high unmet medical need. It is hypothesised that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) through P2X purinoceptor 3 (P2X3) receptors. Transient receptor potential vanilloid 4 (TRPV4) activation has been shown to cause ATP release from airway macrophages and airway epithelial cells, and studies have established a role for TRPV4-mediated ATP release and the P2X3 receptor in TRPV4-mediated activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD) – diseases in which cough is a prevalent symptom. It is hypothesised, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough.

GSK2798745 is a potent and selective TRPV4 channel blocker being investigated for the treatment of chronic cough. The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment-resistant chronic cough.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers

Overall Design:

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

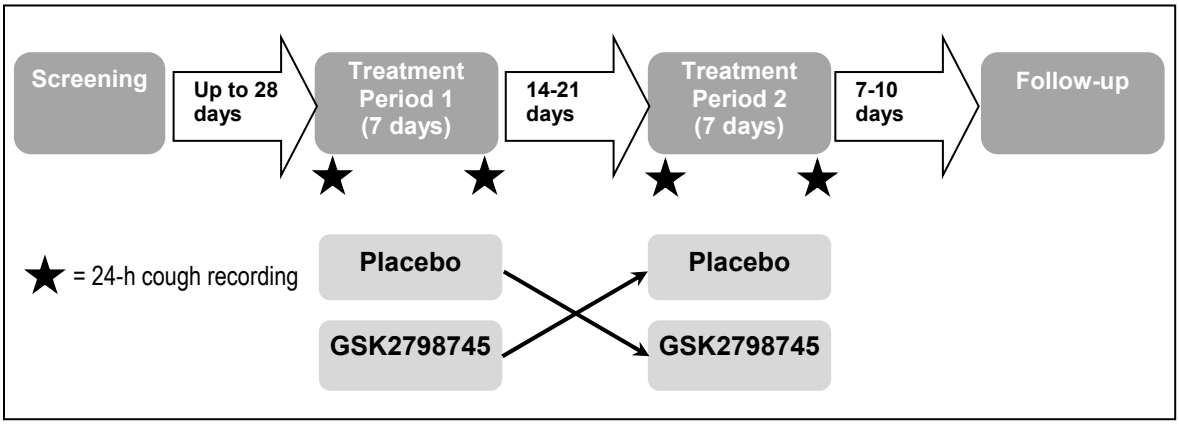
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Study Design Overview



Number of Participants:

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. However, following a sample-size re-estimation when approximately 50% of the target sample size has completed the study, the sample size may be revised upwards or downwards. Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening and Follow-up Schedule of Activities

Procedure	Screening[1] (up to 28 days before Treatment Period 1, Day -1)	Follow up/Early Withdrawal (7-10 days post last dose)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage, and family history of premature cardiovascular (CV) disease	X		Substances: Drugs, Alcohol, tobacco
Full physical exam, including height and weight	X	X	Height to be measured at screening only.
Chest imaging (chest x-ray [CXR] or computed tomography [CT] scan)	X		Not required if chest imaging has been conducted within 12 months of screening with no significant findings.
Simplified Nutritional Appetite Questionnaire (SNAQ)		X	
Columbia Suicidality Severity Rating Scale (CSSRS)	X		Use 'Baseline' CSSRS.
Human immunodeficiency virus (HIV), hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Clinical chemistry, haematology and urinalysis (including cardiac troponin)	X	X	Non Fasting
Follicle-stimulating hormone and estradiol	X		As needed in women of non-childbearing potential only
Faecal Occult Blood Test (FOBT)	X		FOBT cards will be provided at screening and must be returned to the laboratory and analysed before Day -1.
Vital signs (blood pressure, heart rate and temperature)	X	X	Triplicate vital signs required at screening.
12-lead ECG	X	X	Triplicate ECG required at screening.
Forced Expiratory Volume in One Second (FEV1)	X		Not required if documented evidence of FEV1 ≥ 80% and ≤ 120% within the 6 months before screening.

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Cough Severity & Urge to Cough Visual Analogue Scale (VAS)	X (Severity only)	X (Severity & Urge)	Urge to cough VAS will not be completed at screening.
Audiometry		X	Audiometry to be done anytime between end of Treatment Period 2 and Follow-up.
Concomitant Medication review	X	X	
Adverse event (AE)/serious adverse event (SAE) review	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose (see Section 9.2.1).

1. Screening assessments may be conducted at multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).

2.2. Treatment Period 1 and 2 Schedule of Activities

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Study Treatment						
Randomisation		X (TP1 only)				Can be done on Day –1 or Pre-dose Day 1. Participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months).
Study Treatment dispensed		X				
Study Treatment dosing		X	X	X		Home dosing on Days 2-6. Dosing to be at about the same time each day (±2 hours relative to dosing on Day 1).
Diary Card dispensed		X		X (TP1 only)		Diary card used to collect dosing information, AEs and concomitant medications. Diary card dispensed on Day 7 in Treatment Period 1 only (to collect AEs and concomitant medications during washout period).
Efficacy Assessments						
24- hour Cough Counting Starts	X			X		On Day 7, the cough counter must be attached immediately after dosing. Participant to be advised to avoid noisy environments whilst wearing the counter, and to stay awake for 10 h after attachment of the monitor.
24- hour Cough Counting Ends		X			X	On Day 1, the cough counter must be removed before dosing.
Cough Severity & Urge to Cough VAS	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.2).
Leicester Cough Questionnaire (LCQ)	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.3).
Safety Assessments						
Brief physical exam	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Weight	X				X	Baseline can be done on Day –1 or Pre-dose Day 1

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Vital signs (blood pressure, heart rate and temperature)		X (pre-dose)			X	Single measurements
12-lead ECG		X (pre-dose)			X	Single measurements
Clinical chemistry, haematology and urinalysis (including cardiac troponin)		X (pre-dose)			X	Can be done on Day –1 or Pre-dose Day 1. Non-fasting.
FOBT				X		FOBT cards will be provided on Day 7 and returned on Day 8, if possible (or returned by post).
CSSRS	X				X	Use the 'Since Last Visit' CSSRS questionnaire. The pre-dose CSSRS in each Treatment Period can be done on Day –1 or Pre-dose Day 1.
SNAQ	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Audiometry	X					Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).
Concomitant Medication review	X	X	X	X	X	Concomitant medications collected in Diary Card during washout period.
SAE/AE review	X	X	X	X	X	AEs collected in Diary Card during washout period.
Other Assessments						
PK blood samples		X		X	X	**Day 1 and Day 7:** predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h post dose **Day 8:** 24 h post dose For participants taking atorvastatin, an extra sample will be taken at each time-point.
Optional Genetic Sample		X				Can be taken any time after consent has been signed and the participant has been randomised.

- The Cough Severity & Urge to Cough VAS should be completed before the LCQ, and both questionnaires should be completed before any other assessments.
- When scheduled at the same time-points, 12-lead ECGs and vital signs should be completed before any blood draws.
- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point.
- The timing and number of planned study assessments, including: safety and pharmacokinetic 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.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

GSK2798745 is a potent and selective transient receptor potential vanilloid 4 (TRPV4) channel blocker being investigated for the treatment of chronic cough.

GSK2798745 is a potent *in vitro* blocker of recombinant human TRPV4 channels, with:

- agonist-evoked Ca^{2+} influx 50% maximal inhibitory concentration (IC_{50}) value of 1.6 to 2.0 nM;
- hypotonicity-evoked Ca^{2+} influx IC_{50} value of 1.6 to 2.0 nM; and
- blocks native human endothelial TRPV4 channels (agonist-evoked impedance reduction in the presence of human whole blood IC_{50}=6.5nM).

GSK2798745 is a potent *in vivo* blocker of rat TRPV4 channels where full block of TRPV4-induced pulmonary edema was observed at a 38 nM total plasma concentration. Further information regarding the pre-clinical and clinical studies performed with GSK2798745 is available in the investigator brochure (IB) (GSK Document Number 2013N162862_03).

GSK2798745 has been administered orally to healthy participants as single doses ranging from 0.25 to 12.5 mg. A dosage of 5 mg once daily has been administered for up to 14 days in healthy participants. Further, GSK2798745 at a dose of 2.4 mg has been evaluated as a single dose and subsequently as a repeat dose for 7 days in participants with heart failure.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure indicates that there are no clinically significant safety concerns with repeat administration up to 7 days.

TRPV4 is widely expressed in the respiratory tract and is activated by a wide range of stimuli including temperature, pH and osmolarity [Toft-Bertelsen, 2017]. It is hypothesized that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) [Basoglu, 2005] through P2X purinoceptor 3 (P2X3) receptors [Ford, 2013]. TRPV4 activation causes ATP release from airway epithelial cells [Baxter, 2014], and studies have established a role for TRPV4-mediated ATP release and P2X3 receptor in activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma [Idzko, 2007] and chronic obstructive pulmonary disease (COPD) [Baxter, 2014], diseases in which cough is a prevalent symptom. It is hypothesized, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough [Bonvini, 2016].

3.1. Study Rationale

The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment refractory chronic cough.

TRPV4 and P2X3 antagonists have been shown to reduce cough effectively in a pre-clinical cough model in guinea pigs [Bonvini, 2016]. Moreover, clinical data suggest that pharmacological inhibition of P2X3 receptors reduces cough frequency and improves patient reported outcomes and quality of life in a subset of patients with chronic cough [Abdulqawi, 2015].

Therefore, blocking TRPV4 channels may be a viable therapeutic strategy for treating chronic idiopathic or treatment-resistant cough.

3.2. Background

Chronic cough is defined in clinical practice as cough lasting greater than 8 weeks. It is highly prevalent worldwide and is a leading cause of unplanned visits to the doctor's office [Schappert, 2006]. Chronic cough patients can be broadly divided into 3 groups: those with idiopathic cough, those with treatment refractory cough secondary to otherwise controlled triggers such as allergic rhinitis or mild asthma, and those with cough associated with underlying chronic lung diseases, such as COPD or Idiopathic Pulmonary Fibrosis (IPF) [Smith, 2017].

Large epidemiological studies that include all 3 patient groups suggest that the prevalence of chronic cough is as high as 10% worldwide. The epidemiology of idiopathic and treatment refractory chronic cough is more difficult to determine precisely, though it is probable that these groups of patients represent a minority of the total compared with diseases such as COPD. However, the amount of coughing (coughs per hour) measured in patients with idiopathic or treatment refractory chronic cough tends to be much higher than in patients with COPD [Abdulqawi, 2015; Sumner, 2013]. Moreover, cough suppression in suppurative lung diseases such as COPD may carry additional risks that would require establishing a benefit risk ratio in a dedicated study. Therefore, demonstrating efficacy in idiopathic and treatment refractory chronic cough populations is a logical first step before exploring other populations.

Regardless of etiology, chronic cough is by nature difficult to treat and significantly diminishes quality of life. The commonly used therapies for cough are opioid-derived over-the-counter medicines, which tend to be relatively ineffective when compared with placebo. In addition, these medicines have significant side-effects and potential for abuse that limit their usability. Likewise, the opiate codeine is among the most commonly prescribed medicines for cough despite similar limitations to its clinical efficacy and even greater potential for abuse. Overall, there is a significant unmet medical need for safe and effective medicines to treat chronic cough.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2798745 may be found in the IB.

3.3.1. Risk Assessment

All potential risks of GSK2798745 are based on pre-clinical data. No risks have been identified in the clinical studies of GSK2798745 conducted prior to the effective date of this protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Vascular lesions	Dogs (4-week study): at 30 mg/kg/day, 2 males had arterial lesions • One male: Heart – Coronary artery inflammation; Thymus – Arteriole inflammation with fibroplasia • One male: Epididymides – Artery degeneration/necrosis with inflammation Dogs (12-week study): At 10 mg/kg/day, 1 male and 1 female had arterial lesions • One male: Epididymides – Arteriole degeneration/necrosis with lymphocytic inflammation • One female: Bladder – Arteriole degeneration/necrosis with lymphocytic inflammation	**Participant Monitoring:** The arterial lesions noted in heart, thymus, epididymides, and urinary bladder cannot be monitored directly. There is currently no human translation biomarker or understanding of the underlying mechanism. **Participant Exposure:** Since these effects cannot be monitored directly in clinical studies, coverage of ≥30 fold will be maintained from the no-effect dose (3 mg/kg/day); exposure will not intentionally exceed the average daily area under concentration-time curve (AUC) of 0.513 hr*ug/mL and/or maximum observed plasma concentration (C_{max}) of 0.050 ug/mL on an individual basis.
Myocardial toxicity	Dogs (4-week study): at 30 mg/kg/day, myofiber degeneration/necrosis and inflammation (2 animals)	**Participant Selection:** Participants with history of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months will be excluded. **Participant Monitoring:** Cardiac troponin levels

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		will be monitored throughout the study. **Participant Exposure:** Exposure levels will be maintained below the threshold detailed in the Dose Justification Section (see Section 5.5).
Mortality/moribund condition; poor viability	Dogs (4-week study): at 30 mg/kg/day, one male terminated early (Day 6) due to poor clinical condition. Another male had transient whole body shaking on Days 8 and 9. Dogs (13-week study): at 10 mg/kg/day one male was terminated early (Day 74) due to welfare reasons. Rats (micronucleus and comet study): mortality occurred following 1 to 3 doses at ≥600mg/kg/day	**Participant Monitoring:** Weight and adverse events reported by participants will be monitored.
Gastrointestinal and/or hepatic toxicity	GI toxicity: ≥3 mg/kg/day in dogs and at 30 and 300 mg/kg/day in rats, consisting of mucosal erosion/ulceration in the stomach and/or duodenum. Hepatic Toxicity: Biliary epithelial hypertrophy/hyperplasia and periductal mixed inflammatory cell infiltrate into the liver was observed at 300 mg/kg/day in rat (7-day study) and focal hepatocellular degeneration in 1 male dog at 30 mg/kg/day (4-week study)	**Participant Selection:** Participants with active ulcer disease or gastrointestinal (GI) bleeding will be excluded. **Participant Monitoring:** Assessment of faecal occult blood will be performed at screening and at the end of each study period. Participants will be monitored for GI intolerance and sequential clinical chemistry analysis, including liver enzymes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Testicular toxicity	Inconsistent finding in Rats (4-week study): Spermatid retention at ≥60 mg/kg/day, however no effect observed in 13-week study. The observations in the 4-week study were not associated with degenerative changes in testes or epididymides. No spermatogenic abnormalities were observed in dogs.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Skeletal muscle toxicity	Rat (4-week study): Myofiber necrosis: myofiber degeneration/regeneration; fibroplasia, at 300 mg/kg/day in the soleus muscle.	**Participant Monitoring:** Creatinine phosphokinase (CPK) levels will be monitored throughout the study.
Seizures and convulsions	Rats (micronucleus and comet study): convulsions observed at ≥600 mg/kg/day. Convulsions were not related to C_{max}, nor occurred at any predictable time from dose administration. Dogs: No central nervous system (CNS) findings at 12 mg/kg/day in the dog 7-day Electroencephalography (EEG)/CV study. In other compounds in the same series, convulsions have been observed.	**Participant Selection:** Participants with a history of seizure disorder or stroke within the last 5 years will be excluded from the study.
Low food consumption	Dogs (4-week study): 30 mg/kg/day reduced food consumption. Two males were terminated early (Day 10) due to extremely reduced food consumption. Rats (4-week study): 300 mg/kg/day had decreased food consumption.	**Participant Monitoring:** Weight and appetite will be monitored. The Simplified Nutritional Appetite Questionnaire (SNAQ) will be used to monitor appetite.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects on macrophages (Phospholipid accumulation)	Inconsistent effects observed in Rats (4-week study): ≥60 mg/kg/day in the lung (prominent alveolar macrophages); 300 mg/kg/day in the mesenteric lymph node (increased cellularity of sinus macrophages) and thymus (macrophage vacuolation; increased thymus weight). Consistent with phospholipid accumulation (phospholipidosis) based on ultrastructural appearance of mesenteric lymph nodes at 300 mg/kg/day. Findings were not associated with degenerative changes. In 13-week studies in rats, these effects were not observed.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Theoretical Risk: Potential effects on vasoregulation.	TRPV4 mediates prostaglandin release from isolated human endothelial cells and in vivo in rats, supporting the potential for TRPV4 blockade to modulate blood pressure via prostaglandin release. No effect of GSK2798745 on blood pressure was observed in preclinical studies.	**Participant Monitoring:** Blood pressure will be monitored throughout the study.
Theoretical Risk: Potential effect on hearing.	Genetic deletion of TRPV4 in mice has been shown to effect hearing. TRPV4 knockout (KO) mice at age 8 weeks exhibited normal hearing thresholds, but at age 24 weeks, had delayed-onset hearing loss; additionally, the cochlea was found to be vulnerable to acoustic injury with sound overexposure [Tabuchi, 2005]. Patients with Charcot-Marie-Tooth Disease Type 2C (CMT2C), an autosomal dominant axonal	**Participant Monitoring:** Despite the very low risk that hearing will be affected, audiometry will be conducted during the study at baseline in each Treatment Period and at the Follow Up Visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	neuropathy related to TRPV4 gene mutations, demonstrate symptoms that include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss). These are predominantly gain of function TRPV4 abnormalities, in which the hearing loss is sporadic among family members; and relegated to some TRPV4 defects, but not in others. Although the exact mechanism is unclear, it has been suggested that the TRPV4 channel plays an important role in peripheral nerve function and that the alterations in TRPV4 in CMT2C may be due to increased channel activity leading to excessive calcium influx and a calcium overload. However, these findings are academic, and have not been observed in any drug induced model. There is potential for benefit with GSK2798745, in that with cells (HEK293) expressing the CMT2C mutant channel, inhibitors of the TRPV4 channel were found to block the increased intracellular calcium concentrations and resultant cell death [Landouré, 2010].	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at a phlebotomy site may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Risk associated with cough monitoring	Mild contact dermatitis (skin irritation) or redness may be associated at the sites where a microphone is adhered.	Site staff will follow standard approaches for managing events related to application of self-adherent pads.
Risks associated with chest imaging (if required for participant selection)	The approximate effective radiation dose for a chest X-ray is 0.1 milliSievert (mSv) and 7 mSv for a chest CT-scan.	If a participant has had chest imaging within the 12 months prior to starting the study, the procedure does not need to be repeated.

3.3.2. Benefit Assessment

- Potential benefit of receiving GSK2798745 that may have clinical utility during study duration.
- Medical evaluations and assessments associated with study procedures, e.g. physical examination, electrocardiogram, laboratory assessments, chest x-ray (CXR) (if applicable).
- Contributing to the process of developing new therapies in idiopathic or treatment resistant chronic cough, an area of unmet medical need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study (e.g. dose selection, careful participant selection and risk monitoring), the potential risks identified in association with GSK2798745 are justified by the anticipated benefits that may be afforded to participants with idiopathic or treatment resistant chronic cough.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers
Exploratory	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts over 24 hours following 7 days of dosing
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo at improving patient reported outcomes in participants with idiopathic or treatment-resistant chronic cough	• Change from baseline cough severity and urge to cough visual analogue scale (VAS) • Change from baseline Leicester Cough Questionnaire (LCQ) score
• To evaluate the pharmacokinetics (PK) of GSK2798745 and its M1 metabolite in participants with idiopathic or treatment-resistant chronic cough	• Plasma concentrations of GSK2798745, and derived PK parameters, as data permit

5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

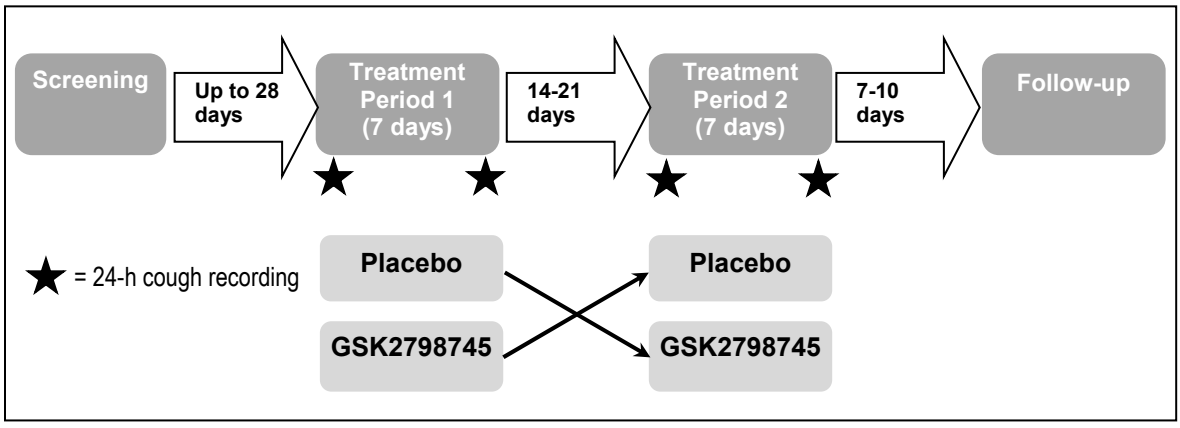
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Figure 1 Study Design Overview



5.2. Number of Participants

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. A participant will be considered evaluable

if they have completed at least one Treatment Period and have evaluable cough counting data from at least one Treatment Period. A sample-size re-estimation will be conducted when approximately 50% of the target sample size has completed the study. The sample size may be revised upwards or downwards (see Section 10.3.3). Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up visit.

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

5.4. Scientific Rationale for Study Design

- A multicentre, randomised, double-blind, placebo-controlled crossover trial is a well-established strategy to evaluate efficacy and safety of investigational medicinal products, such as GSK2798745.

- A placebo arm is included to determine the absolute effect of GSK2798745. In addition, the placebo-controlled design is appropriate as there are no effective, currently approved prescription medicines for chronic cough, and over-the-counter cough medicines have generally not shown benefit over placebo.

- Cough will be measured using a VitaloJAK cough device which is a validated, dedicated high fidelity recording device that provides ambulatory objective monitoring of cough with post-recording signal processing and expert systems to analyse coughs. Coughs will be recorded for 24 hours prior to dosing of each treatment period (baseline) and for 24 hours following dosing on Day 7 of each treatment period.

- The crossover design will be employed to minimise, as much as possible, the potential for variability in randomisation in a relatively small sample size.

- As chronic cough can significantly impact physical and emotional wellbeing, patient reported outcomes are important factors in determining the impact of a cough treatment. The Leicester Cough Questionnaire (LCQ) will be utilised as it is an established self-completed health related quality of life measure of chronic cough. The LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change [Birring, 2003].

5.5. Dose Justification

In this study, participants will take a 4.8 mg starting dose on Day 1, followed by a 2.4 mg GSK2798745 (tablet) once daily for remaining 6 days.

In the first time in human study with GSK2798745 (GlaxoSmithKline [GSK] study TR4113787), single doses up to 12.5 mg, and repeat doses of 5 mg once daily for 14 days, were tested in healthy participants. In addition, participants with heart failure were treated for 7 days with once daily doses of 2.4 mg GSK2798745 (as a capsule with food). There were no serious adverse events (SAEs) in study TR4117387. In other studies, with GSK2798745, there has been only one SAE to date. A participant with heart failure (Study 201881) had orthostatic hypotension during the washout period between the 2 treatment periods. The Principal Investigator (PI) deemed it not related to study treatment.

Another healthy participant study was conducted to compare the pharmacokinetics (PK) of different tablet formulations administered with or without food (GSK study 204725). A population PK (POP PK) approach was used to analyse all available clinical PK data (taking into consideration participant weight, formulation, impact of food, and other variables). Trial simulations were performed with this POP PK model with different dosing regimen.

A rat study was conducted assessing the ability of different doses of GSK2798745 infusion to reduce the increased lung-to-bodyweight ratio induced by the TRPV4 agonist, GSK1016790. Based on this study, the estimated human IC_{50} is 2.1–3.2 ng/mL. To evaluate drug activity/efficacy at the intended dosing regimen, TRPV4 blockade was estimated using the population model, and the potency values derived from the rat pulmonary study.

Based on the simulations, the intended dosing scheme for this study with up to 40 evaluable participants is a 4.8 mg dose on Day 1 followed by a 2.4 mg dose once daily for the following 6 days. Table 1 lists the predicted average TRPV4 inhibition over the 24-hour period on Day 7 based on this potency range. The schematic in Figure 2 also depicts the range of GSK2798745 systemic exposure and the predicted percent inhibition of TRPV4 with the intended regimen. With a loading dose of 4.8 mg, both GSK2798745 exposure and TRPV4 inhibition reach steady state from the first dose, compared with after 4 to 6 days without the loading dose.

This dose regimen was selected to ensure that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL while simultaneously providing sufficiently high channel blockade. That is the exposure observed at the no observed adverse effect level (NOAEL) of 3 mg/kg in the 3-month dog safety study with a 30-fold safety margin. The likelihood of one or more participants of the 40 participants to be dosed with this regimen, exceeding the threshold on Day 1 and Day 7 is listed in Table 1.

Food does not significantly impact the predicted exposures of GSK2798745 and the resulting TRPV4 inhibition as displayed in Table 1. So, GSK2798745 can be administered with or without food.

Figure 2 GSK2798745 exposure and % TRPV4 inhibition

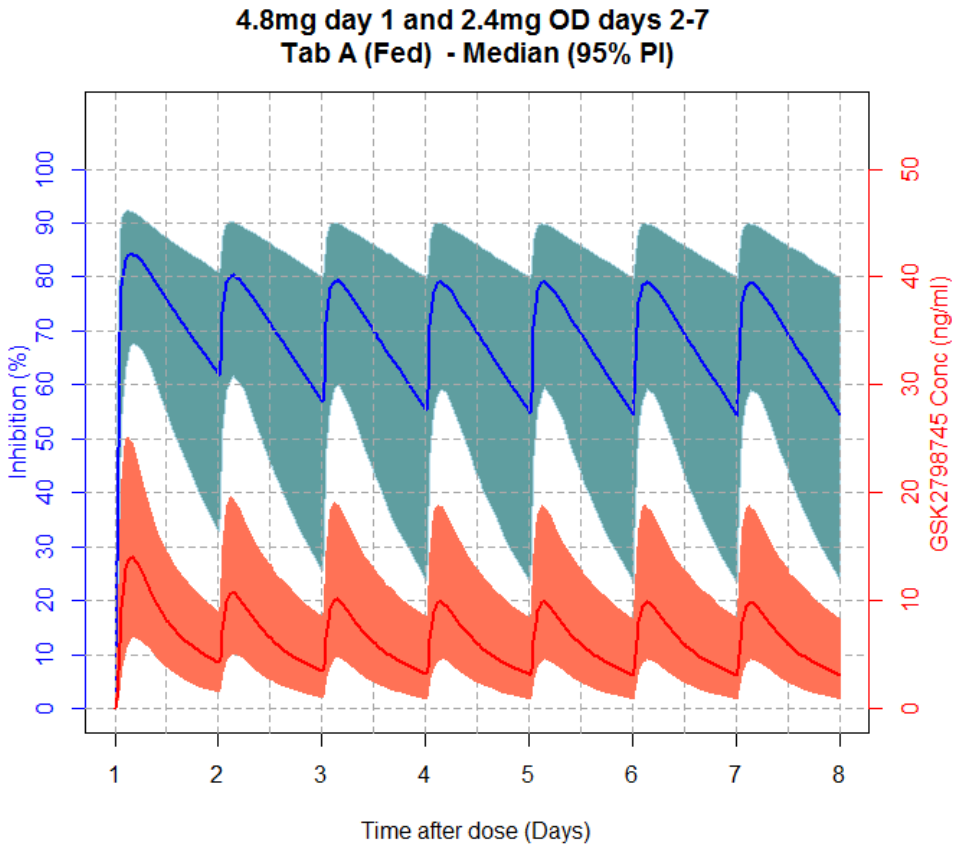


Table 1 Predicted exposure, probability of exceeding threshold and TRPV4 percent inhibition

4.8 mg on Day 1 and 2.4 mg OD Days 2–7	24 h exposure	Median (95% PI)		% Probability that ≥ 1 of 40 participants exceed threshold of		%TRPV4 inhibition over 24-hour period Median (95% PI)
		AUC24 (ng*hr/mL)	C_{max} (ug/mL)	AUC24 (513 ng*hr/mL)	C_{max} (50 ng/mL)	
With food	Day 1	201.5 (127.5 – 302.8)	18.7 (11.2 – 29.8)	0	0	72.0 (56.5 – 82.6)
	Day 7	147.6 (79.4 – 281.1)	13.1 (7.5 – 22.8)	2.0	0.2	67.3 (46.6 – 83.6)
Without food	Day 1	202.0 (128.3 – 303.5)	22.7 (15.3 – 34.2)	0	0.6	72.0 (55.3 – 83.4)
	Day 7	141.5 (76.6 – 269.7)	14.9 (9.1 – 24.8)	1.8	0.4	65.7 (44.2 – 82.7)

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Chronic idiopathic cough for ≥1 year (before screening), defined as: • a cough that is unresponsive to at least 8 weeks of targeted treatment, **or** • a cough for which no objective evidence of an underlying trigger has been determined, despite medical investigations. 3. No significant findings on chest imaging (CXR or CT scan) within 12 months before screening (participants with an abnormal CXR within 12 months, from a temporary process, will be allowed to participate if a repeat CXR is normal). 4. FEV1 ≥80% and ≤120% of the predicted normal value (at screening), or documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening. 5. Score of ≥40 mm on the Cough Severity VAS at Screening.

WEIGHT
6. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 32 kg/m^2 (inclusive) at screening.

SEX
7. Male or female **a.Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of this protocol from the time of first dose of study treatment until 2 weeks after last dose of study treatment, and refrain from donating sperm during this period. **b.Female participants:** A female participant is eligible to participate if she is **not of childbearing potential** as defined in Appendix 5.

INFORMED CONSENT
8. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or current evidence of any serious or clinically significant gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the investigator or the medical monitor, make the participant unsuitable for inclusion in this study.
2. History or current evidence of chronic productive cough.
3. History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the 6 months before screening.
4. Active ulcer disease or gastrointestinal bleeding at the time of screening (positive fecal occult blood test [FOBT] at screening).
5. History of stroke or seizure disorder within 5 years of screening.
6. Respiratory tract infection within 6 weeks of screening.
7. Participant who, in the investigator's opinion, poses a significant suicide risk. Evidence of serious suicide risk may include any history of suicidal behaviour and/or any evidence of suicidal ideation on any questionnaires e.g. Type 4 or 5 on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last 6 months (assessed at screening).
8. Alanine transferase (ALT) >2x upper limit of normal (ULN) at screening.
9. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. QTc >450 msec or QTc >480 msec in participants with bundle branch block at screening. *NOTE: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.*

PRIOR/CONCOMITANT THERAPY
12. Use of a listed prohibited medication (Section 7.7) within the restricted timeframe relative to the first dose of study treatment. 13. Use of a strong inhibitors or inducers of cytochrome P450 (CYP) 3A or p-glycoprotein (Section 7.7).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months of screening. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. Current enrollment or past participation within the 3 months before screening in any clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS
17. Positive human immunodeficiency virus (HIV) antibody test at screening. 18. Presence of Hepatitis B surface antigen (HBsAg) at screening. 19. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. *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.* 20. 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 are not required to also undergo Hepatitis C RNA testing.* 21. Cardiac troponin at screening > ULN for the assay.

OTHER EXCLUSIONS
22. History of alcohol abuse within 6 months of screening, in the opinion of the investigator. 23. Current smoker or history of smoking within the 6 months before screening, or a cumulative history of ≥ 20 pack years. *Pack years = (No. of cigarettes smoked/day/20) x (No. of years smoked)* 24. 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.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants are not permitted to consume red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the start of study treatment until the end of study treatment (in both Treatment Periods).

6.3.2. Alcohol and Tobacco

- During each Treatment Period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample on Day 7.
- Only non-smokers may be recruited into this study.

6.3.3. 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 (e.g. walking, watching television, reading).
- Participants will be instructed to avoid noisy environments 24 hours before the audiometry assessments.
- Participants will be asked to stay awake for 10 hours after attachment of the cough monitor, and to avoid noisy environments whilst wearing the cough monitor

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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, and any SAEs.

Participants may be rescreened once. If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated. See the study reference manual (SRM) for more details.

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the subject will be considered a screen failure.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK2798745	Matching Placebo
Dosage formulation:	White to almost white, round, film-coated tablet. Tablet A (micronized active pharmaceutical ingredient [API])	White to almost white, round, film-coated tablet
Unit dose strength:	2.4 mg	Not applicable
Route of Administration	Oral	Oral
Dosing instructions:	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).
Packaging and Labelling	GSK2798745 tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.	Placebo tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- The VitaloJAK (Model 7100; manufactured by Vitalograph Ltd) will be used to sense and record coughs for up to 24 hours (baseline and Day 7 in each treatment period). The VitaloJAK has a CE mark, indicating compliance to the Medical Devices Directive of the European Community (see Section 9.1.1).
- Instructions for using the VitaloJAK will be provided in a study-specific manual provided by Vitalograph.

7.2. Dose Modification

No dose modifications are permitted without submission of a substantial amendment to the protocol.

7.3. Method of Treatment Assignment

All participants will be centrally randomised using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and instructions for the IWRS will be provided to each site. Participants will be registered using the IWRS, and assigned a unique number (randomisation number). The randomisation number encodes the participant's assignment to one of the 2 treatment sequences shown in Table 2, according to the randomisation schedule generated prior to the study by the Clinical Statistics Department at GSK. In the randomisation, participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months). Each participant will be dispensed blinded study treatment, labelled with his/her unique randomisation number.

Table 2 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2
AB	Placebo tablets for 7 days	GSK2798745 tablets for 7 days
BA	GSK2798745 tablets for 7 days	Placebo tablets for 7 days

Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (SOA) (Section 2.2). Returned study treatment should not be re-dispensed.

7.4. Blinding

This will be a double blind (sponsor open) study. All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the participant will be blinded to the treatment allocated to individual participants. Selected sponsor study team members (and delegates if programming activities are outsourced) will be unblinded to perform the interim analysis. This may include the medical monitor, study statistician, study programmer (and delegates) and study pharmacokineticist; however, only the statistician and programmer (and delegates) will have access to individual participant level data. Access to unblinded data will be kept to the minimum set of individuals required to implement any interim analyses, but may include GSK management/review committees if alterations to the study conduct are required. Details of who were unblinded to what data and when will be included in the clinical study report.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that

unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

A participant will be withdrawn if the participant's treatment 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.

A participant whose treatment sequence assignment is inadvertently unblinded (either to investigative staff or the participant themselves) will be permitted to remain in the study, although the accidental unblinding will be recorded as a protocol deviation and hence the participant will be subject to review as to their inclusion in analyses.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. 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.

7.6. Treatment Compliance

Participants will take the study treatment at home on Day 2 to 6. Compliance will be assessed at the end of each Treatment Period by reviewing the participant diary card and questioning the participant. A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will be recorded in the CRF for Day 1, 6 and 7 of each Treatment Period.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), approved by the investigator, in consultation with the GSK Medical Monitor, that the participant is receiving at the time of enrolment, or receives during the study, must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications

Paracetamol at doses of ≤3 grams/day is permitted for use any time during the study.

Other concomitant medication will be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

Stable use of some medications may be permitted if the dose is stable for at least 28 days prior to Day 1, and the medication was prescribed for an indication other than cough. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. These willl be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

7.7.2. Prohibited Medications

Except for the permitted medication noted above and those approved by the investigator in consultation with the GSK Medical Monitor (Section 7.7.1), participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) or 30 days for ACE inhibitors, before the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study.

During the study, participants should not use drugs that are strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp), because they may alter

GSK2798745 concentrations. The list of background therapy/drugs may be modified based on emerging data. These include, but are not limited to, those listed in Table 3.

Table 3 Strong inducers/inhibitors of CYP3A4 and P-gp

Antiretrovirals:	atazanavir, danoprevir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir
Antibiotics:	clarithromycin, telithromycin, troleandomycin, rifampin
Oral antifungals:	ketoconazole, itraconazole, voriconazole
Antidepressant	nefazadone
Immunosuppressant	cyclosporine
Anti-Epileptic	carbamazepine, phenytoin

GSK2798745 has weak CYP3A4 inhibition potential. It is possible that concentrations of drugs that are substrates of CYP3A4 may be increased. HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, are examples of CYP3A4 substrates that might be taken by the eligible participants. Participants being treated with simvastatin will be allowed to participate in the study, as long as their dose is ≤20 mg once daily. Participants being treated with >20 mg once daily simvastatin will be considered on a case basis by the investigator in consultation with the GSK Medical Monitor. Participants being treated with atorvastatin of any therapeutic dose are allowed to participate in the study. The concentration of atorvastatin may be evaluated after the study. The investigators may also consider substitutions of these medications.

It is strongly recommended that participants avoid using drugs that are sensitive substrates of Cytochrome P450 (CYP) 3A4 and/or P-gp or that have a low therapeutic index because concentrations of these substrates may be increased by GSK2798745. If co-administration of medications with interaction potential with GSK2798745 is necessary, investigators should monitor participants for loss of efficacy or consider substitutions of these medications.

All concomitant medications may be reviewed by the Medical Monitor and it will be up to the discretion of the Investigator in consultation with the GSK Medical Monitor, whether the medication can be continued and/or the participant can participate in the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study, because the indication being studied is not life threatening or seriously debilitating.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who withdraw or who are withdrawn from study treatment will be withdrawn from the study. See the SoA (Section 2.1) for assessments to be performed at early withdrawal.

Participants who start taking a prohibited medication during the study will be withdrawn, unless approved by the investigator in consultation with the GSK Medical Monitor.

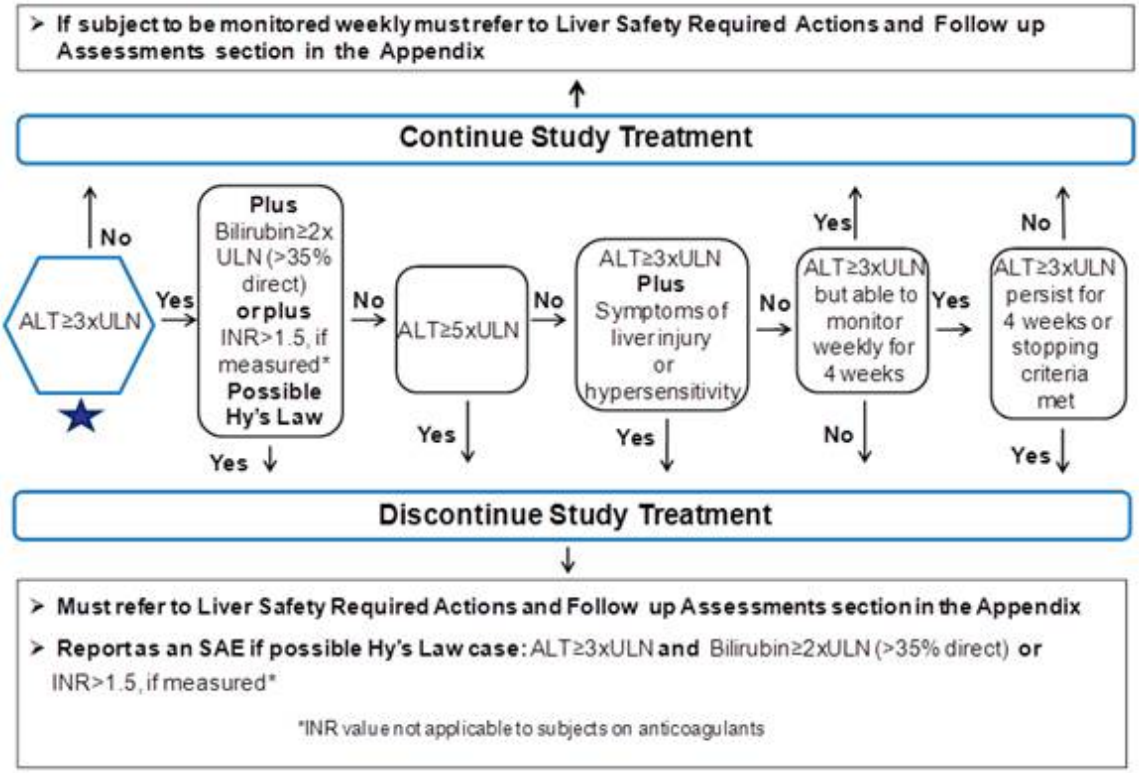
8.1.1. Liver Chemistry Stopping Criteria

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, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 3 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.1.1. Rechallenge

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

8.1.2. QTc Stopping Criteria

If a participant meets either bulleted criterion below, two further ECG recordings should be done (obtained over a brief [e.g. 5 to 10 minute] recording period). A participant who meets either bulleted criterion, based on the average of the triplicate ECG readings, will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

8.1.3. Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria

8.1.3.1. Symptomatic Participant:

If a participant experiences symptoms of cardiac ischemia (e.g. chest pain, increased shortness of breath, and diaphoresis), cardiology consultation should be obtained immediately. GSK2798745 should be discontinued permanently. The participant should be evaluated by a cardiologist and undergo any clinically appropriate testing. The participant should be followed up until symptoms are resolved.

8.1.3.2. Asymptomatic Participant:

Cardiac troponin will be measured pre-dose and at the end of dosing, in each Treatment Period. If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (screening value), the participant should be assessed for symptoms of cardiac ischemia (as above). If the participant is asymptomatic, the participant can continue in the study after discussion with the Medical Monitor and close monitoring for symptoms.

8.2. 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, behavioural, compliance or administrative reasons.

- 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.
- Refer to the SoA for data to be collected at the time of withdrawal (early withdrawal visit).

8.3. 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 with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA.
- Protocol waivers or exemptions are not allowed
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- 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.

9.1. Efficacy Assessments

9.1.1. Cough Counting

Cough monitoring will be conducted at the beginning and end of each treatment period, as shown in Section 2 (SOA).

The VitaloJAK cough monitor will be used. The VitaloJAK cough monitor was developed by Prof PPD Dr PPD and Prof PPD at University Hospital of South Manchester NHS Foundation Trust (UHSM), and has been fully validated in clinical studies. The VitaloJAK cough monitor has CE registration and Food and Drug Administration (FDA) 510K clearance.

The VitaloJAK Cough Monitor requires a disposable, single use chest sensor that is attached to the participant's chest, and a 'lapel microphone' that is attached to the participant's clothing. The monitor collects high fidelity recordings, recording all sound frequencies required for the semi-automated analysis of cough. The recording automatically stops at 24 hours.

Kits will be supplied by Vitalograph to the site containing all items required for each 24-hour recording, including the monitor, memory card and battery packs.

Recordings from the VitaloJAK Cough Monitor will be sent to Vitalograph for analysis via the Vitalograph Web Portal. Recordings will be processed through the semi-automated cough analysis system developed by UHSM. Vitalograph will QC check the recordings on receipt. The recording will then be processed to remove non-cough sounds and silences, leaving a set of segmented files for analysis by a Cough Analyst at Vitalograph.

9.1.2. Cough Visual Analogue Scale (VAS)

Participants will be asked to complete 2 VAS forms, one each to rate the severity of their cough, and their urge to cough (see SRM).

The VAS forms should be completed before other clinical assessments (and before the LCQ), and participants should be given instructions on how to complete the form. The forms will be provided by GSK – the site should **not** make photocopies of the forms, or print from the PDF file.

9.1.2.1. Cough Severity VAS

The participant will be asked: '*How severe was your cough today?*'

The participant will place a mark on a 100 mm horizontal line, rating the severity of their cough from 'Not at all' to 'Extremely'.

9.1.2.2. Urge to Cough VAS

The participant will be asked: '*Please rate the intensity of your urge to cough today*'

The participant will place a mark on a 100 mm horizontal line, rating their urge to cough from 'No urge' to 'Severe urge'.

9.1.3. Leicester Cough Questionnaire (LCQ)

The LCQ is a validated, self-completed, quality of life measure of chronic cough [Birring, 2003]. The questionnaire is designed to assess the impact of cough on various aspects of the participant's life.

The LCQ should be completed after the Cough VAS, but before other clinical assessments, and participants should be given instructions on how to complete the questionnaire. The participant will be asked to read 19 statements, and rate their answer on a 7 point Likert response scale (see SRM).

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the start of treatment until the follow-up visit. However, any SAEs assessed as related to study participation (e.g. study treatment, 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 AEs will be collected from the start of treatment until the follow-up visit.
- Medical occurrences that begin before the start of study treatment, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.
- 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 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- 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 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. 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 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor, will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 Medical Dictionary for Regulatory Activities (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.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

9.3. Treatment of Overdose

For this study, any dose of GSK2798745 greater than the planned dose in the protocol, will be considered an overdose.

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

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2798745 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 24 h from the date of the last dose of study treatment 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 will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A full physical examination will include, at a minimum, measuring weight, and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, measuring weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height will be measured at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate.
- At screening, three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. At all other time-points, single measurements will be taken.

9.4.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At screening, triplicate ECG are required: 3 individual ECG tracings should be obtained over a brief (e.g. 5 to 10 minute) recording period.

9.4.4. Audiometry

Audiometry will be performed by authorised, trained staff using standard audiometry techniques. Participants will be instructed to avoid noisy environments 24 h prior to the audiometry assessments. Only air conductance will be performed. It will be at the discretion of the Investigator, Medical Monitor and/or the audiologist to determine if significant changes from baseline are seen and if a bone conductance test should be performed. Details of the audiometry testing are in the SRM.

9.4.5. Simplified Nutritional Appetite Questionnaire (SNAQ)

The SNAQ is a participant completed, short questionnaire (4 questions) to assess appetite [Wilson, 2005] (see SRM).

9.4.6. Chest Imaging

Chest imaging (CXR or CT scan) is only required if a participant has not had chest imaging within 12 months of screening. If a participant has had an abnormal CXR within 12 months, from a temporary process, the CXR may be repeated to determine eligibility.

Chest imaging will be performed by authorised, trained staff.

9.4.7. FEV_1

- FEV1 will be measured to assess eligibility. It does not need to be repeated if there is documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening.
- Spirometry assessments will be performed whilst the subject is in a seated position (if the assessment is done on a bed, the subject's legs should be over the edge).
- Spirometry assessments will be repeated until 3 technically acceptable measurements have been made.

9.4.8. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 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 7 to 10 days after the last dose of study treatment 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 aetiology 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.

9.4.9. Faecal Occult Blood Test

Based on the preclinical finding of gastric erosions (See Section 3.3.1), FOBT will be performed to determine eligibility and assess any possible study treatment-related GI blood loss.

At each time-point, participants will be given 2 FOBT cards with instructions for completing (using 2 different bowel movements) and returning the tests (in person or by post).

9.4.10. Columbia Suicidality Severity Rating Scale (CSSRS)

Based on preclinical studies that have been conducted, GSK2798745 is considered to be a central nervous system (CNS)-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although GSK2798745 has not been shown to be associated with an increased risk of suicidal thinking or behaviour, GSK considers it important to monitor for such events.

Participants being treated with GSK2798745 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour. Consideration should be given to discontinuing GSK2798745 in participants who experience signs of suicidal ideation or behaviour.

The CSSRS is a measure of suicidal ideation and behaviour, with demonstrated predictive validity and reliability. Sections of the CSSRS include suicidal ideation, intensity of ideation, suicidal behaviour, and actual suicide attempt(s). The CSSRS assesses lifetime and current suicidal thoughts and behaviours across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the Principal Investigator or a sub-investigator for the study. See SRM for details of the scale.

At screening, the 'Baseline' CSSRS questionnaire will be completed. At all other time-points, the 'Since Last Visit' CSSRS questionnaire will be used (see Section 2, SOA).

9.4.11. Diary card

In each Treatment Period, a diary card will be used to collect:

- dosing information for Days 2 to 6 (Date and Time of Dose);
- AEs; and
- concomitant medications.

Between Treatment Periods 1 and 2 (the 'Washout Period'), a diary card will be used to collect AEs and concomitant medications.

Paper diary cards will be used (see SRM).

9.5. Pharmacokinetics

- Blood samples for pharmacokinetic analysis of GSK2798745 will be collected at the timepoints indicated in the SOA (Section 2).

- Approximately 2 mL of blood will be collected in ethylenediaminetetraacetic acid (EDTA) tubes. The actual date and time of each blood sample collection will be recorded.
- The timing and volume of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring of GSK2798745 and, if possible, any relevant GSK2798745 metabolites.
- Additional collection, processing, storage and shipping procedures are provided in the laboratory manual.
- PK analysis will be performed under the control of Platform Technologies and Science-In Vitro/In Vivo Translation (PTS-IVIVT)/ and Third Party Resourcing (TPR) GlaxoSmithKline. Plasma concentrations of GSK2798745 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).
- Plasma samples may be analyzed for the metabolite M1. GSK may store the remaining plasma from the PK plasma samples for future possible additional metabolite analysis. Additional analysis of compound-related metabolites may be reported under a separate protocol.
- For participants taking atorvastatin, an extra sample will be taken at each PK time-point for analysis of atorvastatin concentration, and possible analysis of atorvastatin metabolites.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Laboratory Manual.

10. STATISTICAL CONSIDERATIONS

This study is designed to estimate the effect of GSK2798745 relative to placebo on day-time cough count totals following seven days of dosing. Day-time cough count totals will be derived from the total number of coughs during the first 10 hours following dosing, during which time the participant is expected to be awake.

The inference to be carried out will be with respect to the following hypothesis:

- Treatment with GSK2798745 leads to an improvement in day-time 10-hour cough count totals compared with placebo.

The above hypothesis will be investigated in this study by means of a Bayesian approach, which will assume a non-informative prior distribution. It is anticipated that the day-time 10-hour cough count totals will be log-transformed before statistical analysis, and hence the treatment effect will be evaluated in terms of a ratio of day-time cough count totals (GSK2798745 / placebo). A day-time cough count total of at least 30% less for GSK2798745 than for placebo is of interest. The posterior probability that the true ratio of the mean effect size of the test treatment and the mean effect size of the reference treatment μ(test) / μ(reference), is less than 0.7, and corresponding 90% credible intervals, will be obtained. The posterior probability that the true ratio is less than 0.7 will be referred to as PP (ratio<0.7).

10.1. Sample Size Determination

A simulation approach has been employed to investigate the chance of correctly determining a positive study with the planned number of participants. An estimate of 0.28 for the within subject variability in cough count totals was obtained from previous studies and this estimate was used in the simulations.

A treatment ratio (active:placebo) of 0.7 is considered to indicate an effective treatment. A treatment ratio of 0.5 is considered to represent a very effective treatment.

A positive study will be declared if the posterior probability that the true treatment ratio is less than 0.7 is more than 70% (PP(ratio <0.7) >70%). Given the planned sample size of 24 participants, if our variability assumptions are correct, then if the true treatment ratio is 0.5, there is a 95.3% probability of correctly declaring success. Conversely, if the true treatment ratio is 1, there is a 0.2% probability of declaring success at the end of the study.

An unblinded sample size re-estimation is planned in addition to the final analysis. This will be performed when at least 12 participants have completed both dosing periods and key assessment data is available. Cleaned efficacy data will be provided by Data Management to the unblinded study statistician.

Estimated treatment ratio of day-time cough counts between GSK2798745 and placebo will be calculated together with 90% credible intervals assuming a non-informative prior. This analysis will be supplemented by deriving predictive and/or conditional power in order to support sample size re-estimation. As a result of the sample size re-estimation, the sample size could be revised either upwards or downwards from the planned sample size of 24 evaluable participants, but the target number of evaluable participants will not exceed 40 participants.

Full details of the plan for the sample size re-estimation will be described in the Reporting and Analysis Plan (RAP).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants screened and for whom a record exists on the study database.
All Subjects	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	All randomised participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Day-time 10-hour cough counts following seven days' dosing of GSK2798745 as compared with placebo will be analysed by first log transforming the day-time 10-hour cough counts recorded on day 7 of each dosing period. The difference between GSK2798745 and placebo in log-transformed count rates will be investigated using a mixed effects model with fixed effects terms for treatment and period. Centre effects and the effect of whether or not the participant has participated in a cough clinical trial (which will be included as a stratification factor in the randomisation) in the previous 12 months will also be investigated. Baseline cough counts may be included in the model as a covariate. Participant will be treated as a random effect in the model. The posterior probability and corresponding 90% credible intervals that the ratio of the mean effect size of the test treatment and the mean effect size of the placebo treatment μ(test) - μ(placebo), is less than 1 will be constructed. In addition, the posterior probability true effect size distribution will be used to obtain estimates for the probabilities that the true effect size falls below thresholds of interest (e.g. what is the probability the true ratio is less than 0.7 and less than 0.5). The presence of carryover effects or treatment by period interaction will also be investigated and, if deemed appropriate, an analysis by period will be undertaken.
Exploratory	Will be described in the reporting and analysis plan.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	For the safety data, no formal hypotheses are being tested and no statistical analyses will be performed. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) will be summarized by treatment and time-point.

10.3.3. Interim Analyses

At least one interim analysis will be conducted during the course of the study. The treatment level results will be made available to the GSK study team who will review the available cough count data before making a decision on whether to:

i) stop the study on the grounds of futility
ii) adjust the sample size, in the event that futility criteria have not been met.

The interim analysis will also include a preliminary assessment of whether there is any evidence for the presence of carryover effects or treatment by period interaction.

Following the interim analysis, any adjustment to the sample size will be communicated to the sites.

The interim analysis will be conducted after at least 12 participants have completed both dosing periods and will look at day-time 10-hour cough count data only.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statisticians (including QC statistician) and programmers will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.3.4. Exploratory Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacokinetics Modelling & Simulation Department within GlaxoSmithKline. Calculations will be based on the actual sampling times recorded during the study. The systemic concentrations of GSK2798745, any metabolites, and atorvastatin will be summarised, as data permit. The details of the PK analysis will be listed in the RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
C_{max}	Maximum observed plasma concentration
CMT2C	Charcot-Marie-Tooth Disease Type 2C
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CSSRS	Columbia Suicidality Severity Rating Scale
CT	Computed tomography
CXR	Chest X-ray
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FOBT	Faecal Occult Blood Test
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICF	Informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IVIVT	In Vitro/In Vivo Translations
IWRS	Interactive Web Response System
kg	kilogram
KO	Knockout
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemogloin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSV	MilliSievert
NOAEL	No observed adverse effect level
nM	Nano Molar
P2X3	P2X purinoceptor 3
P-gp	p-glycoprotein
PK	Pharmacokinetic
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SNAQ	Simplified Nutritional Appetite Questionnaire
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPR	Third Party Resourcing
TRPV4	Transient receptor potential vanilloid 4
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White blood cells
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Vitalograph
VitaloJAK

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (Fasting not required)	Calcium	Alkaline phosphatase	Creatinine phosphokinase (CPK)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Cardiac troponin			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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 8.1.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and 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 as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

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 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 substantial 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.
- 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.

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative 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 centre.
- 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 multi-centre 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.

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 the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

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 can be found in the source document agreement (to be signed by the investigator (or delegate) at each site).

Study and Site Closure

GSK or its 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:

- 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 treatment development.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> 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 (eg, 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 /AE/SAE CRF page.
- 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 sufficiently 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) **within 72 hours** of SAE entry into the eCRF.
- 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 (who is also the SAE coordinator) by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF (only necessary when electronic data collection tool is not available)
• The SAE paper CRF should be emailed to the medical monitor (who is also the SAE coordinator). • In rare circumstances, if email is not possible, 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of 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) and estradiol 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, a single FSH and estradiol measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 6.1.

- In addition, male participants must refrain from donating sperm from the time of first dose of study treatment until 2 weeks after last dose of study treatment.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*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 drug. 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.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- 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 2 weeks of learning of the partner's pregnancy.
- 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.

12.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2798745 or chronic cough and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2798745 (or study treatments of this drug class), and chronic cough. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analysed if it is hypothesised that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2798745 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2798745 (or study treatments of this class) or chronic cough continues, but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **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 chemistry event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (defined as Day -1; Treatment Period 1) (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment (not allowed under this protocol) • Permanently discontinue study treatment and continue any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis, within 24 hours after last dose[5] • 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

MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 h** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in 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 pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant'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 laboratory manual.

References

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

TITLE PAGE

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Protocol Number: 207702

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Compound Number: GSK2798745

Development Phase: 2

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): 2017-002265-21

Protocol Amendment Number: 01

Approval Date: 09-OCT-2017

SPONSOR SIGNATORY:

PPD

09-OCT-2017

Date

PPD

James L. Kreindler, MD
Director Clinical Development, Respiratory R&D

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Version	**Document**	**Date**
Protocol Amendment 1	2017N319286_01	09-OCT-2017
Original Protocol	2017N319286_00	31-MAY-2017

The original protocol (31-May-2017) was published internally only, it was not reviewed by the competent authority or the research ethics committee.

Protocol Amendment 1 09-OCT-2017

Overall Rationale for the Amendment: The primary reason for amending the protocol is the removal of the Simplified Nutritional Appetite Questionnaire (SNAQ). The original protocol included the SNAQ, because of the preclinical finding of reduced food consumption in dogs (30 mg/kg/day) and rats (300 mg/kg/day). Since the publication of the original protocol, data has been reviewed from a study of GSK2798745 in heart failure patients. Participants took 2.4 mg GSK2798745 (n=10) or placebo (n=12) for 7 days. As shown in the table below, there was no observable difference in weight and appetite in participants receiving GSK2798745 and placebo. Therefore, the GSK Global Safety Board agreed to the removal of the SNAQ from future protocols. Weight will be measured at screening, follow-up, and the beginning and end of each Treatment Period, and adverse events that may be associated with low food consumption will be reviewed.

	Baseline (mean ± SD)	**Day 7 (mean ± SD)**	**Change from Baseline**
Weight (kg)			
2.4 mg	87.44 ± 18.54	87.67± 17.50	0.23
Placebo	83.58 ± 10.46	83.33 ± 10.56	-0.25
SNAQ Score (Maximum = 20)			
2.4 mg	16.2 ± 1.69	16.7 ± 1.95	0.5 ± 1.18
Placebo	15.3 ± 1.83	16.2 ± 1.53	0.8 ± 1.11

Section # and Name	Description of Change	Brief Rationale
Section 2.1 (Screening and Follow-up Schedule of Activities)	Removal of the SNAQ at the follow-up visit. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. The option for a CT scan at screening was included in the original protocol, in error. If chest imaging (chest x-ray or CT scan) has not been conducted within 12 months of screening, a chest x-ray will be conducted.
Section 2.2 (Treatment Period 1 and 2 Schedule of Activities)	Removal of the SNAQ at Day -1 and Day 8, in each Treatment Period.	Rationale for removal of the SNAQ described above.
Section 3.3.1 (Risk Assessment)	Removal of the SNAQ. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. Rationale for removal of CT scan at screening described above.
Section 7.7.1 (Permitted Medications)	The following change was made: *Stable use of some medications may be permitted if the dose is stable for at least ~~28 days~~ **3 months** prior to Day 1.*	Time period of stable dose changed from 28 days to 3 months, because 28 days might not be sufficient to achieve stable dosing of some permitted medications.
Section 8.1.3.2 (Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria: Asymptomatic Participant)	The following change was made: *If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (~~Screening~~ **Day -1, Treatment Period 1**), the participant should be assessed for symptoms of cardiac ischemia (as above).*	Definition of baseline changed from Screening to Treatment Period 1, Day -1 to be consistent with the baseline used for other laboratory tests.
Section 9.4.5 (Simplified Nutritional Appetite Questionnaire)	Removal of complete section.	Rationale for removal of the SNAQ described above.
Section 9.4.6 (Chest Imaging)	Removal of the option for a CT scan at screening.	Rationale for removal of CT scan at screening described above.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.9 (Columbia Suicidality Severity Rating Scale (CSSRS)	Addition of text stating that families of participants should be alerted about monitoring for emergence of suicidal ideation and behaviour.	New text added to ensure compliance with GSK's *Global Safety Board-Approved Recommendations for Prospective Assessment of Suicidal Ideation and Behaviour in Relevant Clinical Studies*.
Section 9.5 (Pharmacokinetics)	Blood sample volume removed.	Blood volume of sample removed, as this is still to be confirmed. Sample collection instructions to be provided in the laboratory manual.

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1. SYNOPSIS

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Rationale: Chronic cough is a disease with high unmet medical need. It is hypothesised that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) through P2X purinoceptor 3 (P2X3) receptors. Transient receptor potential vanilloid 4 (TRPV4) activation has been shown to cause ATP release from airway macrophages and airway epithelial cells, and studies have established a role for TRPV4-mediated ATP release and the P2X3 receptor in TRPV4-mediated activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD) – diseases in which cough is a prevalent symptom. It is hypothesised, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough.

GSK2798745 is a potent and selective TRPV4 channel blocker being investigated for the treatment of chronic cough. The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment-resistant chronic cough.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers

Overall Design:

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

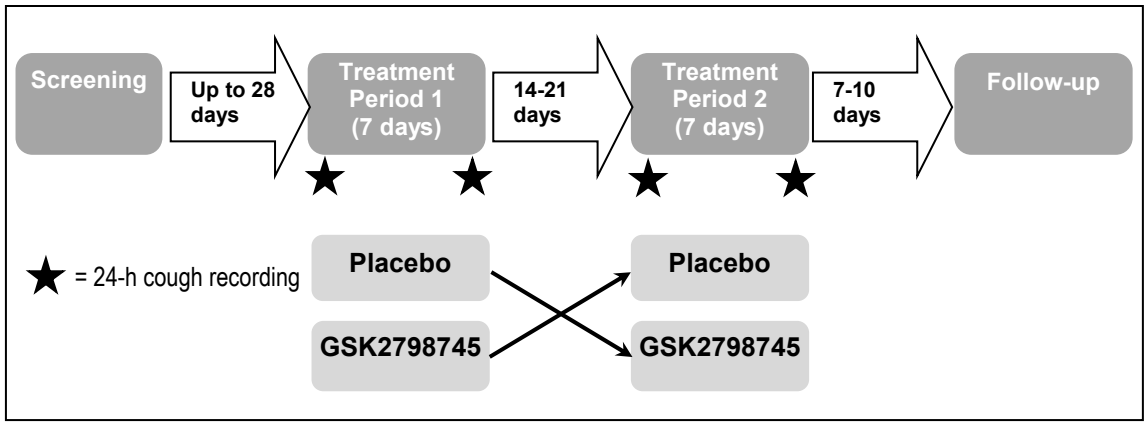
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Study Design Overview



Number of Participants:

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. However, following a sample-size re-estimation when approximately 50% of the target sample size has completed the study, the sample size may be revised upwards or downwards. Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening and Follow-up Schedule of Activities

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage, and family history of premature cardiovascular (CV) disease	X		Substances: Drugs, Alcohol, tobacco
Full physical exam, including height and weight	X	X	Height to be measured at screening only.
Chest x-ray [CXR]	X		Not required if chest imaging has been conducted within 12 months of screening with no significant findings.
Columbia Suicidality Severity Rating Scale (CSSRS)	X		Use 'Baseline' CSSRS.
Human immunodeficiency virus (HIV), hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Clinical chemistry, haematology and urinalysis (including cardiac troponin)	X	X	Non Fasting
Follicle-stimulating hormone and estradiol	X		As needed in women of non-childbearing potential only
Faecal Occult Blood Test (FOBT)	X		FOBT cards will be provided at screening and must be returned to the laboratory and analysed before Day -1.
Vital signs (blood pressure, heart rate and temperature)	X	X	Triplicate vital signs required at screening.
12-lead ECG	X	X	Triplicate ECG required at screening.
Forced Expiratory Volume in One Second (FEV1)	X		Not required if documented evidence of FEV1 ≥ 80% and ≤ 120% within the 6 months before screening.

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Cough Severity & Urge to Cough Visual Analogue Scale (VAS)	X (Severity only)	X (Severity & Urge)	Urge to cough VAS will not be completed at screening.
Audiometry		X	Audiometry to be done anytime between end of Treatment Period 2 and Follow-up.
Concomitant Medication review	X	X	
Adverse event (AE)/serious adverse event (SAE) review	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose (see Section 9.2.1).

1. Screening assessments may be conducted at multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).

2.2. Treatment Period 1 and 2 Schedule of Activities

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Study Treatment						
Randomisation		X (TP1 only)				Can be done on Day –1 or Pre-dose Day 1. Participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months).
Study Treatment dispensed		X				
Study Treatment dosing		X	X	X		Home dosing on Days 2-6. Dosing to be at about the same time each day (±2 hours relative to dosing on Day 1).
Diary Card dispensed		X		X (TP1 only)		Diary card used to collect dosing information, AEs and concomitant medications. Diary card dispensed on Day 7 in Treatment Period 1 only (to collect AEs and concomitant medications during washout period).
Efficacy Assessments						
24- hour Cough Counting Starts	X			X		On Day 7, the cough counter must be attached immediately after dosing. Participant to be advised to avoid noisy environments whilst wearing the counter, and to stay awake for 10 h after attachment of the monitor.
24- hour Cough Counting Ends		X			X	On Day 1, the cough counter must be removed before dosing.
Cough Severity & Urge to Cough VAS	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.2).
Leicester Cough Questionnaire (LCQ)	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.3).
Safety Assessments						
Brief physical exam	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Weight	X				X	Baseline can be done on Day –1 or Pre-dose Day 1

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Vital signs (blood pressure, heart rate and temperature)		X (pre-dose)			X	Single measurements
12-lead ECG		X (pre-dose)			X	Single measurements
Clinical chemistry, haematology and urinalysis (including cardiac troponin)		X (pre-dose)			X	Non-fasting.
FOBT				X		FOBT cards will be provided on Day 7 and returned on Day 8, if possible (or returned by post).
CSSRS	X				X	Use the 'Since Last Visit' CSSRS questionnaire. The pre-dose CSSRS in each Treatment Period can be done on Day –1 or Pre-dose Day 1.
Audiometry	X					Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).
Concomitant Medication review	X	X	X	X	X	Concomitant medications collected in Diary Card during washout period.
SAE/AE review	X	X	X	X	X	AEs collected in Diary Card during washout period.
Other Assessments						
PK blood samples		X		X	X	**Day 1 and Day 7:** predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h post dose **Day 8:** 24 h post dose For participants taking atorvastatin, an extra sample will be taken at each time-point.
Optional Genetic Sample		X				Can be taken any time after consent has been signed and the participant has been randomised.

- The Cough Severity & Urge to Cough VAS should be completed before the LCQ, and both questionnaires should be completed before any other assessments.

- When scheduled at the same time-points, 12-lead ECGs and vital signs should be completed before any blood draws.

- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point.

- The timing and number of planned study assessments, including: safety and pharmacokinetic 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.

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

GSK2798745 is a potent and selective transient receptor potential vanilloid 4 (TRPV4) channel blocker being investigated for the treatment of chronic cough.

GSK2798745 is a potent *in vitro* blocker of recombinant human TRPV4 channels, with:

- agonist-evoked Ca^{2+} influx 50% maximal inhibitory concentration (IC_{50}) value of 1.6 to 2.0 nM;
- hypotonicity-evoked Ca^{2+} influx IC_{50} value of 1.6 to 2.0 nM; and
- blocks native human endothelial TRPV4 channels (agonist-evoked impedance reduction in the presence of human whole blood IC_{50}=6.5nM).

GSK2798745 is a potent *in vivo* blocker of rat TRPV4 channels where full block of TRPV4-induced pulmonary edema was observed at a 38 nM total plasma concentration. Further information regarding the pre-clinical and clinical studies performed with GSK2798745 is available in the investigator brochure (IB) (GSK Document Number 2013N162862_03).

GSK2798745 has been administered orally to healthy participants as single doses ranging from 0.25 to 12.5 mg. A dosage of 5 mg once daily has been administered for up to 14 days in healthy participants. Further, GSK2798745 at a dose of 2.4 mg has been evaluated as a single dose and subsequently as a repeat dose for 7 days in participants with heart failure.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure indicates that there are no clinically significant safety concerns with repeat administration up to 7 days.

TRPV4 is widely expressed in the respiratory tract and is activated by a wide range of stimuli including temperature, pH and osmolarity [Toft-Bertelsen, 2017]. It is hypothesized that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) [Basoglu, 2005] through P2X purinoceptor 3 (P2X3) receptors [Ford, 2013]. TRPV4 activation causes ATP release from airway epithelial cells [Baxter, 2014], and studies have established a role for TRPV4-mediated ATP release and P2X3 receptor in activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma [Idzko, 2007] and chronic obstructive pulmonary disease (COPD) [Baxter, 2014], diseases in which cough is a prevalent symptom. It is hypothesized, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough [Bonvini, 2016].

3.1. Study Rationale

The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment refractory chronic cough.

TRPV4 and P2X3 antagonists have been shown to reduce cough effectively in a pre-clinical cough model in guinea pigs [Bonvini, 2016]. Moreover, clinical data suggest that pharmacological inhibition of P2X3 receptors reduces cough frequency and improves patient reported outcomes and quality of life in a subset of patients with chronic cough [Abdulqawi, 2015].

Therefore, blocking TRPV4 channels may be a viable therapeutic strategy for treating chronic idiopathic or treatment-resistant cough.

3.2. Background

Chronic cough is defined in clinical practice as cough lasting greater than 8 weeks. It is highly prevalent worldwide and is a leading cause of unplanned visits to the doctor's office [Schappert, 2006]. Chronic cough patients can be broadly divided into 3 groups: those with idiopathic cough, those with treatment refractory cough secondary to otherwise controlled triggers such as allergic rhinitis or mild asthma, and those with cough associated with underlying chronic lung diseases, such as COPD or Idiopathic Pulmonary Fibrosis (IPF) [Smith, 2017].

Large epidemiological studies that include all 3 patient groups suggest that the prevalence of chronic cough is as high as 10% worldwide. The epidemiology of idiopathic and treatment refractory chronic cough is more difficult to determine precisely, though it is probable that these groups of patients represent a minority of the total compared with diseases such as COPD. However, the amount of coughing (coughs per hour) measured in patients with idiopathic or treatment refractory chronic cough tends to be much higher than in patients with COPD [Abdulqawi, 2015; Sumner, 2013]. Moreover, cough suppression in suppurative lung diseases such as COPD may carry additional risks that would require establishing a benefit risk ratio in a dedicated study. Therefore, demonstrating efficacy in idiopathic and treatment refractory chronic cough populations is a logical first step before exploring other populations.

Regardless of etiology, chronic cough is by nature difficult to treat and significantly diminishes quality of life. The commonly used therapies for cough are opioid-derived over-the-counter medicines, which tend to be relatively ineffective when compared with placebo. In addition, these medicines have significant side-effects and potential for abuse that limit their usability. Likewise, the opiate codeine is among the most commonly prescribed medicines for cough despite similar limitations to its clinical efficacy and even greater potential for abuse. Overall, there is a significant unmet medical need for safe and effective medicines to treat chronic cough.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2798745 may be found in the IB.

3.3.1. Risk Assessment

All potential risks of GSK2798745 are based on pre-clinical data. No risks have been identified in the clinical studies of GSK2798745 conducted prior to the effective date of this protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Vascular lesions	Dogs (4-week study): at 30 mg/kg/day, 2 males had arterial lesions • One male: Heart – Coronary artery inflammation; Thymus – Arteriole inflammation with fibroplasia • One male: Epididymides – Artery degeneration/necrosis with inflammation Dogs (12-week study): At 10 mg/kg/day, 1 male and 1 female had arterial lesions • One male: Epididymides – Arteriole degeneration/necrosis with lymphocytic inflammation • One female: Bladder – Arteriole degeneration/necrosis with lymphocytic inflammation	**Participant Monitoring:** The arterial lesions noted in heart, thymus, epididymides, and urinary bladder cannot be monitored directly. There is currently no human translation biomarker or understanding of the underlying mechanism. **Participant Exposure:** Since these effects cannot be monitored directly in clinical studies, coverage of ≥30 fold will be maintained from the no-effect dose (3 mg/kg/day); exposure will not intentionally exceed the average daily area under concentration-time curve (AUC) of 0.513 hr*ug/mL and/or maximum observed plasma concentration (C_{max}) of 0.050 ug/mL on an individual basis.
Myocardial toxicity	Dogs (4-week study): at 30 mg/kg/day, myofiber degeneration/necrosis and inflammation (2 animals)	**Participant Selection:** Participants with history of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months will be excluded. **Participant Monitoring:** Cardiac troponin levels

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		will be monitored throughout the study. **Participant Exposure:** Exposure levels will be maintained below the threshold detailed in the Dose Justification Section (see Section 5.5).
Mortality/moribund condition; poor viability	Dogs (4-week study): at 30 mg/kg/day, one male terminated early (Day 6) due to poor clinical condition. Another male had transient whole body shaking on Days 8 and 9. Dogs (13-week study): at 10 mg/kg/day one male was terminated early (Day 74) due to welfare reasons. Rats (micronucleus and comet study): mortality occurred following 1 to 3 doses at ≥600mg/kg/day	**Participant Monitoring:** Weight and adverse events reported by participants will be monitored.
Gastrointestinal and/or hepatic toxicity	GI toxicity: ≥3 mg/kg/day in dogs and at 30 and 300 mg/kg/day in rats, consisting of mucosal erosion/ulceration in the stomach and/or duodenum. Hepatic Toxicity: Biliary epithelial hypertrophy/hyperplasia and periductal mixed inflammatory cell infiltrate into the liver was observed at 300 mg/kg/day in rat (7-day study) and focal hepatocellular degeneration in 1 male dog at 30 mg/kg/day (4-week study)	**Participant Selection:** Participants with active ulcer disease or gastrointestinal (GI) bleeding will be excluded. **Participant Monitoring:** Assessment of faecal occult blood will be performed at screening and at the end of each study period. Participants will be monitored for GI intolerance and sequential clinical chemistry analysis, including liver enzymes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Testicular toxicity	Inconsistent finding in Rats (4-week study): Spermatid retention at ≥60 mg/kg/day, however no effect observed in 13-week study. The observations in the 4-week study were not associated with degenerative changes in testes or epididymides. No spermatogenic abnormalities were observed in dogs.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Skeletal muscle toxicity	Rat (4-week study): Myofiber necrosis: myofiber degeneration/regeneration; fibroplasia, at 300 mg/kg/day in the soleus muscle.	**Participant Monitoring:** Creatinine phosphokinase (CPK) levels will be monitored throughout the study.
Seizures and convulsions	Rats (micronucleus and comet study): convulsions observed at ≥600 mg/kg/day. Convulsions were not related to C_{max}, nor occurred at any predictable time from dose administration. Dogs: No central nervous system (CNS) findings at 12 mg/kg/day in the dog 7-day Electroencephalography (EEG)/CV study. In other compounds in the same series, convulsions have been observed.	**Participant Selection:** Participants with a history of seizure disorder or stroke within the last 5 years will be excluded from the study.
Low food consumption	Dogs (4-week study): 30 mg/kg/day reduced food consumption. Two males were terminated early (Day 10) due to extremely reduced food consumption. Rats (4-week study): 300 mg/kg/day had decreased food consumption.	**Participant Monitoring:** Weight will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects on macrophages (Phospholipid accumulation)	Inconsistent effects observed in Rats (4-week study): ≥60 mg/kg/day in the lung (prominent alveolar macrophages); 300 mg/kg/day in the mesenteric lymph node (increased cellularity of sinus macrophages) and thymus (macrophage vacuolation; increased thymus weight). Consistent with phospholipid accumulation (phospholipidosis) based on ultrastructural appearance of mesenteric lymph nodes at 300 mg/kg/day. Findings were not associated with degenerative changes. In 13-week studies in rats, these effects were not observed.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Theoretical Risk: Potential effects on vasoregulation.	TRPV4 mediates prostaglandin release from isolated human endothelial cells and in vivo in rats, supporting the potential for TRPV4 blockade to modulate blood pressure via prostaglandin release. No effect of GSK2798745 on blood pressure was observed in preclinical studies.	**Participant Monitoring:** Blood pressure will be monitored throughout the study.
Theoretical Risk: Potential effect on hearing.	Genetic deletion of TRPV4 in mice has been shown to effect hearing. TRPV4 knockout (KO) mice at age 8 weeks exhibited normal hearing thresholds, but at age 24 weeks, had delayed-onset hearing loss; additionally, the cochlea was found to be vulnerable to acoustic injury with sound overexposure [Tabuchi, 2005]. Patients with Charcot-Marie-Tooth Disease Type 2C (CMT2C), an autosomal dominant axonal	**Participant Monitoring:** Despite the very low risk that hearing will be affected, audiometry will be conducted during the study at baseline in each Treatment Period and at the Follow Up Visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	neuropathy related to TRPV4 gene mutations, demonstrate symptoms that include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss). These are predominantly gain of function TRPV4 abnormalities, in which the hearing loss is sporadic among family members; and relegated to some TRPV4 defects, but not in others. Although the exact mechanism is unclear, it has been suggested that the TRPV4 channel plays an important role in peripheral nerve function and that the alterations in TRPV4 in CMT2C may be due to increased channel activity leading to excessive calcium influx and a calcium overload. However, these findings are academic, and have not been observed in any drug induced model. There is potential for benefit with GSK2798745, in that with cells (HEK293) expressing the CMT2C mutant channel, inhibitors of the TRPV4 channel were found to block the increased intracellular calcium concentrations and resultant cell death [Landouré, 2010].	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at a phlebotomy site may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Risk associated with cough monitoring	Mild contact dermatitis (skin irritation) or redness may be associated at the sites where a microphone is adhered.	Site staff will follow standard approaches for managing events related to application of self-adherent pads.
Risks associated with CXR (if required for participant selection)	The approximate effective radiation dose for a chest X-ray is 0.1 milliSievert (mSv).	If a participant has had chest imaging within the 12 months prior to starting the study, the procedure does not need to be repeated.

3.3.2. Benefit Assessment

- Potential benefit of receiving GSK2798745 that may have clinical utility during study duration.
- Medical evaluations and assessments associated with study procedures, e.g. physical examination, electrocardiogram, laboratory assessments, chest x-ray (CXR) (if applicable).
- Contributing to the process of developing new therapies in idiopathic or treatment resistant chronic cough, an area of unmet medical need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study (e.g. dose selection, careful participant selection and risk monitoring), the potential risks identified in association with GSK2798745 are justified by the anticipated benefits that may be afforded to participants with idiopathic or treatment resistant chronic cough.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers
Exploratory	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts over 24 hours following 7 days of dosing
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo at improving patient reported outcomes in participants with idiopathic or treatment-resistant chronic cough	• Change from baseline cough severity and urge to cough visual analogue scale (VAS) • Change from baseline Leicester Cough Questionnaire (LCQ) score
• To evaluate the pharmacokinetics (PK) of GSK2798745 and its M1 metabolite in participants with idiopathic or treatment-resistant chronic cough	• Plasma concentrations of GSK2798745, and derived PK parameters, as data permit

5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

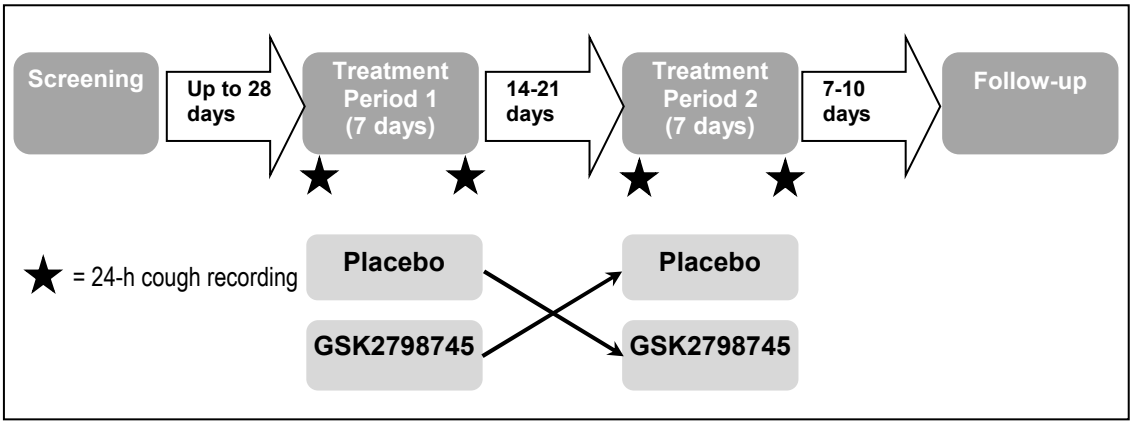
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Figure 1 Study Design Overview



5.2. Number of Participants

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. A participant will be considered evaluable if they have completed at least one Treatment Period and have evaluable cough counting

data from at least one Treatment Period. A sample-size re-estimation will be conducted when approximately 50% of the target sample size has completed the study. The sample size may be revised upwards or downwards (see Section 10.3.3). Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up visit.

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

5.4. Scientific Rationale for Study Design

- A multicentre, randomised, double-blind, placebo-controlled crossover trial is a well-established strategy to evaluate efficacy and safety of investigational medicinal products, such as GSK2798745.

- A placebo arm is included to determine the absolute effect of GSK2798745. In addition, the placebo-controlled design is appropriate as there are no effective, currently approved prescription medicines for chronic cough, and over-the-counter cough medicines have generally not shown benefit over placebo.

- Cough will be measured using a VitaloJAK cough device which is a validated, dedicated high fidelity recording device that provides ambulatory objective monitoring of cough with post-recording signal processing and expert systems to analyse coughs. Coughs will be recorded for 24 hours prior to dosing of each treatment period (baseline) and for 24 hours following dosing on Day 7 of each treatment period.

- The crossover design will be employed to minimise, as much as possible, the potential for variability in randomisation in a relatively small sample size.

- As chronic cough can significantly impact physical and emotional wellbeing, patient reported outcomes are important factors in determining the impact of a cough treatment. The Leicester Cough Questionnaire (LCQ) will be utilised as it is an established self-completed health related quality of life measure of chronic cough. The LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change [Birring, 2003].

5.5. Dose Justification

In this study, participants will take a 4.8 mg starting dose on Day 1, followed by a 2.4 mg GSK2798745 (tablet) once daily for remaining 6 days.

In the first time in human study with GSK2798745 (GlaxoSmithKline [GSK] study TR4113787), single doses up to 12.5 mg, and repeat doses of 5 mg once daily for

14 days, were tested in healthy participants. In addition, participants with heart failure were treated for 7 days with once daily doses of 2.4 mg GSK2798745 (as a capsule with food). There were no serious adverse events (SAEs) in study TR4117387. In other studies, with GSK2798745, there has been only one SAE to date. A participant with heart failure (Study 201881) had orthostatic hypotension during the washout period between the 2 treatment periods. The Principal Investigator (PI) deemed it not related to study treatment.

Another healthy participant study was conducted to compare the pharmacokinetics (PK) of different tablet formulations administered with or without food (GSK study 204725). A population PK (POP PK) approach was used to analyse all available clinical PK data (taking into consideration participant weight, formulation, impact of food, and other variables). Trial simulations were performed with this POP PK model with different dosing regimen.

A rat study was conducted assessing the ability of different doses of GSK2798745 infusion to reduce the increased lung-to-bodyweight ratio induced by the TRPV4 agonist, GSK1016790. Based on this study, the estimated human IC_{50} is 2.1–3.2 ng/mL. To evaluate drug activity/efficacy at the intended dosing regimen, TRPV4 blockade was estimated using the population model, and the potency values derived from the rat pulmonary study.

Based on the simulations, the intended dosing scheme for this study with up to 40 evaluable participants is a 4.8 mg dose on Day 1 followed by a 2.4 mg dose once daily for the following 6 days. Table 1 lists the predicted average TRPV4 inhibition over the 24-hour period on Day 7 based on this potency range. The schematic in Figure 2 also depicts the range of GSK2798745 systemic exposure and the predicted percent inhibition of TRPV4 with the intended regimen. With a loading dose of 4.8 mg, both GSK2798745 exposure and TRPV4 inhibition reach steady state from the first dose, compared with after 4 to 6 days without the loading dose.

This dose regimen was selected to ensure that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL while simultaneously providing sufficiently high channel blockade. That is the exposure observed at the no observed adverse effect level (NOAEL) of 3 mg/kg in the 3-month dog safety study with a 30-fold safety margin. The likelihood of one or more participants of the 40 participants to be dosed with this regimen, exceeding the threshold on Day 1 and Day 7 is listed in Table 1.

Food does not significantly impact the predicted exposures of GSK2798745 and the resulting TRPV4 inhibition as displayed in Table 1. So, GSK2798745 can be administered with or without food.

Figure 2 GSK2798745 exposure and % TRPV4 inhibition

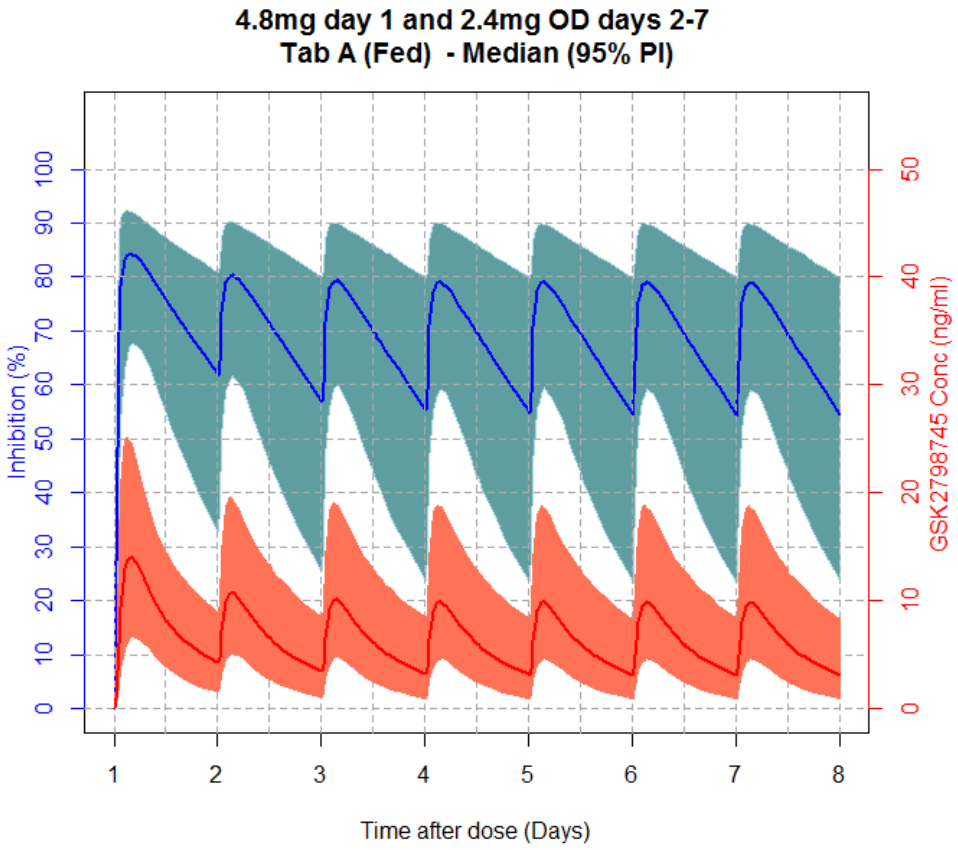


Table 1 Predicted exposure, probability of exceeding threshold and TRPV4 percent inhibition

4.8 mg on Day 1 and 2.4 mg OD Days 2–7	24 h exposure	Median (95% PI)		% Probability that ≥ 1 of 40 participants exceed threshold of		%TRPV4 inhibition over 24-hour period Median (95% PI)
		AUC24 (ng*hr/mL)	C_{max} (ug/mL)	AUC24 (513 ng*hr/mL)	C_{max} (50 ng/mL)	
With food	Day 1	201.5 (127.5 – 302.8)	18.7 (11.2 – 29.8)	0	0	72.0 (56.5 – 82.6)
	Day 7	147.6 (79.4 – 281.1)	13.1 (7.5 – 22.8)	2.0	0.2	67.3 (46.6 – 83.6)
Without food	Day 1	202.0 (128.3 – 303.5)	22.7 (15.3 – 34.2)	0	0.6	72.0 (55.3 – 83.4)
	Day 7	141.5 (76.6 – 269.7)	14.9 (9.1 – 24.8)	1.8	0.4	65.7 (44.2 – 82.7)

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Chronic idiopathic cough for ≥1 year (before screening), defined as: • a cough that is unresponsive to at least 8 weeks of targeted treatment, **or** • a cough for which no objective evidence of an underlying trigger has been determined, despite medical investigations. 3. No significant findings on chest imaging (CXR or CT scan) within 12 months before screening (participants with an abnormal CXR within 12 months, from a temporary process, will be allowed to participate if a repeat CXR is normal). 4. FEV1 ≥80% and ≤120% of the predicted normal value (at screening), or documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening. 5. Score of ≥40 mm on the Cough Severity VAS at Screening.

WEIGHT
6. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 32 kg/m^2 (inclusive) at screening.

SEX
7. Male or female **a.Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of this protocol from the time of first dose of study treatment until 2 weeks after last dose of study treatment, and refrain from donating sperm during this period. **b.Female participants:** A female participant is eligible to participate if she is **not of childbearing potential** as defined in Appendix 5.

INFORMED CONSENT
8. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or current evidence of any serious or clinically significant gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the investigator or the medical monitor, make the participant unsuitable for inclusion in this study.
2. History or current evidence of chronic productive cough.
3. History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the 6 months before screening.
4. Active ulcer disease or gastrointestinal bleeding at the time of screening (positive fecal occult blood test [FOBT] at screening).
5. History of stroke or seizure disorder within 5 years of screening.
6. Respiratory tract infection within 6 weeks of screening.
7. Participant who, in the investigator's opinion, poses a significant suicide risk. Evidence of serious suicide risk may include any history of suicidal behaviour and/or any evidence of suicidal ideation on any questionnaires e.g. Type 4 or 5 on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last 6 months (assessed at screening).
8. Alanine transferase (ALT) >2x upper limit of normal (ULN) at screening.
9. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. QTc >450 msec or QTc >480 msec in participants with bundle branch block at screening. *NOTE: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.*

PRIOR/CONCOMITANT THERAPY
12. Use of a listed prohibited medication (Section 7.7) within the restricted timeframe relative to the first dose of study treatment. 13. Use of a strong inhibitors or inducers of cytochrome P450 (CYP) 3A or p-glycoprotein (Section 7.7).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months of screening. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. Current enrollment or past participation within the 3 months before screening in any clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS
17. Positive human immunodeficiency virus (HIV) antibody test at screening. 18. Presence of Hepatitis B surface antigen (HBsAg) at screening. 19. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. *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.* 20. 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 are not required to also undergo Hepatitis C RNA testing.* 21. Cardiac troponin at screening > ULN for the assay.

OTHER EXCLUSIONS
22. History of alcohol abuse within 6 months of screening, in the opinion of the investigator. 23. Current smoker or history of smoking within the 6 months before screening, or a cumulative history of ≥ 20 pack years. *Pack years = (No. of cigarettes smoked/day/20) x (No. of years smoked)* 24. 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.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants are not permitted to consume red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the start of study treatment until the end of study treatment (in both Treatment Periods).

6.3.2. Alcohol and Tobacco

- During each Treatment Period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample on Day 7.
- Only non-smokers may be recruited into this study.

6.3.3. 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 (e.g. walking, watching television, reading).
- Participants will be instructed to avoid noisy environments 24 hours before the audiometry assessments.
- Participants will be asked to stay awake for 10 hours after attachment of the cough monitor, and to avoid noisy environments whilst wearing the cough monitor

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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, and any SAEs.

Participants may be rescreened once. If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated. See the study reference manual (SRM) for more details.

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the subject will be considered a screen failure.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK2798745	Matching Placebo
Dosage formulation:	White to almost white, round, film-coated tablet. Tablet A (micronized active pharmaceutical ingredient [API])	White to almost white, round, film-coated tablet
Unit dose strength:	2.4 mg	Not applicable
Route of Administration	Oral	Oral
Dosing instructions:	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).
Packaging and Labelling	GSK2798745 tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.	Placebo tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- The VitaloJAK (Model 7100; manufactured by Vitalograph Ltd) will be used to sense and record coughs for up to 24 hours (baseline and Day 7 in each treatment period). The VitaloJAK has a CE mark, indicating compliance to the Medical Devices Directive of the European Community (see Section 9.1.1).
- Instructions for using the VitaloJAK will be provided in a study-specific manual provided by Vitalograph.

7.2. Dose Modification

No dose modifications are permitted without submission of a substantial amendment to the protocol.

7.3. Method of Treatment Assignment

All participants will be centrally randomised using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and instructions for the IWRS will be provided to each site. Participants will be registered using the IWRS, and assigned a unique number (randomisation number). The randomisation number encodes the participant's assignment to one of the 2 treatment sequences shown in Table 2, according to the randomisation schedule generated prior to the study by the Clinical Statistics Department at GSK. In the randomisation, participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months). Each participant will be dispensed blinded study treatment, labelled with his/her unique randomisation number.

Table 2 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2
AB	Placebo tablets for 7 days	GSK2798745 tablets for 7 days
BA	GSK2798745 tablets for 7 days	Placebo tablets for 7 days

Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (SOA) (Section 2.2). Returned study treatment should not be re-dispensed.

7.4. Blinding

This will be a double blind (sponsor open) study. All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the participant will be blinded to the treatment allocated to individual participants. Selected sponsor study team members (and delegates if programming activities are outsourced) will be unblinded to perform the interim analysis. This may include the medical monitor, study statistician, study programmer (and delegates) and study pharmacokineticist; however, only the statistician and programmer (and delegates) will have access to individual participant level data. Access to unblinded data will be kept to the minimum set of individuals required to implement any interim analyses, but may include GSK management/review committees if alterations to the study conduct are required. Details of who were unblinded to what data and when will be included in the clinical study report.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior

to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

A participant will be withdrawn if the participant's treatment 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.

A participant whose treatment sequence assignment is inadvertently unblinded (either to investigative staff or the participant themselves) will be permitted to remain in the study, although the accidental unblinding will be recorded as a protocol deviation and hence the participant will be subject to review as to their inclusion in analyses.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. 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.

7.6. Treatment Compliance

Participants will take the study treatment at home on Day 2 to 6. Compliance will be assessed at the end of each Treatment Period by reviewing the participant diary card and questioning the participant. A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will be recorded in the CRF for Day 1, 6 and 7 of each Treatment Period.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), approved by the investigator, in consultation with the GSK Medical Monitor, that the participant is receiving at the time of enrolment, or receives during the study, must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications

Paracetamol at doses of ≤3 grams/day is permitted for use any time during the study.

Other concomitant medication will be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

Stable use of some medications may be permitted if the dose is stable for at least 3 months prior to Day 1, and the medication was prescribed for an indication other than cough. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. These willl be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

7.7.2. Prohibited Medications

Except for the permitted medication noted above and those approved by the investigator in consultation with the GSK Medical Monitor (Section 7.7.1), participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) or 30 days for ACE inhibitors, before the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study.

During the study, participants should not use drugs that are strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp), because they may alter

GSK2798745 concentrations. The list of background therapy/drugs may be modified based on emerging data. These include, but are not limited to, those listed in Table 3.

Table 3 Strong inducers/inhibitors of CYP3A4 and P-gp

Antiretrovirals:	atazanavir, danoprevir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir
Antibiotics:	clarithromycin, telithromycin, troleandomycin, rifampin
Oral antifungals:	ketoconazole, itraconazole, voriconazole
Antidepressant	nefazadone
Immunosuppressant	cyclosporine
Anti-Epileptic	carbamazepine, phenytoin

GSK2798745 has weak CYP3A4 inhibition potential. It is possible that concentrations of drugs that are substrates of CYP3A4 may be increased. HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, are examples of CYP3A4 substrates that might be taken by the eligible participants. Participants being treated with simvastatin will be allowed to participate in the study, as long as their dose is ≤20 mg once daily. Participants being treated with >20 mg once daily simvastatin will be considered on a case basis by the investigator in consultation with the GSK Medical Monitor. Participants being treated with atorvastatin of any therapeutic dose are allowed to participate in the study. The concentration of atorvastatin may be evaluated after the study. The investigators may also consider substitutions of these medications.

It is strongly recommended that participants avoid using drugs that are sensitive substrates of Cytochrome P450 (CYP) 3A4 and/or P-gp or that have a low therapeutic index because concentrations of these substrates may be increased by GSK2798745. If co-administration of medications with interaction potential with GSK2798745 is necessary, investigators should monitor participants for loss of efficacy or consider substitutions of these medications.

All concomitant medications may be reviewed by the Medical Monitor and it will be up to the discretion of the Investigator in consultation with the GSK Medical Monitor, whether the medication can be continued and/or the participant can participate in the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study, because the indication being studied is not life threatening or seriously debilitating.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who withdraw or who are withdrawn from study treatment will be withdrawn from the study. See the SoA (Section 2.1) for assessments to be performed at early withdrawal.

Participants who start taking a prohibited medication during the study will be withdrawn, unless approved by the investigator in consultation with the GSK Medical Monitor.

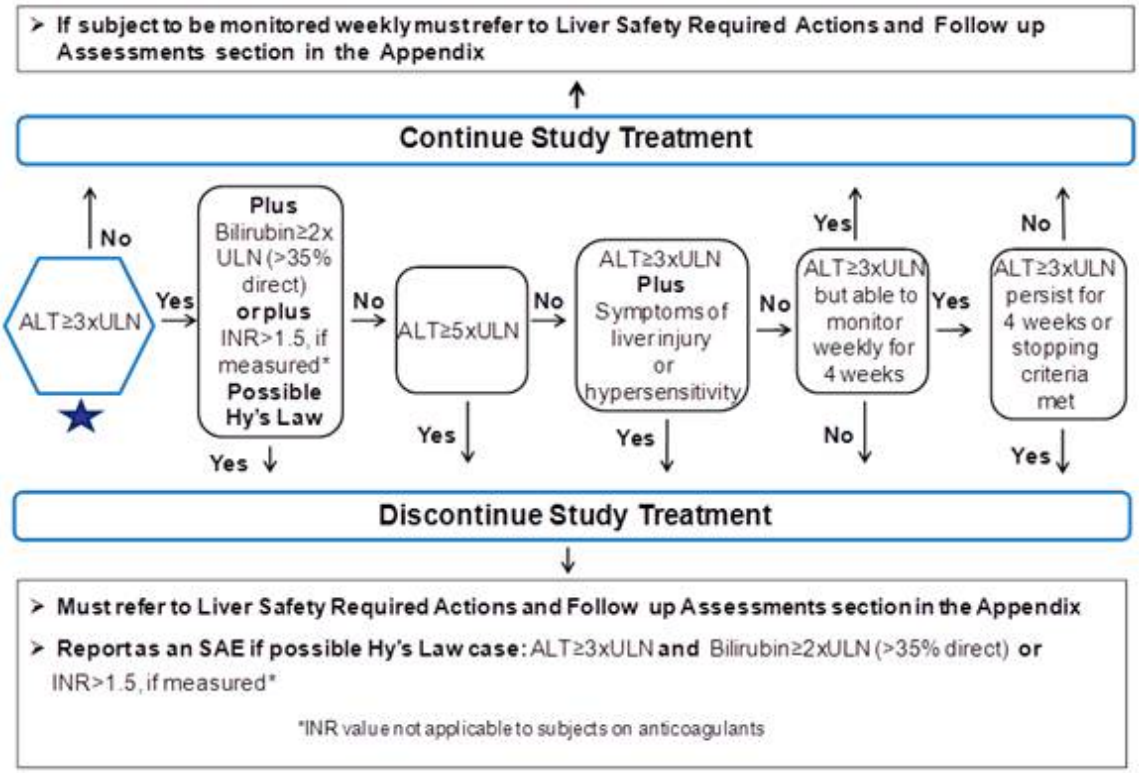
8.1.1. Liver Chemistry Stopping Criteria

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, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 3 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.1.1. Rechallenge

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

8.1.2. QTc Stopping Criteria

If a participant meets either bulleted criterion below, two further ECG recordings should be done (obtained over a brief [e.g. 5 to 10 minute] recording period). A participant who meets either bulleted criterion, based on the average of the triplicate ECG readings, will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

8.1.3. Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria

8.1.3.1. Symptomatic Participant:

If a participant experiences symptoms of cardiac ischemia (e.g. chest pain, increased shortness of breath, and diaphoresis), cardiology consultation should be obtained immediately. GSK2798745 should be discontinued permanently. The participant should be evaluated by a cardiologist and undergo any clinically appropriate testing. The participant should be followed up until symptoms are resolved.

8.1.3.2. Asymptomatic Participant:

Cardiac troponin will be measured pre-dose and at the end of dosing, in each Treatment Period. If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (Day -1, Treatment Period 1), the participant should be assessed for symptoms of cardiac ischemia (as above). If the participant is asymptomatic, the participant can continue in the study after discussion with the Medical Monitor and close monitoring for symptoms.

8.2. 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, behavioural, compliance or administrative reasons.
- 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.
- Refer to the SoA for data to be collected at the time of withdrawal (early withdrawal visit).

8.3. 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 with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA.
- Protocol waivers or exemptions are not allowed
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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.

9.1. Efficacy Assessments

9.1.1. Cough Counting

Cough monitoring will be conducted at the beginning and end of each treatment period, as shown in Section 2 (SOA).

The VitaloJAK cough monitor will be used. The VitaloJAK cough monitor was developed by Prof PPD Dr PPD and Prof PPD at University Hospital of South Manchester NHS Foundation Trust (UHSM), and has been fully validated in clinical studies. The VitaloJAK cough monitor has CE registration and Food and Drug Administration (FDA) 510K clearance.

The VitaloJAK Cough Monitor requires a disposable, single use chest sensor that is attached to the participant's chest, and a 'lapel microphone' that is attached to the participant's clothing. The monitor collects high fidelity recordings, recording all sound frequencies required for the semi-automated analysis of cough. The recording automatically stops at 24 hours.

Kits will be supplied by Vitalograph to the site containing all items required for each 24-hour recording, including the monitor, memory card and battery packs.

Recordings from the VitaloJAK Cough Monitor will be sent to Vitalograph for analysis via the Vitalograph Web Portal. Recordings will be processed through the semi-automated cough analysis system developed by UHSM. Vitalograph will QC check the recordings on receipt. The recording will then be processed to remove non-cough sounds

and silences, leaving a set of segmented files for analysis by a Cough Analyst at Vitalograph.

9.1.2. Cough Visual Analogue Scale (VAS)

Participants will be asked to complete 2 VAS forms, one each to rate the severity of their cough, and their urge to cough (see SRM).

The VAS forms should be completed before other clinical assessments (and before the LCQ), and participants should be given instructions on how to complete the form. The forms will be provided by GSK – the site should **not** make photocopies of the forms, or print from the PDF file.

9.1.2.1. Cough Severity VAS

The participant will be asked: '*How severe was your cough today?*'

The participant will place a mark on a 100 mm horizontal line, rating the severity of their cough from 'Not at all' to 'Extremely'.

9.1.2.2. Urge to Cough VAS

The participant will be asked: '*Please rate the intensity of your urge to cough today*'

The participant will place a mark on a 100 mm horizontal line, rating their urge to cough from 'No urge' to 'Severe urge'.

9.1.3. Leicester Cough Questionnaire (LCQ)

The LCQ is a validated, self-completed, quality of life measure of chronic cough [Birring, 2003]. The questionnaire is designed to assess the impact of cough on various aspects of the participant's life.

The LCQ should be completed after the Cough VAS, but before other clinical assessments, and participants should be given instructions on how to complete the questionnaire. The participant will be asked to read 19 statements, and rate their answer on a 7 point Likert response scale (see SRM).

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the start of treatment until the follow-up visit. However, any SAEs assessed as related to study participation (e.g. study treatment, 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 AEs will be collected from the start of treatment until the follow-up visit.
- Medical occurrences that begin before the start of study treatment, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.
- 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 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- 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 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. 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 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor, will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 Medical Dictionary for Regulatory Activities (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.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

9.3. Treatment of Overdose

For this study, any dose of GSK2798745 greater than the planned dose in the protocol, will be considered an overdose.

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

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

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2798745 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 24 h from the date of the last dose of study treatment 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 will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A full physical examination will include, at a minimum, measuring weight, and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, measuring weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height will be measured at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate.
- At screening, three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. At all other time-points, single measurements will be taken.

9.4.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At screening, triplicate ECG are required: 3 individual ECG tracings should be obtained over a brief (e.g. 5 to 10 minute) recording period.

9.4.4. Audiometry

Audiometry will be performed by authorised, trained staff using standard audiometry techniques. Participants will be instructed to avoid noisy environments 24 h prior to the audiometry assessments. Only air conductance will be performed. It will be at the discretion of the Investigator, Medical Monitor and/or the audiologist to determine if significant changes from baseline are seen and if a bone conductance test should be performed. Details of the audiometry testing are in the SRM.

9.4.5. Chest X-ray

CXR is only required if a participant has not had chest imaging within 12 months of screening. If a participant has had an abnormal CXR within 12 months, from a temporary process, the CXR may be repeated to determine eligibility.

CXR will be performed by authorised, trained staff.

9.4.6. FEV_1

- FEV1 will be measured to assess eligibility. It does not need to be repeated if there is documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening.
- Spirometry assessments will be performed whilst the subject is in a seated position (if the assessment is done on a bed, the subject's legs should be over the edge).
- Spirometry assessments will be repeated until 3 technically acceptable measurements have been made.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 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 7 to 10 days after the last dose of study treatment 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 aetiology 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.

9.4.8. Faecal Occult Blood Test

Based on the preclinical finding of gastric erosions (See Section 3.3.1), FOBT will be performed to determine eligibility and assess any possible study treatment-related GI blood loss.

At each time-point, participants will be given 2 FOBT cards with instructions for completing (using 2 different bowel movements) and returning the tests (in person or by post).

9.4.9. Columbia Suicidality Severity Rating Scale (CSSRS)

Based on preclinical studies that have been conducted, GSK2798745 is considered to be a central nervous system (CNS)-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although GSK2798745 has not been shown to be associated with an increased risk of suicidal thinking or behaviour, GSK considers it important to monitor for such events.

Participants being treated with GSK2798745 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour. Consideration should be given to discontinuing GSK2798745 in participants who experience signs of suicidal ideation or behaviour. Families of participants being treated with GSK2798745 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour, and to report such symptoms immediately to the study investigator.

The CSSRS is a measure of suicidal ideation and behaviour, with demonstrated predictive validity and reliability. Sections of the CSSRS include suicidal ideation, intensity of ideation, suicidal behaviour, and actual suicide attempt(s). The CSSRS assesses lifetime and current suicidal thoughts and behaviours across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the Principal Investigator or a sub-investigator for the study. See SRM for details of the scale.

At screening, the ‘Baseline’ CSSRS questionnaire will be completed. At all other time-points, the ‘Since Last Visit’ CSSRS questionnaire will be used (see Section 2, SOA).

9.4.10. Diary card

In each Treatment Period, a diary card will be used to collect:

- dosing information for Days 2 to 6 (Date and Time of Dose);
- AEs; and
- concomitant medications.

Between Treatment Periods 1 and 2 (the 'Washout Period'), a diary card will be used to collect AEs and concomitant medications.

Paper diary cards will be used (see SRM).

9.5. Pharmacokinetics

- Blood samples for pharmacokinetic analysis of GSK2798745 will be collected at the timepoints indicated in the SOA (Section 2).
- Blood will be collected in ethylenediaminetetraacetic acid (EDTA) tubes. The actual date and time of each blood sample collection will be recorded.
- The timing and volume of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring of GSK2798745 and, if possible, any relevant GSK2798745 metabolites.
- Additional collection, processing, storage and shipping procedures are provided in the laboratory manual.
- PK analysis will be performed under the control of Platform Technologies and Science-In Vitro/In Vivo Translation (PTS-IVIVT)/ and Third Party Resourcing (TPR) GlaxoSmithKline. Plasma concentrations of GSK2798745 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).
- Plasma samples may be analyzed for the metabolite M1. GSK may store the remaining plasma from the PK plasma samples for future possible additional metabolite analysis. Additional analysis of compound-related metabolites may be reported under a separate protocol.
- For participants taking atorvastatin, an extra sample will be taken at each PK time-point for analysis of atorvastatin concentration, and possible analysis of atorvastatin metabolites.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Laboratory Manual.

10. STATISTICAL CONSIDERATIONS

This study is designed to estimate the effect of GSK2798745 relative to placebo on day-time cough count totals following seven days of dosing. Day-time cough count totals will be derived from the total number of coughs during the first 10 hours following dosing, during which time the participant is expected to be awake.

The inference to be carried out will be with respect to the following hypothesis:

- Treatment with GSK2798745 leads to an improvement in day-time 10-hour cough count totals compared with placebo.

The above hypothesis will be investigated in this study by means of a Bayesian approach, which will assume a non-informative prior distribution. It is anticipated that the day-time 10-hour cough count totals will be log-transformed before statistical analysis, and hence the treatment effect will be evaluated in terms of a ratio of day-time cough count totals (GSK2798745 / placebo). A day-time cough count total of at least 30% less for GSK2798745 than for placebo is of interest. The posterior probability that the true ratio of the mean effect size of the test treatment and the mean effect size of the reference treatment μ(test) / μ(reference), is less than 0.7, and corresponding 90% credible intervals, will be obtained. The posterior probability that the true ratio is less than 0.7 will be referred to as PP (ratio<0.7).

10.1. Sample Size Determination

A simulation approach has been employed to investigate the chance of correctly determining a positive study with the planned number of participants. An estimate of 0.28 for the within subject variability in cough count totals was obtained from previous studies and this estimate was used in the simulations.

A treatment ratio (active:placebo) of 0.7 is considered to indicate an effective treatment. A treatment ratio of 0.5 is considered to represent a very effective treatment.

A positive study will be declared if the posterior probability that the true treatment ratio is less than 0.7 is more than 70% (PP(ratio <0.7) >70%). Given the planned sample size of 24 participants, if our variability assumptions are correct, then if the true treatment ratio is 0.5, there is a 95.3% probability of correctly declaring success. Conversely, if the true treatment ratio is 1, there is a 0.2% probability of declaring success at the end of the study.

An unblinded sample size re-estimation is planned in addition to the final analysis. This will be performed when at least 12 participants have completed both dosing periods and key assessment data is available. Cleaned efficacy data will be provided by Data Management to the unblinded study statistician.

Estimated treatment ratio of day-time cough counts between GSK2798745 and placebo will be calculated together with 90% credible intervals assuming a non-informative prior. This analysis will be supplemented by deriving predictive and/or conditional power in order to support sample size re-estimation. As a result of the sample size re-estimation, the sample size could be revised either upwards or downwards from the planned sample size of 24 evaluable participants, but the target number of evaluable participants will not exceed 40 participants.

Full details of the plan for the sample size re-estimation will be described in the Reporting and Analysis Plan (RAP).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants screened and for whom a record exists on the study database.
All Subjects	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	All randomised participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Day-time 10-hour cough counts following seven days' dosing of GSK2798745 as compared with placebo will be analysed by first log transforming the day-time 10-hour cough counts recorded on day 7 of each dosing period. The difference between GSK2798745 and placebo in log-transformed count rates will be investigated using a mixed effects model with fixed effects terms for treatment and period. Centre effects and the effect of whether or not the participant has participated in a cough clinical trial (which will be included as a stratification factor in the randomisation) in the previous 12 months will also be investigated. Baseline cough counts may be included in the model as a covariate. Participant will be treated as a random effect in the model. The posterior probability and corresponding 90% credible intervals that the ratio of the mean effect size of the test treatment and the mean effect size of the placebo treatment μ(test) - μ(placebo), is less than 1 will be constructed. In addition, the posterior probability true effect size distribution will be used to obtain estimates for the probabilities that the true effect size falls below thresholds of interest (e.g. what is the probability the true ratio is less than 0.7 and less than 0.5). The presence of carryover effects or treatment by period interaction will also be investigated and, if deemed appropriate, an analysis by period will be undertaken.
Exploratory	Will be described in the reporting and analysis plan.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	For the safety data, no formal hypotheses are being tested and no statistical analyses will be performed. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) will be summarized by treatment and time-point.

10.3.3. Interim Analyses

At least one interim analysis will be conducted during the course of the study. The treatment level results will be made available to the GSK study team who will review the available cough count data before making a decision on whether to:

i) stop the study on the grounds of futility
ii) adjust the sample size, in the event that futility criteria have not been met.

The interim analysis will also include a preliminary assessment of whether there is any evidence for the presence of carryover effects or treatment by period interaction.

Following the interim analysis, any adjustment to the sample size will be communicated to the sites.

The interim analysis will be conducted after at least 12 participants have completed both dosing periods and will look at day-time 10-hour cough count data only.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statisticians (including QC statistician) and programmers will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.3.4. Exploratory Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacokinetics Modelling & Simulation Department within GlaxoSmithKline. Calculations will be based on the actual sampling times recorded during the study. The systemic concentrations of GSK2798745, any metabolites, and atorvastatin will be summarised, as data permit. The details of the PK analysis will be listed in the RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
C_{max}	Maximum observed plasma concentration
CMT2C	Charcot-Marie-Tooth Disease Type 2C
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CSSRS	Columbia Suicidality Severity Rating Scale
CT	Computed tomography
CXR	Chest X-ray
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FOBT	Faecal Occult Blood Test
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICF	Informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IVIVT	In Vitro/In Vivo Translations
IWRS	Interactive Web Response System
kg	kilogram
KO	Knockout
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemogloin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSV	MilliSievert
NOAEL	No observed adverse effect level
nM	Nano Molar
P2X3	P2X purinoceptor 3
P-gp	p-glycoprotein
PK	Pharmacokinetic
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPR	Third Party Resourcing
TRPV4	Transient receptor potential vanilloid 4
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White blood cells
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Vitalograph
VitaloJAK

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (Fasting not required)	Calcium	Alkaline phosphatase	Creatinine phosphokinase (CPK)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Cardiac troponin			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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 8.1.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and 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 as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

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 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 substantial 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.
- 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.

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative 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 centre.
- 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 multi-centre 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.

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 the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

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 can be found in the source document agreement (to be signed by the investigator (or delegate) at each site).

Study and Site Closure

GSK or its 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:

- 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 treatment development.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of 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 (eg, 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 /AE/SAE CRF page.
- 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 sufficiently 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) **within 72 hours** of SAE entry into the eCRF.
- 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 (who is also the SAE coordinator) by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF (only necessary when electronic data collection tool is not available)
• The SAE paper CRF should be emailed to the medical monitor (who is also the SAE coordinator). • In rare circumstances, if email is not possible, 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of 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) and estradiol 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, a single FSH and estradiol measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 6.1.

- In addition, male participants must refrain from donating sperm from the time of first dose of study treatment until 2 weeks after last dose of study treatment.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*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 drug. 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.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- 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 2 weeks of learning of the partner's pregnancy.
- 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.

12.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2798745 or chronic cough and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2798745 (or study treatments of this drug class), and chronic cough. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analysed if it is hypothesised that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2798745 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2798745 (or study treatments of this class) or chronic cough continues, but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II 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 ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</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 chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (defined as Day -1; Treatment Period 1) (see MONITORING below)
• Do not restart/rechallenge participant with study treatment (not allowed under this protocol)
• Permanently discontinue study treatment and continue any protocol specified follow up assessments</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis, within 24 hours after last dose[5]
• 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</td></tr>
</table>

MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 h** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 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 pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant'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 laboratory manual.

References

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

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (Protocol Amendment 1) is located directly before the Table of Contents (TOC).

TITLE PAGE

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised,crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Protocol Number: 207702 /Amendment 02

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Compound Number: GSK2798745

Development Phase: 2

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): 2017-002265-21

Approval Date: 22-NOV-2017

SPONSOR SIGNATORY:

PPD

PPD

mes L. Kreindler, MD
rector Clinical Development, Respiratory R&D

22 NOVEMBER 2017
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Version	**Document**	**Date**
Protocol Amendment 2	2017N319286_02	22-NOV-2017
Protocol Amendment 1	2017N319286_01	09-OCT-2017
Original Protocol	2017N319286_00	31-MAY-2017

The original protocol (31-May-2017) was published internally only, it was not reviewed by the competent authority or the research ethics committee.

Protocol Amendment 1 (09-OCT-2017) was submitted to both the competent authority and the research ethics committee. The Summary of Changes table for Amendment 1 is in Section 12.8 (Appendix 8).

Protocol Amendment 2 (22-NOV-2017)

Overall Rationale for the Amendment: The protocol was amended in response to comments from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Section # and Name	Description of Change	Brief Rationale
Section 2.1 (Screening and Follow-up Schedule of Activities)	Addition of the Columbia Suicidality Severity Rating Scale (CSSRS) at Follow-up.	Requested by the MHRA.
Section 7.4 (Blinding)	The following change was made*: In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. ~~If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.~~ If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.*	Requested by the MHRA.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 (Adverse Event Stopping Criteria)	Addition of the following section: ***8.1.1 Adverse Event Stopping Criteria*** *Participants who experience an adverse event, which in the opinion of the investigator could jeopardise the participant's safety, will be withdrawn from the study.*	Requested by the MHRA.

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1. SYNOPSIS

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised,crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Rationale: Chronic cough is a disease with high unmet medical need. It is hypothesised that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) through P2X purinoceptor 3 (P2X3) receptors. Transient receptor potential vanilloid 4 (TRPV4) activation has been shown to cause ATP release from airway macrophages and airway epithelial cells, and studies have established a role for TRPV4-mediated ATP release and the P2X3 receptor in TRPV4-mediated activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD) – diseases in which cough is a prevalent symptom. It is hypothesised, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough.

GSK2798745 is a potent and selective TRPV4 channel blocker being investigated for the treatment of chronic cough. The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment-resistant chronic cough.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers

Overall Design:

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

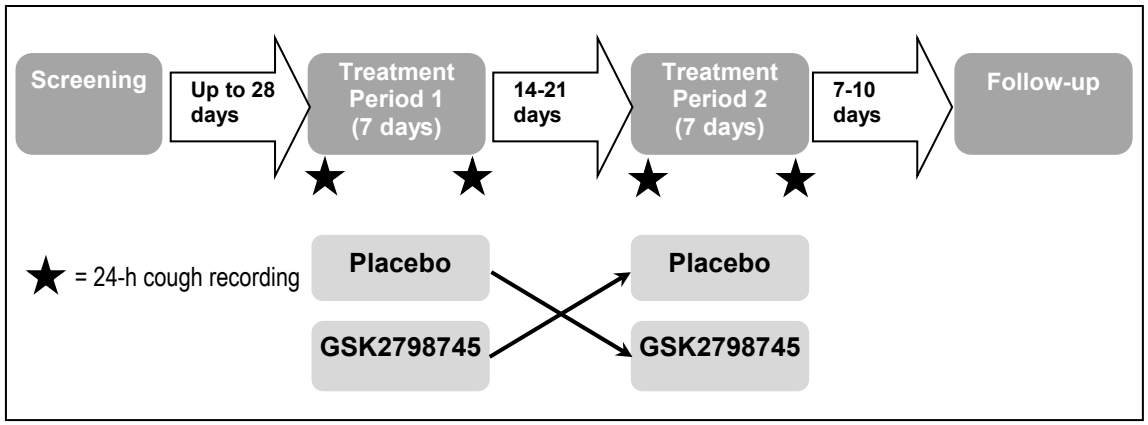
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Study Design Overview



Number of Participants:

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. However, following a sample-size re-estimation when approximately 50% of the target sample size has completed the study, the sample size may be revised upwards or downwards. Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening and Follow-up Schedule of Activities

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage, and family history of premature cardiovascular (CV) disease	X		Substances: Drugs, Alcohol, tobacco
Full physical exam, including height and weight	X	X	Height to be measured at screening only.
Chest x-ray [CXR]	X		Not required if chest imaging has been conducted within 12 months of screening with no significant findings.
Columbia Suicidality Severity Rating Scale (CSSRS)	X	X	Use 'Baseline' CSSRS at Screening. Use the 'Since Last Visit' CSSRS at Follow-up.
Human immunodeficiency virus (HIV), hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Clinical chemistry, haematology and urinalysis (including cardiac troponin)	X	X	Non Fasting
Follicle-stimulating hormone and estradiol	X		As needed in women of non-childbearing potential only
Faecal Occult Blood Test (FOBT)	X		FOBT cards will be provided at screening and must be returned to the laboratory and analysed before Day -1.
Vital signs (blood pressure, heart rate and temperature)	X	X	Triplicate vital signs required at screening.
12-lead ECG	X	X	Triplicate ECG required at screening.
Forced Expiratory Volume in One Second (FEV1)	X		Not required if documented evidence of FEV1 ≥ 80% and ≤ 120% within the 6 months before screening.

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Cough Severity & Urge to Cough Visual Analogue Scale (VAS)	X (Severity only)	X (Severity & Urge)	Urge to cough VAS will not be completed at screening.
Audiometry		X	Audiometry to be done anytime between end of Treatment Period 2 and Follow-up.
Concomitant Medication review	X	X	
Adverse event (AE)/serious adverse event (SAE) review	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose (see Section 9.2.1).

1. Screening assessments may be conducted at multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).

2.2. Treatment Period 1 and 2 Schedule of Activities

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Study Treatment						
Randomisation		X (TP1 only)				Can be done on Day –1 or Pre-dose Day 1. Participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months).
Study Treatment dispensed		X				
Study Treatment dosing		X	X	X		Home dosing on Days 2-6. Dosing to be at about the same time each day (±2 hours relative to dosing on Day 1).
Diary Card dispensed		X		X (TP1 only)		Diary card used to collect dosing information, AEs and concomitant medications. Diary card dispensed on Day 7 in Treatment Period 1 only (to collect AEs and concomitant medications during washout period).
Efficacy Assessments						
24- hour Cough Counting Starts	X			X		On Day 7, the cough counter must be attached immediately after dosing. Participant to be advised to avoid noisy environments whilst wearing the counter, and to stay awake for 10 h after attachment of the monitor.
24- hour Cough Counting Ends		X			X	On Day 1, the cough counter must be removed before dosing.
Cough Severity & Urge to Cough VAS	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.2).
Leicester Cough Questionnaire (LCQ)	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.3).
Safety Assessments						
Brief physical exam	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Weight	X				X	Baseline can be done on Day –1 or Pre-dose Day 1

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Vital signs (blood pressure, heart rate and temperature)		X (pre-dose)			X	Single measurements
12-lead ECG		X (pre-dose)			X	Single measurements
Clinical chemistry, haematology and urinalysis (including cardiac troponin)		X (pre-dose)			X	Non-fasting.
FOBT				X		FOBT cards will be provided on Day 7 and returned on Day 8, if possible (or returned by post).
CSSRS	X				X	Use the 'Since Last Visit' CSSRS questionnaire. The pre-dose CSSRS in each Treatment Period can be done on Day –1 or Pre-dose Day 1.
Audiometry	X					Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).
Concomitant Medication review	X	X	X	X	X	Concomitant medications collected in Diary Card during washout period.
SAE/AE review	X	X	X	X	X	AEs collected in Diary Card during washout period.
Other Assessments						
PK blood samples		X		X	X	**Day 1 and Day 7:** predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h post dose **Day 8:** 24 h post dose For participants taking atorvastatin, an extra sample will be taken at each time-point.
Optional Genetic Sample		X				Can be taken any time after consent has been signed and the participant has been randomised.

- The Cough Severity & Urge to Cough VAS should be completed before the LCQ, and both questionnaires should be completed before any other assessments.

- When scheduled at the same time-points, 12-lead ECGs and vital signs should be completed before any blood draws.

- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point.

- The timing and number of planned study assessments, including: safety and pharmacokinetic 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.

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

GSK2798745 is a potent and selective transient receptor potential vanilloid 4 (TRPV4) channel blocker being investigated for the treatment of chronic cough.

GSK2798745 is a potent *in vitro* blocker of recombinant human TRPV4 channels, with:

- agonist-evoked Ca^{2+} influx 50% maximal inhibitory concentration (IC_{50}) value of 1.6 to 2.0 nM;
- hypotonicity-evoked Ca^{2+} influx IC_{50} value of 1.6 to 2.0 nM; and
- blocks native human endothelial TRPV4 channels (agonist-evoked impedance reduction in the presence of human whole blood IC_{50}=6.5nM).

GSK2798745 is a potent *in vivo* blocker of rat TRPV4 channels where full block of TRPV4-induced pulmonary edema was observed at a 38 nM total plasma concentration. Further information regarding the pre-clinical and clinical studies performed with GSK2798745 is available in the investigator brochure (IB) (GSK Document Number 2013N162862_03).

GSK2798745 has been administered orally to healthy participants as single doses ranging from 0.25 to 12.5 mg. A dosage of 5 mg once daily has been administered for up to 14 days in healthy participants. Further, GSK2798745 at a dose of 2.4 mg has been evaluated as a single dose and subsequently as a repeat dose for 7 days in participants with heart failure.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure indicates that there are no clinically significant safety concerns with repeat administration up to 7 days.

TRPV4 is widely expressed in the respiratory tract and is activated by a wide range of stimuli including temperature, pH and osmolarity [Toft-Bertelsen, 2017]. It is hypothesized that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) [Basoglu, 2005] through P2X purinoceptor 3 (P2X3) receptors [Ford, 2013]. TRPV4 activation causes ATP release from airway epithelial cells [Baxter, 2014], and studies have established a role for TRPV4-mediated ATP release and P2X3 receptor in activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma [Idzko, 2007] and chronic obstructive pulmonary disease (COPD) [Baxter, 2014], diseases in which cough is a prevalent symptom. It is hypothesized, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough [Bonvini, 2016].

3.1. Study Rationale

The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment refractory chronic cough.

TRPV4 and P2X3 antagonists have been shown to reduce cough effectively in a pre-clinical cough model in guinea pigs [Bonvini, 2016]. Moreover, clinical data suggest that pharmacological inhibition of P2X3 receptors reduces cough frequency and improves patient reported outcomes and quality of life in a subset of patients with chronic cough [Abdulqawi, 2015].

Therefore, blocking TRPV4 channels may be a viable therapeutic strategy for treating chronic idiopathic or treatment-resistant cough.

3.2. Background

Chronic cough is defined in clinical practice as cough lasting greater than 8 weeks. It is highly prevalent worldwide and is a leading cause of unplanned visits to the doctor's office [Schappert, 2006]. Chronic cough patients can be broadly divided into 3 groups: those with idiopathic cough, those with treatment refractory cough secondary to otherwise controlled triggers such as allergic rhinitis or mild asthma, and those with cough associated with underlying chronic lung diseases, such as COPD or Idiopathic Pulmonary Fibrosis (IPF) [Smith, 2017].

Large epidemiological studies that include all 3 patient groups suggest that the prevalence of chronic cough is as high as 10% worldwide. The epidemiology of idiopathic and treatment refractory chronic cough is more difficult to determine precisely, though it is probable that these groups of patients represent a minority of the total compared with diseases such as COPD. However, the amount of coughing (coughs per hour) measured in patients with idiopathic or treatment refractory chronic cough tends to be much higher than in patients with COPD [Abdulqawi, 2015; Sumner, 2013]. Moreover, cough suppression in suppurative lung diseases such as COPD may carry additional risks that would require establishing a benefit risk ratio in a dedicated study. Therefore, demonstrating efficacy in idiopathic and treatment refractory chronic cough populations is a logical first step before exploring other populations.

Regardless of etiology, chronic cough is by nature difficult to treat and significantly diminishes quality of life. The commonly used therapies for cough are opioid-derived over-the-counter medicines, which tend to be relatively ineffective when compared with placebo. In addition, these medicines have significant side-effects and potential for abuse that limit their usability. Likewise, the opiate codeine is among the most commonly prescribed medicines for cough despite similar limitations to its clinical efficacy and even greater potential for abuse. Overall, there is a significant unmet medical need for safe and effective medicines to treat chronic cough.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2798745 may be found in the IB.

3.3.1. Risk Assessment

All potential risks of GSK2798745 are based on pre-clinical data. No risks have been identified in the clinical studies of GSK2798745 conducted prior to the effective date of this protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Vascular lesions	Dogs (4-week study): at 30 mg/kg/day, 2 males had arterial lesions • One male: Heart – Coronary artery inflammation; Thymus – Arteriole inflammation with fibroplasia • One male: Epididymides – Artery degeneration/necrosis with inflammation Dogs (12-week study): At 10 mg/kg/day, 1 male and 1 female had arterial lesions • One male: Epididymides – Arteriole degeneration/necrosis with lymphocytic inflammation • One female: Bladder – Arteriole degeneration/necrosis with lymphocytic inflammation	**Participant Monitoring:** The arterial lesions noted in heart, thymus, epididymides, and urinary bladder cannot be monitored directly. There is currently no human translation biomarker or understanding of the underlying mechanism. **Participant Exposure:** Since these effects cannot be monitored directly in clinical studies, coverage of ≥30 fold will be maintained from the no-effect dose (3 mg/kg/day); exposure will not intentionally exceed the average daily area under concentration-time curve (AUC) of 0.513 hr*ug/mL and/or maximum observed plasma concentration (C_{max}) of 0.050 ug/mL on an individual basis.
Myocardial toxicity	Dogs (4-week study): at 30 mg/kg/day, myofiber degeneration/necrosis and inflammation (2 animals)	**Participant Selection:** Participants with history of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months will be excluded. **Participant Monitoring:** Cardiac troponin levels

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		will be monitored throughout the study. **Participant Exposure:** Exposure levels will be maintained below the threshold detailed in the Dose Justification Section (see Section 5.5).
Mortality/moribund condition; poor viability	Dogs (4-week study): at 30 mg/kg/day, one male terminated early (Day 6) due to poor clinical condition. Another male had transient whole body shaking on Days 8 and 9. Dogs (13-week study): at 10 mg/kg/day one male was terminated early (Day 74) due to welfare reasons. Rats (micronucleus and comet study): mortality occurred following 1 to 3 doses at ≥600mg/kg/day	**Participant Monitoring:** Weight and adverse events reported by participants will be monitored.
Gastrointestinal and/or hepatic toxicity	GI toxicity: ≥3 mg/kg/day in dogs and at 30 and 300 mg/kg/day in rats, consisting of mucosal erosion/ulceration in the stomach and/or duodenum. Hepatic Toxicity: Biliary epithelial hypertrophy/hyperplasia and periductal mixed inflammatory cell infiltrate into the liver was observed at 300 mg/kg/day in rat (7-day study) and focal hepatocellular degeneration in 1 male dog at 30 mg/kg/day (4-week study)	**Participant Selection:** Participants with active ulcer disease or gastrointestinal (GI) bleeding will be excluded. **Participant Monitoring:** Assessment of faecal occult blood will be performed at screening and at the end of each study period. Participants will be monitored for GI intolerance and sequential clinical chemistry analysis, including liver enzymes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Testicular toxicity	Inconsistent finding in Rats (4-week study): Spermatid retention at ≥60 mg/kg/day, however no effect observed in 13-week study. The observations in the 4-week study were not associated with degenerative changes in testes or epididymides. No spermatogenic abnormalities were observed in dogs.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Skeletal muscle toxicity	Rat (4-week study): Myofiber necrosis: myofiber degeneration/regeneration; fibroplasia, at 300 mg/kg/day in the soleus muscle.	**Participant Monitoring:** Creatinine phosphokinase (CPK) levels will be monitored throughout the study.
Seizures and convulsions	Rats (micronucleus and comet study): convulsions observed at ≥600 mg/kg/day. Convulsions were not related to C_{max}, nor occurred at any predictable time from dose administration. Dogs: No central nervous system (CNS) findings at 12 mg/kg/day in the dog 7-day Electroencephalography (EEG)/CV study. In other compounds in the same series, convulsions have been observed.	**Participant Selection:** Participants with a history of seizure disorder or stroke within the last 5 years will be excluded from the study.
Low food consumption	Dogs (4-week study): 30 mg/kg/day reduced food consumption. Two males were terminated early (Day 10) due to extremely reduced food consumption. Rats (4-week study): 300 mg/kg/day had decreased food consumption.	**Participant Monitoring:** Weight will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects on macrophages (Phospholipid accumulation)	Inconsistent effects observed in Rats (4-week study): ≥60 mg/kg/day in the lung (prominent alveolar macrophages); 300 mg/kg/day in the mesenteric lymph node (increased cellularity of sinus macrophages) and thymus (macrophage vacuolation; increased thymus weight). Consistent with phospholipid accumulation (phospholipidosis) based on ultrastructural appearance of mesenteric lymph nodes at 300 mg/kg/day. Findings were not associated with degenerative changes. In 13-week studies in rats, these effects were not observed.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Theoretical Risk: Potential effects on vasoregulation.	TRPV4 mediates prostaglandin release from isolated human endothelial cells and in vivo in rats, supporting the potential for TRPV4 blockade to modulate blood pressure via prostaglandin release. No effect of GSK2798745 on blood pressure was observed in preclinical studies.	**Participant Monitoring:** Blood pressure will be monitored throughout the study.
Theoretical Risk: Potential effect on hearing.	Genetic deletion of TRPV4 in mice has been shown to effect hearing. TRPV4 knockout (KO) mice at age 8 weeks exhibited normal hearing thresholds, but at age 24 weeks, had delayed-onset hearing loss; additionally, the cochlea was found to be vulnerable to acoustic injury with sound overexposure [Tabuchi, 2005]. Patients with Charcot-Marie-Tooth Disease Type 2C (CMT2C), an autosomal dominant axonal	**Participant Monitoring:** Despite the very low risk that hearing will be affected, audiometry will be conducted during the study at baseline in each Treatment Period and at the Follow Up Visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	neuropathy related to TRPV4 gene mutations, demonstrate symptoms that include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss). These are predominantly gain of function TRPV4 abnormalities, in which the hearing loss is sporadic among family members; and relegated to some TRPV4 defects, but not in others. Although the exact mechanism is unclear, it has been suggested that the TRPV4 channel plays an important role in peripheral nerve function and that the alterations in TRPV4 in CMT2C may be due to increased channel activity leading to excessive calcium influx and a calcium overload. However, these findings are academic, and have not been observed in any drug induced model. There is potential for benefit with GSK2798745, in that with cells (HEK293) expressing the CMT2C mutant channel, inhibitors of the TRPV4 channel were found to block the increased intracellular calcium concentrations and resultant cell death [Landouré, 2010].	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at a phlebotomy site may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Risk associated with cough monitoring	Mild contact dermatitis (skin irritation) or redness may be associated at the sites where a microphone is adhered.	Site staff will follow standard approaches for managing events related to application of self-adherent pads.
Risks associated with CXR (if required for participant selection)	The approximate effective radiation dose for a chest X-ray is 0.1 milliSievert (mSv).	If a participant has had chest imaging within the 12 months prior to starting the study, the procedure does not need to be repeated.

3.3.2. Benefit Assessment

- Potential benefit of receiving GSK2798745 that may have clinical utility during study duration.
- Medical evaluations and assessments associated with study procedures, e.g. physical examination, electrocardiogram, laboratory assessments, chest x-ray (CXR) (if applicable).
- Contributing to the process of developing new therapies in idiopathic or treatment resistant chronic cough, an area of unmet medical need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study (e.g. dose selection, careful participant selection and risk monitoring), the potential risks identified in association with GSK2798745 are justified by the anticipated benefits that may be afforded to participants with idiopathic or treatment resistant chronic cough.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers
Exploratory	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts over 24 hours following 7 days of dosing
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo at improving patient reported outcomes in participants with idiopathic or treatment-resistant chronic cough	• Change from baseline cough severity and urge to cough visual analogue scale (VAS) • Change from baseline Leicester Cough Questionnaire (LCQ) score
• To evaluate the pharmacokinetics (PK) of GSK2798745 and its M1 metabolite in participants with idiopathic or treatment-resistant chronic cough	• Plasma concentrations of GSK2798745, and derived PK parameters, as data permit

5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

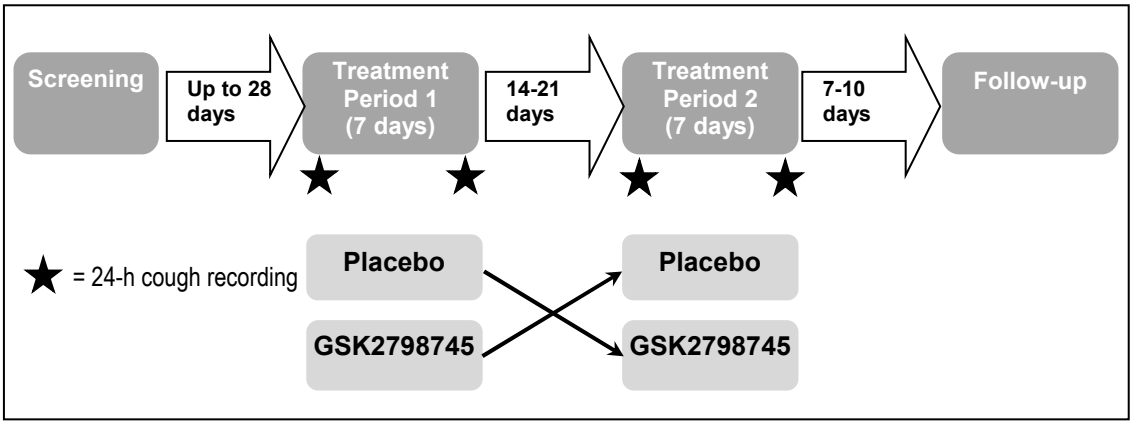
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Figure 1 Study Design Overview



5.2. Number of Participants

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. A participant will be considered evaluable if they have completed at least one Treatment Period and have evaluable cough counting

data from at least one Treatment Period. A sample-size re-estimation will be conducted when approximately 50% of the target sample size has completed the study. The sample size may be revised upwards or downwards (see Section 10.3.3). Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up visit.

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

5.4. Scientific Rationale for Study Design

- A multicentre, randomised, double-blind, placebo-controlled crossover trial is a well-established strategy to evaluate efficacy and safety of investigational medicinal products, such as GSK2798745.

- A placebo arm is included to determine the absolute effect of GSK2798745. In addition, the placebo-controlled design is appropriate as there are no effective, currently approved prescription medicines for chronic cough, and over-the-counter cough medicines have generally not shown benefit over placebo.

- Cough will be measured using a VitaloJAK cough device which is a validated, dedicated high fidelity recording device that provides ambulatory objective monitoring of cough with post-recording signal processing and expert systems to analyse coughs. Coughs will be recorded for 24 hours prior to dosing of each treatment period (baseline) and for 24 hours following dosing on Day 7 of each treatment period.

- The crossover design will be employed to minimise, as much as possible, the potential for variability in randomisation in a relatively small sample size.

- As chronic cough can significantly impact physical and emotional wellbeing, patient reported outcomes are important factors in determining the impact of a cough treatment. The Leicester Cough Questionnaire (LCQ) will be utilised as it is an established self-completed health related quality of life measure of chronic cough. The LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change [Birring, 2003].

5.5. Dose Justification

In this study, participants will take a 4.8 mg starting dose on Day 1, followed by a 2.4 mg GSK2798745 (tablet) once daily for remaining 6 days.

In the first time in human study with GSK2798745 (GlaxoSmithKline [GSK] study TR4113787), single doses up to 12.5 mg, and repeat doses of 5 mg once daily for

14 days, were tested in healthy participants. In addition, participants with heart failure were treated for 7 days with once daily doses of 2.4 mg GSK2798745 (as a capsule with food). There were no serious adverse events (SAEs) in study TR4117387. In other studies, with GSK2798745, there has been only one SAE to date. A participant with heart failure (Study 201881) had orthostatic hypotension during the washout period between the 2 treatment periods. The Principal Investigator (PI) deemed it not related to study treatment.

Another healthy participant study was conducted to compare the pharmacokinetics (PK) of different tablet formulations administered with or without food (GSK study 204725). A population PK (POP PK) approach was used to analyse all available clinical PK data (taking into consideration participant weight, formulation, impact of food, and other variables). Trial simulations were performed with this POP PK model with different dosing regimen.

A rat study was conducted assessing the ability of different doses of GSK2798745 infusion to reduce the increased lung-to-bodyweight ratio induced by the TRPV4 agonist, GSK1016790. Based on this study, the estimated human IC_{50} is 2.1–3.2 ng/mL. To evaluate drug activity/efficacy at the intended dosing regimen, TRPV4 blockade was estimated using the population model, and the potency values derived from the rat pulmonary study.

Based on the simulations, the intended dosing scheme for this study with up to 40 evaluable participants is a 4.8 mg dose on Day 1 followed by a 2.4 mg dose once daily for the following 6 days. Table 1 lists the predicted average TRPV4 inhibition over the 24-hour period on Day 7 based on this potency range. The schematic in Figure 2 also depicts the range of GSK2798745 systemic exposure and the predicted percent inhibition of TRPV4 with the intended regimen. With a loading dose of 4.8 mg, both GSK2798745 exposure and TRPV4 inhibition reach steady state from the first dose, compared with after 4 to 6 days without the loading dose.

This dose regimen was selected to ensure that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL while simultaneously providing sufficiently high channel blockade. That is the exposure observed at the no observed adverse effect level (NOAEL) of 3 mg/kg in the 3-month dog safety study with a 30-fold safety margin. The likelihood of one or more participants of the 40 participants to be dosed with this regimen, exceeding the threshold on Day 1 and Day 7 is listed in Table 1.

Food does not significantly impact the predicted exposures of GSK2798745 and the resulting TRPV4 inhibition as displayed in Table 1. So, GSK2798745 can be administered with or without food.

Figure 2 GSK2798745 exposure and % TRPV4 inhibition

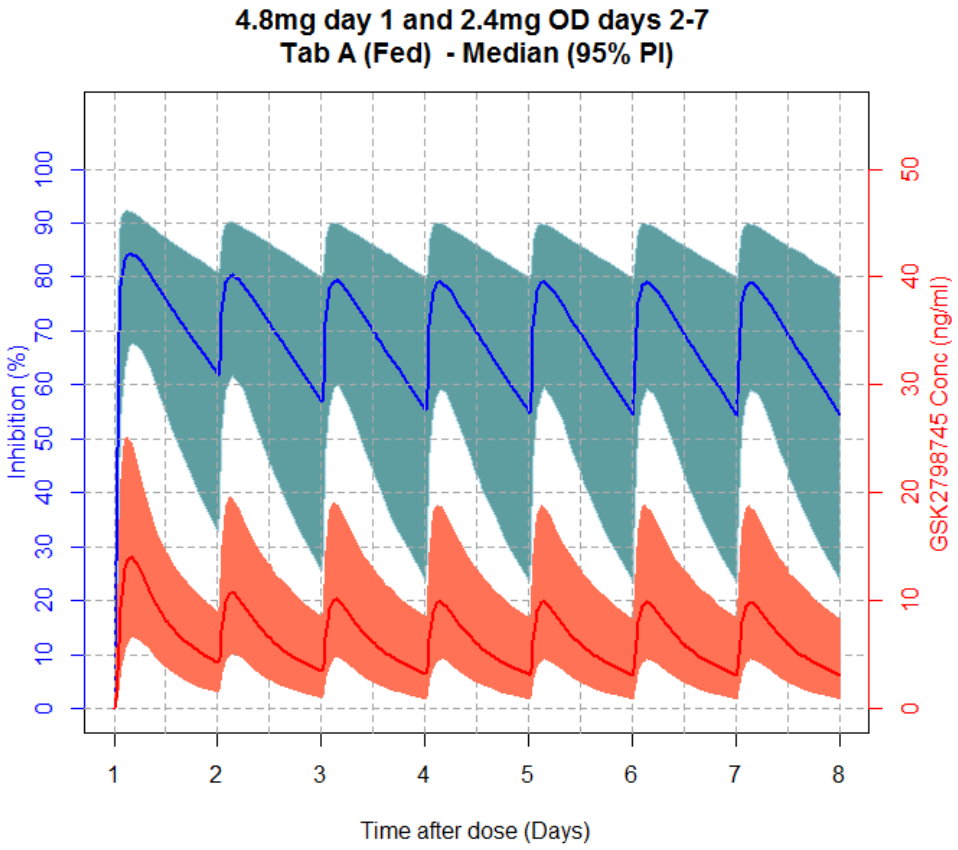


Table 1 Predicted exposure, probability of exceeding threshold and TRPV4 percent inhibition

4.8 mg on Day 1 and 2.4 mg OD Days 2–7	24 h exposure	Median (95% PI)		% Probability that ≥ 1 of 40 participants exceed threshold of		%TRPV4 inhibition over 24-hour period Median (95% PI)
		AUC24 (ng*hr/mL)	C_{max} (ug/mL)	AUC24 (513 ng*hr/mL)	C_{max} (50 ng/mL)	
With food	Day 1	201.5 (127.5 – 302.8)	18.7 (11.2 – 29.8)	0	0	72.0 (56.5 – 82.6)
	Day 7	147.6 (79.4 – 281.1)	13.1 (7.5 – 22.8)	2.0	0.2	67.3 (46.6 – 83.6)
Without food	Day 1	202.0 (128.3 – 303.5)	22.7 (15.3 – 34.2)	0	0.6	72.0 (55.3 – 83.4)
	Day 7	141.5 (76.6 – 269.7)	14.9 (9.1 – 24.8)	1.8	0.4	65.7 (44.2 – 82.7)

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Chronic idiopathic cough for ≥1 year (before screening), defined as: • a cough that is unresponsive to at least 8 weeks of targeted treatment, **or** • a cough for which no objective evidence of an underlying trigger has been determined, despite medical investigations. 3. No significant findings on chest imaging (CXR or CT scan) within 12 months before screening (participants with an abnormal CXR within 12 months, from a temporary process, will be allowed to participate if a repeat CXR is normal). 4. FEV1 ≥80% and ≤120% of the predicted normal value (at screening), or documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening. 5. Score of ≥40 mm on the Cough Severity VAS at Screening.

WEIGHT
6. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 32 kg/m^2 (inclusive) at screening.

SEX
7. Male or female **a.Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of this protocol from the time of first dose of study treatment until 2 weeks after last dose of study treatment, and refrain from donating sperm during this period. **b.Female participants:** A female participant is eligible to participate if she is **not of childbearing potential** as defined in Appendix 5.

INFORMED CONSENT
8. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or current evidence of any serious or clinically significant gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the investigator or the medical monitor, make the participant unsuitable for inclusion in this study.
2. History or current evidence of chronic productive cough.
3. History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the 6 months before screening.
4. Active ulcer disease or gastrointestinal bleeding at the time of screening (positive fecal occult blood test [FOBT] at screening).
5. History of stroke or seizure disorder within 5 years of screening.
6. Respiratory tract infection within 6 weeks of screening.
7. Participant who, in the investigator's opinion, poses a significant suicide risk. Evidence of serious suicide risk may include any history of suicidal behaviour and/or any evidence of suicidal ideation on any questionnaires e.g. Type 4 or 5 on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last 6 months (assessed at screening).
8. Alanine transferase (ALT) >2x upper limit of normal (ULN) at screening.
9. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. QTc >450 msec or QTc >480 msec in participants with bundle branch block at screening. *NOTE: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.*

PRIOR/CONCOMITANT THERAPY
12. Use of a listed prohibited medication (Section 7.7) within the restricted timeframe relative to the first dose of study treatment. 13. Use of a strong inhibitors or inducers of cytochrome P450 (CYP) 3A or p-glycoprotein (Section 7.7).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months of screening. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. Current enrollment or past participation within the 3 months before screening in any clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS
17. Positive human immunodeficiency virus (HIV) antibody test at screening. 18. Presence of Hepatitis B surface antigen (HBsAg) at screening. 19. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. *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.* 20. 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 are not required to also undergo Hepatitis C RNA testing.* 21. Cardiac troponin at screening > ULN for the assay.

OTHER EXCLUSIONS
22. History of alcohol abuse within 6 months of screening, in the opinion of the investigator. 23. Current smoker or history of smoking within the 6 months before screening, or a cumulative history of ≥ 20 pack years. *Pack years = (No. of cigarettes smoked/day/20) x (No. of years smoked)* 24. 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.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants are not permitted to consume red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the start of study treatment until the end of study treatment (in both Treatment Periods).

6.3.2. Alcohol and Tobacco

- During each Treatment Period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample on Day 7.
- Only non-smokers may be recruited into this study.

6.3.3. 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 (e.g. walking, watching television, reading).
- Participants will be instructed to avoid noisy environments 24 hours before the audiometry assessments.
- Participants will be asked to stay awake for 10 hours after attachment of the cough monitor, and to avoid noisy environments whilst wearing the cough monitor

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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, and any SAEs.

Participants may be rescreened once. If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated. See the study reference manual (SRM) for more details.

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the subject will be considered a screen failure.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK2798745	Matching Placebo
Dosage formulation:	White to almost white, round, film-coated tablet. Tablet A (micronized active pharmaceutical ingredient [API])	White to almost white, round, film-coated tablet
Unit dose strength:	2.4 mg	Not applicable
Route of Administration	Oral	Oral
Dosing instructions:	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).
Packaging and Labelling	GSK2798745 tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.	Placebo tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- The VitaloJAK (Model 7100; manufactured by Vitalograph Ltd) will be used to sense and record coughs for up to 24 hours (baseline and Day 7 in each treatment period). The VitaloJAK has a CE mark, indicating compliance to the Medical Devices Directive of the European Community (see Section 9.1.1).
- Instructions for using the VitaloJAK will be provided in a study-specific manual provided by Vitalograph.

7.2. Dose Modification

No dose modifications are permitted without submission of a substantial amendment to the protocol.

7.3. Method of Treatment Assignment

All participants will be centrally randomised using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and instructions for the IWRS will be provided to each site. Participants will be registered using the IWRS, and assigned a unique number (randomisation number). The randomisation number encodes the participant's assignment to one of the 2 treatment sequences shown in Table 2, according to the randomisation schedule generated prior to the study by the Clinical Statistics Department at GSK. In the randomisation, participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months). Each participant will be dispensed blinded study treatment, labelled with his/her unique randomisation number.

Table 2 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2
AB	Placebo tablets for 7 days	GSK2798745 tablets for 7 days
BA	GSK2798745 tablets for 7 days	Placebo tablets for 7 days

Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (SOA) (Section 2.2). Returned study treatment should not be re-dispensed.

7.4. Blinding

This will be a double blind (sponsor open) study. All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the participant will be blinded to the treatment allocated to individual participants. Selected sponsor study team members (and delegates if programming activities are outsourced) will be unblinded to perform the interim analysis. This may include the medical monitor, study statistician, study programmer (and delegates) and study pharmacokineticist; however, only the statistician and programmer (and delegates) will have access to individual participant level data. Access to unblinded data will be kept to the minimum set of individuals required to implement any interim analyses, but may include GSK management/review committees if alterations to the study conduct are required. Details of who were unblinded to what data and when will be included in the clinical study report.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.

The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

A participant will be withdrawn if the participant's treatment 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.

A participant whose treatment sequence assignment is inadvertently unblinded (either to investigative staff or the participant themselves) will be permitted to remain in the study, although the accidental unblinding will be recorded as a protocol deviation and hence the participant will be subject to review as to their inclusion in analyses.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. 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.

7.6. Treatment Compliance

Participants will take the study treatment at home on Day 2 to 6. Compliance will be assessed at the end of each Treatment Period by reviewing the participant diary card and questioning the participant. A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance

records. Treatment start and stop dates will be recorded in the CRF for Day 1, 6 and 7 of each Treatment Period.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), approved by the investigator, in consultation with the GSK Medical Monitor, that the participant is receiving at the time of enrolment, or receives during the study, must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications

Paracetamol at doses of ≤3 grams/day is permitted for use any time during the study.

Other concomitant medication will be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

Stable use of some medications may be permitted if the dose is stable for at least 3 months prior to Day 1, and the medication was prescribed for an indication other than cough. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. These willl be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

7.7.2. Prohibited Medications

Except for the permitted medication noted above and those approved by the investigator in consultation with the GSK Medical Monitor (Section 7.7.1), participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) or 30 days for ACE inhibitors, before the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study.

During the study, participants should not use drugs that are strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp), because they may alter GSK2798745 concentrations. The list of background therapy/drugs may be modified based on emerging data. These include, but are not limited to, those listed in Table 3.

Table 3 Strong inducers/inhibitors of CYP3A4 and P-gp

Antiretrovirals:	atazanavir, danoprevir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir
Antibiotics:	clarithromycin, telithromycin, troleandomycin, rifampin
Oral antifungals:	ketoconazole, itraconazole, voriconazole
Antidepressant	nefazadone
Immunosuppressant	cyclosporine
Anti-Epileptic	carbamazepine, phenytoin

GSK2798745 has weak CYP3A4 inhibition potential. It is possible that concentrations of drugs that are substrates of CYP3A4 may be increased. HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, are examples of CYP3A4 substrates that might be taken by the eligible participants. Participants being treated with simvastatin will be allowed to participate in the study, as long as their dose is ≤20 mg once daily. Participants being treated with >20 mg once daily simvastatin will be considered on a case basis by the investigator in consultation with the GSK Medical Monitor. Participants being treated with atorvastatin of any therapeutic dose are allowed to participate in the study. The concentration of atorvastatin may be evaluated after the study. The investigators may also consider substitutions of these medications.

It is strongly recommended that participants avoid using drugs that are sensitive substrates of Cytochrome P450 (CYP) 3A4 and/or P-gp or that have a low therapeutic index because concentrations of these substrates may be increased by GSK2798745. If co-administration of medications with interaction potential with GSK2798745 is necessary, investigators should monitor participants for loss of efficacy or consider substitutions of these medications.

All concomitant medications may be reviewed by the Medical Monitor and it will be up to the discretion of the Investigator in consultation with the GSK Medical Monitor, whether the medication can be continued and/or the participant can participate in the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study, because the indication being studied is not life threatening or seriously debilitating.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who withdraw or who are withdrawn from study treatment will be withdrawn from the study. See the SoA (Section 2.1) for assessments to be performed at early withdrawal.

Participants who start taking a prohibited medication during the study will be withdrawn, unless approved by the investigator in consultation with the GSK Medical Monitor.

8.1.1. Adverse Event Stopping Criteria

Participants who experience an adverse event, which in the opinion of the investigator could jeopardise the participant's safety, will be withdrawn from the study.

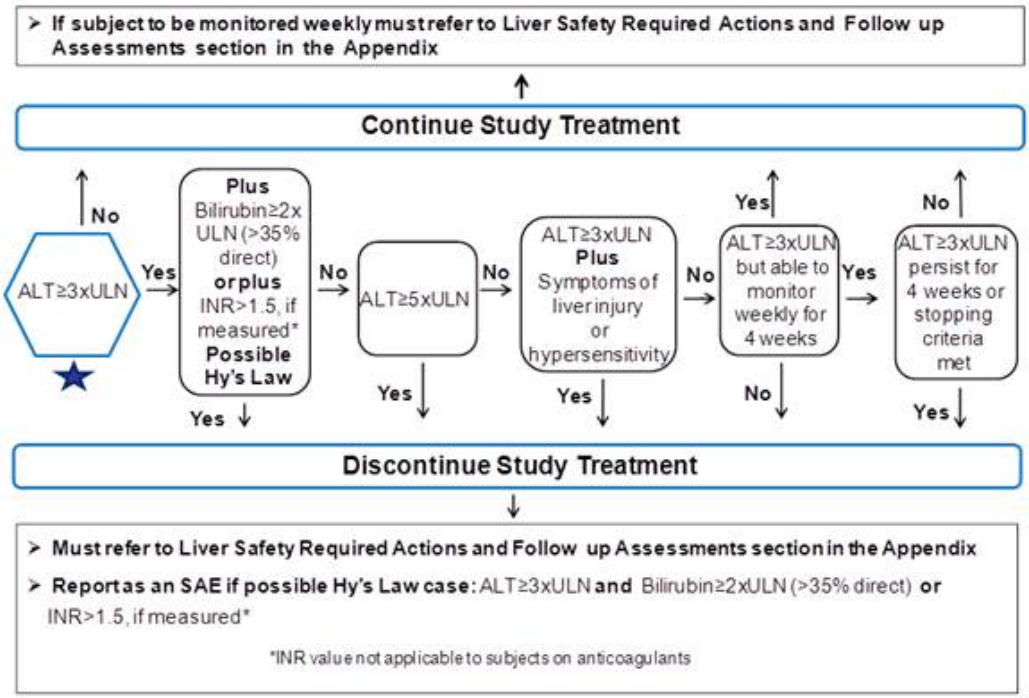
8.1.2. Liver Chemistry Stopping Criteria

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, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 3 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.2.1. Rechallenge

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

8.1.3. QTc Stopping Criteria

If a participant meets either bulleted criterion below, two further ECG recordings should be done (obtained over a brief [e.g. 5 to 10 minute] recording period). A participant who meets either bulleted criterion, based on the average of the triplicate ECG readings, will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

8.1.4. Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria

8.1.4.1. Symptomatic Participant:

If a participant experiences symptoms of cardiac ischemia (e.g. chest pain, increased shortness of breath, and diaphoresis), cardiology consultation should be obtained immediately. GSK2798745 should be discontinued permanently. The participant should be evaluated by a cardiologist and undergo any clinically appropriate testing. The participant should be followed up until symptoms are resolved.

8.1.4.2. Asymptomatic Participant:

Cardiac troponin will be measured pre-dose and at the end of dosing, in each Treatment Period. If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (Day -1, Treatment Period 1), the participant should be assessed for symptoms of cardiac ischemia (as above). If the participant is asymptomatic, the participant can continue in the study after discussion with the Medical Monitor and close monitoring for symptoms.

8.2. 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, behavioural, compliance or administrative reasons.
- 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.
- Refer to the SoA for data to be collected at the time of withdrawal (early withdrawal visit).

8.3. 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 with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA.
- Protocol waivers or exemptions are not allowed
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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.

9.1. Efficacy Assessments

9.1.1. Cough Counting

Cough monitoring will be conducted at the beginning and end of each treatment period, as shown in Section 2 (SOA).

The VitaloJAK cough monitor will be used. The VitaloJAK cough monitor was developed by Prof PPD Dr PPD and Prof PPD at University Hospital of South Manchester NHS Foundation Trust (UHSM), and has been fully validated in clinical studies. The VitaloJAK cough monitor has CE registration and Food and Drug Administration (FDA) 510K clearance.

The VitaloJAK Cough Monitor requires a disposable, single use chest sensor that is attached to the participant's chest, and a 'lapel microphone' that is attached to the participant's clothing. The monitor collects high fidelity recordings, recording all sound frequencies required for the semi-automated analysis of cough. The recording automatically stops at 24 hours.

Kits will be supplied by Vitalograph to the site containing all items required for each 24-hour recording, including the monitor, memory card and battery packs.

Recordings from the VitaloJAK Cough Monitor will be sent to Vitalograph for analysis via the Vitalograph Web Portal. Recordings will be processed through the semi-automated cough analysis system developed by UHSM. Vitalograph will QC check the recordings on receipt. The recording will then be processed to remove non-cough sounds

and silences, leaving a set of segmented files for analysis by a Cough Analyst at Vitalograph.

9.1.2. Cough Visual Analogue Scale (VAS)

Participants will be asked to complete 2 VAS forms, one each to rate the severity of their cough, and their urge to cough (see SRM).

The VAS forms should be completed before other clinical assessments (and before the LCQ), and participants should be given instructions on how to complete the form. The forms will be provided by GSK – the site should **not** make photocopies of the forms, or print from the PDF file.

9.1.2.1. Cough Severity VAS

The participant will be asked: '*How severe was your cough today?*'

The participant will place a mark on a 100 mm horizontal line, rating the severity of their cough from 'Not at all' to 'Extremely'.

9.1.2.2. Urge to Cough VAS

The participant will be asked: '*Please rate the intensity of your urge to cough today*'

The participant will place a mark on a 100 mm horizontal line, rating their urge to cough from 'No urge' to 'Severe urge'.

9.1.3. Leicester Cough Questionnaire (LCQ)

The LCQ is a validated, self-completed, quality of life measure of chronic cough [Birring, 2003]. The questionnaire is designed to assess the impact of cough on various aspects of the participant's life.

The LCQ should be completed after the Cough VAS, but before other clinical assessments, and participants should be given instructions on how to complete the questionnaire. The participant will be asked to read 19 statements, and rate their answer on a 7 point Likert response scale (see SRM).

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the start of treatment until the follow-up visit. However, any SAEs assessed as related to study participation (e.g. study treatment, 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 AEs will be collected from the start of treatment until the follow-up visit.
- Medical occurrences that begin before the start of study treatment, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.
- 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 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- 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 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. 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 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor, will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 Medical Dictionary for Regulatory Activities (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.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

9.3. Treatment of Overdose

For this study, any dose of GSK2798745 greater than the planned dose in the protocol, will be considered an overdose.

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

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

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2798745 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 24 h from the date of the last dose of study treatment 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 will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A full physical examination will include, at a minimum, measuring weight, and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, measuring weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height will be measured at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate.
- At screening, three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. At all other time-points, single measurements will be taken.

9.4.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At screening, triplicate ECG are required: 3 individual ECG tracings should be obtained over a brief (e.g. 5 to 10 minute) recording period.

9.4.4. Audiometry

Audiometry will be performed by authorised, trained staff using standard audiometry techniques. Participants will be instructed to avoid noisy environments 24 h prior to the audiometry assessments. Only air conductance will be performed. It will be at the discretion of the Investigator, Medical Monitor and/or the audiologist to determine if significant changes from baseline are seen and if a bone conductance test should be performed. Details of the audiometry testing are in the SRM.

9.4.5. Chest X-ray

CXR is only required if a participant has not had chest imaging within 12 months of screening. If a participant has had an abnormal CXR within 12 months, from a temporary process, the CXR may be repeated to determine eligibility.

CXR will be performed by authorised, trained staff.

9.4.6. FEV_1

- FEV1 will be measured to assess eligibility. It does not need to be repeated if there is documented evidence of FEV1 ≥80% and ≤120% within the 6 months before screening.
- Spirometry assessments will be performed whilst the subject is in a seated position (if the assessment is done on a bed, the subject's legs should be over the edge).
- Spirometry assessments will be repeated until 3 technically acceptable measurements have been made.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 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 7 to 10 days after the last dose of study treatment 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 aetiology 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.

9.4.8. Faecal Occult Blood Test

Based on the preclinical finding of gastric erosions (See Section 3.3.1), FOBT will be performed to determine eligibility and assess any possible study treatment-related GI blood loss.

At each time-point, participants will be given 2 FOBT cards with instructions for completing (using 2 different bowel movements) and returning the tests (in person or by post).

9.4.9. Columbia Suicidality Severity Rating Scale (CSSRS)

Based on preclinical studies that have been conducted, GSK2798745 is considered to be a central nervous system (CNS)-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although GSK2798745 has not been shown to be associated with an increased risk of suicidal thinking or behaviour, GSK considers it important to monitor for such events.

Participants being treated with GSK2798745 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour. Consideration should be given to discontinuing GSK2798745 in participants who experience signs of suicidal ideation or behaviour. Families of participants being treated with GSK2798745 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour, and to report such symptoms immediately to the study investigator.

The CSSRS is a measure of suicidal ideation and behaviour, with demonstrated predictive validity and reliability. Sections of the CSSRS include suicidal ideation, intensity of ideation, suicidal behaviour, and actual suicide attempt(s). The CSSRS assesses lifetime and current suicidal thoughts and behaviours across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the Principal Investigator or a sub-investigator for the study. See SRM for details of the scale.

At screening, the ‘Baseline’ CSSRS questionnaire will be completed. At all other time-points, the ‘Since Last Visit’ CSSRS questionnaire will be used (see Section 2, SOA).

9.4.10. Diary card

In each Treatment Period, a diary card will be used to collect:

- dosing information for Days 2 to 6 (Date and Time of Dose);
- AEs; and
- concomitant medications.

Between Treatment Periods 1 and 2 (the 'Washout Period'), a diary card will be used to collect AEs and concomitant medications.

Paper diary cards will be used (see SRM).

9.5. Pharmacokinetics

- Blood samples for pharmacokinetic analysis of GSK2798745 will be collected at the timepoints indicated in the SOA (Section 2).
- Blood will be collected in ethylenediaminetetraacetic acid (EDTA) tubes. The actual date and time of each blood sample collection will be recorded.
- The timing and volume of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring of GSK2798745 and, if possible, any relevant GSK2798745 metabolites.
- Additional collection, processing, storage and shipping procedures are provided in the laboratory manual.
- PK analysis will be performed under the control of Platform Technologies and Science-In Vitro/In Vivo Translation (PTS-IVIVT)/ and Third Party Resourcing (TPR) GlaxoSmithKline. Plasma concentrations of GSK2798745 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).
- Plasma samples may be analyzed for the metabolite M1. GSK may store the remaining plasma from the PK plasma samples for future possible additional metabolite analysis. Additional analysis of compound-related metabolites may be reported under a separate protocol.
- For participants taking atorvastatin, an extra sample will be taken at each PK time-point for analysis of atorvastatin concentration, and possible analysis of atorvastatin metabolites.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Laboratory Manual.

10. STATISTICAL CONSIDERATIONS

This study is designed to estimate the effect of GSK2798745 relative to placebo on day-time cough count totals following seven days of dosing. Day-time cough count totals will be derived from the total number of coughs during the first 10 hours following dosing, during which time the participant is expected to be awake.

The inference to be carried out will be with respect to the following hypothesis:

- Treatment with GSK2798745 leads to an improvement in day-time 10-hour cough count totals compared with placebo.

The above hypothesis will be investigated in this study by means of a Bayesian approach, which will assume a non-informative prior distribution. It is anticipated that the day-time 10-hour cough count totals will be log-transformed before statistical analysis, and hence the treatment effect will be evaluated in terms of a ratio of day-time cough count totals (GSK2798745 / placebo). A day-time cough count total of at least 30% less for GSK2798745 than for placebo is of interest. The posterior probability that the true ratio of the mean effect size of the test treatment and the mean effect size of the reference treatment μ(test) / μ(reference), is less than 0.7, and corresponding 90% credible intervals, will be obtained. The posterior probability that the true ratio is less than 0.7 will be referred to as PP (ratio<0.7).

10.1. Sample Size Determination

A simulation approach has been employed to investigate the chance of correctly determining a positive study with the planned number of participants. An estimate of 0.28 for the within subject variability in cough count totals was obtained from previous studies and this estimate was used in the simulations.

A treatment ratio (active:placebo) of 0.7 is considered to indicate an effective treatment. A treatment ratio of 0.5 is considered to represent a very effective treatment.

A positive study will be declared if the posterior probability that the true treatment ratio is less than 0.7 is more than 70% (PP(ratio <0.7) >70%). Given the planned sample size of 24 participants, if our variability assumptions are correct, then if the true treatment ratio is 0.5, there is a 95.3% probability of correctly declaring success. Conversely, if the true treatment ratio is 1, there is a 0.2% probability of declaring success at the end of the study.

An unblinded sample size re-estimation is planned in addition to the final analysis. This will be performed when at least 12 participants have completed both dosing periods and key assessment data is available. Cleaned efficacy data will be provided by Data Management to the unblinded study statistician.

Estimated treatment ratio of day-time cough counts between GSK2798745 and placebo will be calculated together with 90% credible intervals assuming a non-informative prior. This analysis will be supplemented by deriving predictive and/or conditional power in order to support sample size re-estimation. As a result of the sample size re-estimation, the sample size could be revised either upwards or downwards from the planned sample size of 24 evaluable participants, but the target number of evaluable participants will not exceed 40 participants.

Full details of the plan for the sample size re-estimation will be described in the Reporting and Analysis Plan (RAP).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants screened and for whom a record exists on the study database.
All Subjects	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	All randomised participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Day-time 10-hour cough counts following seven days' dosing of GSK2798745 as compared with placebo will be analysed by first log transforming the day-time 10-hour cough counts recorded on day 7 of each dosing period. The difference between GSK2798745 and placebo in log-transformed count rates will be investigated using a mixed effects model with fixed effects terms for treatment and period. Centre effects and the effect of whether or not the participant has participated in a cough clinical trial (which will be included as a stratification factor in the randomisation) in the previous 12 months will also be investigated. Baseline cough counts may be included in the model as a covariate. Participant will be treated as a random effect in the model. The posterior probability and corresponding 90% credible intervals that the ratio of the mean effect size of the test treatment and the mean effect size of the placebo treatment μ(test) - μ(placebo), is less than 1 will be constructed. In addition, the posterior probability true effect size distribution will be used to obtain estimates for the probabilities that the true effect size falls below thresholds of interest (e.g. what is the probability the true ratio is less than 0.7 and less than 0.5). The presence of carryover effects or treatment by period interaction will also be investigated and, if deemed appropriate, an analysis by period will be undertaken.
Exploratory	Will be described in the reporting and analysis plan.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	For the safety data, no formal hypotheses are being tested and no statistical analyses will be performed. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) will be summarized by treatment and time-point.

10.3.3. Interim Analyses

At least one interim analysis will be conducted during the course of the study. The treatment level results will be made available to the GSK study team who will review the available cough count data before making a decision on whether to:

i) stop the study on the grounds of futility
ii) adjust the sample size, in the event that futility criteria have not been met.

The interim analysis will also include a preliminary assessment of whether there is any evidence for the presence of carryover effects or treatment by period interaction.

Following the interim analysis, any adjustment to the sample size will be communicated to the sites.

The interim analysis will be conducted after at least 12 participants have completed both dosing periods and will look at day-time 10-hour cough count data only.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statisticians (including QC statistician) and programmers will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.3.4. Exploratory Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacokinetics Modelling & Simulation Department within GlaxoSmithKline. Calculations will be based on the actual sampling times recorded during the study. The systemic concentrations of GSK2798745, any metabolites, and atorvastatin will be summarised, as data permit. The details of the PK analysis will be listed in the RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
C_{max}	Maximum observed plasma concentration
CMT2C	Charcot-Marie-Tooth Disease Type 2C
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CSSRS	Columbia Suicidality Severity Rating Scale
CT	Computed tomography
CXR	Chest X-ray
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FOBT	Faecal Occult Blood Test
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICF	Informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IVIVT	In Vitro/In Vivo Translations
IWRS	Interactive Web Response System
kg	kilogram
KO	Knockout
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemogloin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSV	MilliSievert
NOAEL	No observed adverse effect level
nM	Nano Molar
P2X3	P2X purinoceptor 3
P-gp	p-glycoprotein
PK	Pharmacokinetic
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPR	Third Party Resourcing
TRPV4	Transient receptor potential vanilloid 4
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White blood cells
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Vitalograph
VitaloJAK

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (Fasting not required)	Calcium	Alkaline phosphatase	Creatinine phosphokinase (CPK)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Cardiac troponin			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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 8.1.2 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and 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 as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

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 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 substantial 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.
- 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.

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative 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 centre.
- 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 multi-centre 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.

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 the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

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 can be found in the source document agreement (to be signed by the investigator (or delegate) at each site).

Study and Site Closure

GSK or its 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:

- 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 treatment development.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> 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 (eg, 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 /AE/SAE CRF page.
- 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 sufficiently 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) **within 72 hours** of SAE entry into the eCRF.
- 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 (who is also the SAE coordinator) by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF (only necessary when electronic data collection tool is not available)
• The SAE paper CRF should be emailed to the medical monitor (who is also the SAE coordinator). • In rare circumstances, if email is not possible, 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of 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) and estradiol 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, a single FSH and estradiol measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 6.1.

- In addition, male participants must refrain from donating sperm from the time of first dose of study treatment until 2 weeks after last dose of study treatment.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*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 drug. 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.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- 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 2 weeks of learning of the partner's pregnancy.
- 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.

12.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2798745 or chronic cough and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2798745 (or study treatments of this drug class), and chronic cough. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analysed if it is hypothesised that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2798745 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2798745 (or study treatments of this class) or chronic cough continues, but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• 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 chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (defined as Day -1; Treatment Period 1) (see MONITORING below)
• Do not restart/rechallenge participant with study treatment (not allowed under this protocol)
• Permanently discontinue study treatment and continue any protocol specified follow up assessments</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis, within 24 hours after last dose[5]
• 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</td></tr>
</table>

MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 h** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 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 pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant'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 laboratory manual.

References

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

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Protocol Amendment 1 09-OCT-2017

Overall Rationale for the Amendment: The primary reason for amending the protocol is the removal of the Simplified Nutritional Appetite Questionnaire (SNAQ). The original protocol included the SNAQ, because of the preclinical finding of reduced food consumption in dogs (30 mg/kg/day) and rats (300 mg/kg/day). Since the publication of the original protocol, data has been reviewed from a study of GSK2798745 in heart failure patients. Participants took 2.4 mg GSK2798745 (n=10) or placebo (n=12) for 7 days. As shown in the table below, there was no observable difference in weight and appetite in participants receiving GSK2798745 and placebo. Therefore, the GSK Global Safety Board agreed to the removal of the SNAQ from future protocols. Weight will be measured at screening, follow-up, and the beginning and end of each Treatment Period, and adverse events that may be associated with low food consumption will be reviewed.

	Baseline (mean ± SD)	Day 7 (mean ± SD)	Change from Baseline
Weight (kg)			
2.4 mg	87.44 ± 18.54	87.67± 17.50	0.23
Placebo	83.58 ± 10.46	83.33 ± 10.56	-0.25
SNAQ Score (Maximum = 20)			
2.4 mg	16.2 ± 1.69	16.7 ± 1.95	0.5 ± 1.18
Placebo	15.3 ± 1.83	16.2 ± 1.53	0.8 ± 1.11

Section # and Name	Description of Change	Brief Rationale
Section 2.1 (Screening and Follow-up Schedule of Activities)	Removal of the SNAQ at the follow-up visit. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. The option for a CT scan at screening was included in the original protocol, in error. If chest imaging (chest x-ray or CT scan) has not been conducted within 12 months of screening, a chest x-ray will be conducted.
Section 2.2 (Treatment Period 1 and 2 Schedule of Activities)	Removal of the SNAQ at Day -1 and Day 8, in each Treatment Period.	Rationale for removal of the SNAQ described above.
Section 3.3.1 (Risk Assessment)	Removal of the SNAQ. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. Rationale for removal of CT scan at screening described above.
Section 7.7.1 (Permitted Medications)	The following change was made: *Stable use of some medications may be permitted if the dose is stable for at least ~~28 days~~ **3 months** prior to Day 1.*	Time period of stable dose changed from 28 days to 3 months, because 28 days might not be sufficient to achieve stable dosing of some permitted medications.
Section 8.1.3.2 (Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria: Asymptomatic Participant)	The following change was made: *If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (~~Screening~~ **Day -1, Treatment Period 1**), the participant should be assessed for symptoms of cardiac ischemia (as above).*	Definition of baseline changed from Screening to Treatment Period 1, Day -1 to be consistent with the baseline used for other laboratory tests.
Section 9.4.5 (Simplified Nutritional Appetite Questionnaire)	Removal of complete section.	Rationale for removal of the SNAQ described above.
Section 9.4.6 (Chest Imaging)	Removal of the option for a CT scan at screening.	Rationale for removal of CT scan at screening described above.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.9 (Columbia Suicidality Severity Rating Scale (CSSRS)	Addition of text stating that families of participants should be alerted about monitoring for emergence of suicidal ideation and behaviour.	New text added to ensure compliance with GSK's *Global Safety Board-Approved Recommendations for Prospective Assessment of Suicidal Ideation and Behaviour in Relevant Clinical Studies*.
Section 9.5 (Pharmacokinetics)	Blood sample volume removed.	Blood volume of sample removed, as this is still to be confirmed. Sample collection instructions to be provided in the laboratory manual.

TITLE PAGE

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Protocol Number: 207702 /Amendment 03

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Compound Number: GSK2798745

Development Phase: 2

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): 2017-002265-21

Approval Date: 25-JUN-2018

SPONSOR SIGNATORY:

PPD

25 JUNE 2018

Date

Joanna Marks-Konczalik, MD PhD
Project Physician Lead, Respiratory Therapy Area Unit

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Version	**Document**	**Date**
Protocol Amendment 3	2017N319286_03	25-JUN-2018
Protocol Amendment 2	2017N319286_02	22-NOV-2017
Protocol Amendment 1	2017N319286_01	09-OCT-2017
Original Protocol	2017N319286_00	31-MAY-2017

The original protocol (31-May-2017) was published internally only, it was not reviewed by the competent authority or the research ethics committee.

Protocol Amendment 1 (09-OCT-2017) was submitted to both the competent authority and the research ethics committee. The Summary of Changes table for Amendment 1 is in Section 12.8 (Appendix 8).

Protocol Amendment 2 (22-NOV-2017) was made in response to comments from the Medicines and Healthcare Products Regulatory Agency (MHRA), and was submitted to both the MHRA and the research ethics committee. The Summary of Changes table for Amendment 2 is in Section 12.8 (Appendix 8).

Protocol Amendment 3 (25-JUN-2018):

Overall Rationale for the Amendment: The protocol was amended after discussion with the study Principal Investigators. Two minor changes have been made to the inclusion criteria (described in the table below), because the original criteria were considered unnecessarily restrictive. The amendment is considered by the sponsor to be non-substantial, because the minor changes to the inclusion criteria (described in the table below) will not have a significant impact on the safety or scientific value of the clinical trial, and will not significantly alter the population recruited for the trial.

Other minor, administrative corrections have been made (described in the table below).
Note: Text added is denoted in **bold** font and deletion of text denoted in strikethrough in the summary of changes table below.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatory	~~James L. Kreindler, MD~~ ~~Director Clinical Development, Respiratory R&D~~ **Joanna Marks-Konczalik, MD PhD** **Project Physician Lead, Respiratory Therapy Area Unit**	Change in project physician lead.
Section 2.1 (Screening and Follow-up Schedule of Activities)	Note for Forced Expiratory Volume in One Second (FEV1): Not required if documented evidence of FEV1 ≥ 80% ~~and ≤ 120%~~ within the 6 months before screening.	Removal of the upper limit for FEV_1 from the eligibility criteria. An upper limit for FEV_1 is not required to ensure participant safety.
Section 2.2 (Treatment Period 1 and 2 Schedule of Activities)	Note for Faecal Occult Blood Test (FOBT): FOBT cards will be provided on Day 1~~-7~~ and returned on Day **7 or** 8, if possible (or returned by post).	For logistical reasons, FOBT cards will be given to participants on Day 1 of each Treatment Period, and returned on Day 7 or Day 8.
Section 6.1 (Inclusion Criteria)	4. FEV_1 ≥80% ~~and ≤120%~~ of the predicted normal value (at screening), or documented evidence of FEV_1 ≥80% ~~and ≤120%~~ within the 6 months before screening.	Removal of the upper limit for FEV_1 from the eligibility criteria. An upper limit for FEV_1 is not required to ensure participant safety.
Section 6.1 (Inclusion Criteria)	6. Body weight ≥50 kg and body mass index (BMI) within the range 18 to ~~32~~ **40** kg/m^2 (inclusive) at screening	The original BMI range included in the protocol is considered unnecessarily restrictive. Increasing the upper limit from 32 to 40 kg/m2 is predicted not to impact GSK2798745 pharmacokinetics (PK).

Section # and Name	Description of Change	Brief Rationale
Section 9.4.6 (FEV_1)	FEV_1 will be measured to assess eligibility. It does not need to be repeated if there is documented evidence of FEV_1 ≥80% ~~and ≤120%~~ within the 6 months before screening. Spirometry assessments will be performed whilst the subject is in a seated position (if the assessment is done on a bed, the subject's legs should be over the edge). Spirometry assessments will be repeated until 3 technically acceptable measurements have been made. **To confirm eligibility, 1 or more of the 3 measurements is required to be ≥80%.**	Removal of the upper limit for FEV_1 from the eligibility criteria. An upper limit for FEV_1 is not required to ensure participant safety. Clarification of the FEV_1 assessment used to confirm eligibility.
Section 10.3.3	The interim analysis will be conducted after at least 12 participants have completed both dosing periods and will look at day-time 10-hour cough count data ~~only~~**, as well as supporting PK data, if required.**	Inclusion of PK data in the interim analysis data review, if required to understand the cough count data.

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1. SYNOPSIS

Protocol Title: A placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough

Short Title: A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough

Rationale: Chronic cough is a disease with high unmet medical need. It is hypothesised that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) through P2X purinoceptor 3 (P2X3) receptors. Transient receptor potential vanilloid 4 (TRPV4) activation has been shown to cause ATP release from airway macrophages and airway epithelial cells, and studies have established a role for TRPV4-mediated ATP release and the P2X3 receptor in TRPV4-mediated activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD) – diseases in which cough is a prevalent symptom. It is hypothesised, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough.

GSK2798745 is a potent and selective TRPV4 channel blocker being investigated for the treatment of chronic cough. The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment-resistant chronic cough.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers

Overall Design:

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

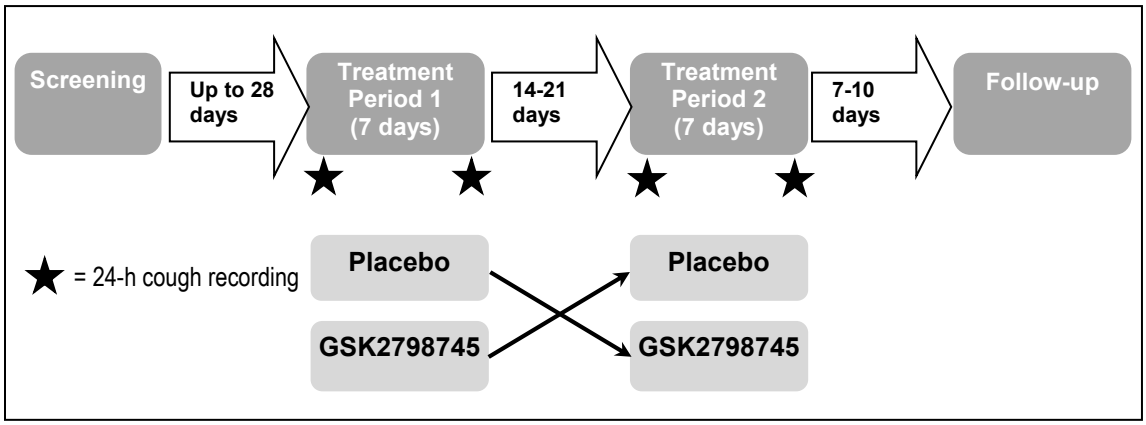
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Study Design Overview



Number of Participants:

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. However, following a sample-size re-estimation when approximately 50% of the target sample size has completed the study, the sample size may be revised upwards or downwards. Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening and Follow-up Schedule of Activities

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage, and family history of premature cardiovascular (CV) disease	X		Substances: Drugs, Alcohol, tobacco
Full physical exam, including height and weight	X	X	Height to be measured at screening only.
Chest x-ray [CXR]	X		Not required if chest imaging has been conducted within 12 months of screening with no significant findings.
Columbia Suicidality Severity Rating Scale (CSSRS)	X	X	Use 'Baseline' CSSRS at Screening. Use the 'Since Last Visit' CSSRS at Follow-up.
Human immunodeficiency virus (HIV), hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Clinical chemistry, haematology and urinalysis (including cardiac troponin)	X	X	Non Fasting
Follicle-stimulating hormone and estradiol	X		As needed in women of non-childbearing potential only
Faecal Occult Blood Test (FOBT)	X		FOBT cards will be provided at screening and must be returned to the laboratory and analysed before Day -1.
Vital signs (blood pressure, heart rate and temperature)	X	X	Triplicate vital signs required at screening.
12-lead ECG	X	X	Triplicate ECG required at screening.
Forced Expiratory Volume in One Second (FEV1)	X		Not required if documented evidence of FEV1 ≥ 80% within the 6 months before screening.

Procedure	**Screening[1] (up to 28 days before Treatment Period 1, Day -1)**	**Follow up/Early Withdrawal (7-10 days post last dose)**	**Notes**
Cough Severity & Urge to Cough Visual Analogue Scale (VAS)	X (Severity only)	X (Severity & Urge)	Urge to cough VAS will not be completed at screening.
Audiometry		X	Audiometry to be done anytime between end of Treatment Period 2 and Follow-up.
Concomitant Medication review	X	X	
Adverse event (AE)/serious adverse event (SAE) review	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose (see Section 9.2.1).

1. Screening assessments may be conducted at multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).

2.2. Treatment Period 1 and 2 Schedule of Activities

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Study Treatment						
Randomisation		X (TP1 only)				Can be done on Day –1 or Pre-dose Day 1. Participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months).
Study Treatment dispensed		X				
Study Treatment dosing		X	X	X		Home dosing on Days 2-6. Dosing to be at about the same time each day (±2 hours relative to dosing on Day 1).
Diary Card dispensed		X		X (TP1 only)		Diary card used to collect dosing information, AEs and concomitant medications. Diary card dispensed on Day 7 in Treatment Period 1 only (to collect AEs and concomitant medications during washout period).
Efficacy Assessments						
24- hour Cough Counting Starts	X			X		On Day 7, the cough counter must be attached immediately after dosing. Participant to be advised to avoid noisy environments whilst wearing the counter, and to stay awake for 10 h after attachment of the monitor.
24- hour Cough Counting Ends		X			X	On Day 1, the cough counter must be removed before dosing.
Cough Severity & Urge to Cough VAS	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.2).
Leicester Cough Questionnaire (LCQ)	X			X (pre-dose)		To be completed before other assessments (see Section 9.1.3).
Safety Assessments						
Brief physical exam	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Weight	X				X	Baseline can be done on Day –1 or Pre-dose Day 1

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Vital signs (blood pressure, heart rate and temperature)		X (pre-dose)			X	Single measurements
12-lead ECG		X (pre-dose)			X	Single measurements
Clinical chemistry, haematology and urinalysis (including cardiac troponin)		X (pre-dose)			X	Non-fasting.
FOBT				X		FOBT cards will be provided on Day 1 and returned on Day 7 or 8, if possible (or returned by post).
CSSRS	X				X	Use the 'Since Last Visit' CSSRS questionnaire. The pre-dose CSSRS in each Treatment Period can be done on Day –1 or Pre-dose Day 1.
Audiometry	X					Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).
Concomitant Medication review	X	X	X	X	X	Concomitant medications collected in Diary Card during washout period.
SAE/AE review	X	X	X	X	X	AEs collected in Diary Card during washout period.
Other Assessments						
PK blood samples		X		X	X	**Day 1 and Day 7:** predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h post dose **Day 8:** 24 h post dose For participants taking atorvastatin, an extra sample will be taken at each time-point.
Optional Genetic Sample		X				Can be taken any time after consent has been signed and the participant has been randomised.

- The Cough Severity & Urge to Cough VAS should be completed before the LCQ, and both questionnaires should be completed before any other assessments.

- When scheduled at the same time-points, 12-lead ECGs and vital signs should be completed before any blood draws.

- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point.

- The timing and number of planned study assessments, including: safety and pharmacokinetic 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.

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

GSK2798745 is a potent and selective transient receptor potential vanilloid 4 (TRPV4) channel blocker being investigated for the treatment of chronic cough.

GSK2798745 is a potent *in vitro* blocker of recombinant human TRPV4 channels, with:

- agonist-evoked Ca^{2+} influx 50% maximal inhibitory concentration (IC_{50}) value of 1.6 to 2.0 nM;
- hypotonicity-evoked Ca^{2+} influx IC_{50} value of 1.6 to 2.0 nM; and
- blocks native human endothelial TRPV4 channels (agonist-evoked impedance reduction in the presence of human whole blood IC_{50}=6.5nM).

GSK2798745 is a potent *in vivo* blocker of rat TRPV4 channels where full block of TRPV4-induced pulmonary edema was observed at a 38 nM total plasma concentration. Further information regarding the pre-clinical and clinical studies performed with GSK2798745 is available in the investigator brochure (IB) (GSK Document Number 2013N162862_03).

GSK2798745 has been administered orally to healthy participants as single doses ranging from 0.25 to 12.5 mg. A dosage of 5 mg once daily has been administered for up to 14 days in healthy participants. Further, GSK2798745 at a dose of 2.4 mg has been evaluated as a single dose and subsequently as a repeat dose for 7 days in participants with heart failure.

Review of data in healthy participants indicates that there were no clinically significant safety concerns with single or repeat administration of GSK2798745. Review of data in participants with heart failure indicates that there are no clinically significant safety concerns with repeat administration up to 7 days.

TRPV4 is widely expressed in the respiratory tract and is activated by a wide range of stimuli including temperature, pH and osmolarity [Toft-Bertelsen, 2017]. It is hypothesized that chronic cough reflects a state of neuronal hypersensitivity involving exaggerated spinal and cortical responses to afferent sensory signals originating from mechanosensitive and chemosensitive neurons. It is thought that cough reflexes are triggered by adenosine triphosphate (ATP) [Basoglu, 2005] through P2X purinoceptor 3 (P2X3) receptors [Ford, 2013]. TRPV4 activation causes ATP release from airway epithelial cells [Baxter, 2014], and studies have established a role for TRPV4-mediated ATP release and P2X3 receptor in activation of airway afferents. ATP-stimulated cough is of particular interest as there are data to suggest that ATP levels are increased in the airways of patients with asthma [Idzko, 2007] and chronic obstructive pulmonary disease (COPD) [Baxter, 2014], diseases in which cough is a prevalent symptom. It is hypothesized, therefore, that a TRPV4-ATP-P2X3 axis contributes to the evolution and persistence of chronic cough [Bonvini, 2016].

3.1. Study Rationale

The aim of this study is to evaluate whether blockade of TRPV4 channels is effective in reducing cough in participants with idiopathic or treatment refractory chronic cough.

TRPV4 and P2X3 antagonists have been shown to reduce cough effectively in a pre-clinical cough model in guinea pigs [Bonvini, 2016]. Moreover, clinical data suggest that pharmacological inhibition of P2X3 receptors reduces cough frequency and improves patient reported outcomes and quality of life in a subset of patients with chronic cough [Abdulqawi, 2015].

Therefore, blocking TRPV4 channels may be a viable therapeutic strategy for treating chronic idiopathic or treatment-resistant cough.

3.2. Background

Chronic cough is defined in clinical practice as cough lasting greater than 8 weeks. It is highly prevalent worldwide and is a leading cause of unplanned visits to the doctor's office [Schappert, 2006]. Chronic cough patients can be broadly divided into 3 groups: those with idiopathic cough, those with treatment refractory cough secondary to otherwise controlled triggers such as allergic rhinitis or mild asthma, and those with cough associated with underlying chronic lung diseases, such as COPD or Idiopathic Pulmonary Fibrosis (IPF) [Smith, 2017].

Large epidemiological studies that include all 3 patient groups suggest that the prevalence of chronic cough is as high as 10% worldwide. The epidemiology of idiopathic and treatment refractory chronic cough is more difficult to determine precisely, though it is probable that these groups of patients represent a minority of the total compared with diseases such as COPD. However, the amount of coughing (coughs per hour) measured in patients with idiopathic or treatment refractory chronic cough tends to be much higher than in patients with COPD [Abdulqawi, 2015; Sumner, 2013]. Moreover, cough suppression in suppurative lung diseases such as COPD may carry additional risks that would require establishing a benefit risk ratio in a dedicated study. Therefore, demonstrating efficacy in idiopathic and treatment refractory chronic cough populations is a logical first step before exploring other populations.

Regardless of etiology, chronic cough is by nature difficult to treat and significantly diminishes quality of life. The commonly used therapies for cough are opioid-derived over-the-counter medicines, which tend to be relatively ineffective when compared with placebo. In addition, these medicines have significant side-effects and potential for abuse that limit their usability. Likewise, the opiate codeine is among the most commonly prescribed medicines for cough despite similar limitations to its clinical efficacy and even greater potential for abuse. Overall, there is a significant unmet medical need for safe and effective medicines to treat chronic cough.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2798745 may be found in the IB.

3.3.1. Risk Assessment

All potential risks of GSK2798745 are based on pre-clinical data. No risks have been identified in the clinical studies of GSK2798745 conducted prior to the effective date of this protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2798745]		
Vascular lesions	Dogs (4-week study): at 30 mg/kg/day, 2 males had arterial lesions • One male: Heart – Coronary artery inflammation; Thymus – Arteriole inflammation with fibroplasia • One male: Epididymides – Artery degeneration/necrosis with inflammation Dogs (12-week study): At 10 mg/kg/day, 1 male and 1 female had arterial lesions • One male: Epididymides – Arteriole degeneration/necrosis with lymphocytic inflammation • One female: Bladder – Arteriole degeneration/necrosis with lymphocytic inflammation	**Participant Monitoring:** The arterial lesions noted in heart, thymus, epididymides, and urinary bladder cannot be monitored directly. There is currently no human translation biomarker or understanding of the underlying mechanism. **Participant Exposure:** Since these effects cannot be monitored directly in clinical studies, coverage of ≥30 fold will be maintained from the no-effect dose (3 mg/kg/day); exposure will not intentionally exceed the average daily area under concentration-time curve (AUC) of 0.513 hr*ug/mL and/or maximum observed plasma concentration (C_{max}) of 0.050 ug/mL on an individual basis.
Myocardial toxicity	Dogs (4-week study): at 30 mg/kg/day, myofiber degeneration/necrosis and inflammation (2 animals)	**Participant Selection:** Participants with history of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months will be excluded. **Participant Monitoring:** Cardiac troponin levels

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		will be monitored throughout the study. **Participant Exposure:** Exposure levels will be maintained below the threshold detailed in the Dose Justification Section (see Section 5.5).
Mortality/moribund condition; poor viability	Dogs (4-week study): at 30 mg/kg/day, one male terminated early (Day 6) due to poor clinical condition. Another male had transient whole body shaking on Days 8 and 9. Dogs (13-week study): at 10 mg/kg/day one male was terminated early (Day 74) due to welfare reasons. Rats (micronucleus and comet study): mortality occurred following 1 to 3 doses at ≥600mg/kg/day	**Participant Monitoring:** Weight and adverse events reported by participants will be monitored.
Gastrointestinal and/or hepatic toxicity	GI toxicity: ≥3 mg/kg/day in dogs and at 30 and 300 mg/kg/day in rats, consisting of mucosal erosion/ulceration in the stomach and/or duodenum. Hepatic Toxicity: Biliary epithelial hypertrophy/hyperplasia and periductal mixed inflammatory cell infiltrate into the liver was observed at 300 mg/kg/day in rat (7-day study) and focal hepatocellular degeneration in 1 male dog at 30 mg/kg/day (4-week study)	**Participant Selection:** Participants with active ulcer disease or gastrointestinal (GI) bleeding will be excluded. **Participant Monitoring:** Assessment of faecal occult blood will be performed at screening and at the end of each study period. Participants will be monitored for GI intolerance and sequential clinical chemistry analysis, including liver enzymes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Testicular toxicity	Inconsistent finding in Rats (4-week study): Spermatid retention at ≥60 mg/kg/day, however no effect observed in 13-week study. The observations in the 4-week study were not associated with degenerative changes in testes or epididymides. No spermatogenic abnormalities were observed in dogs.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Skeletal muscle toxicity	Rat (4-week study): Myofiber necrosis: myofiber degeneration/regeneration; fibroplasia, at 300 mg/kg/day in the soleus muscle.	**Participant Monitoring:** Creatinine phosphokinase (CPK) levels will be monitored throughout the study.
Seizures and convulsions	Rats (micronucleus and comet study): convulsions observed at ≥600 mg/kg/day. Convulsions were not related to C_{max}, nor occurred at any predictable time from dose administration. Dogs: No central nervous system (CNS) findings at 12 mg/kg/day in the dog 7-day Electroencephalography (EEG)/CV study. In other compounds in the same series, convulsions have been observed.	**Participant Selection:** Participants with a history of seizure disorder or stroke within the last 5 years will be excluded from the study.
Low food consumption	Dogs (4-week study): 30 mg/kg/day reduced food consumption. Two males were terminated early (Day 10) due to extremely reduced food consumption. Rats (4-week study): 300 mg/kg/day had decreased food consumption.	**Participant Monitoring:** Weight will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects on macrophages (Phospholipid accumulation)	Inconsistent effects observed in Rats (4-week study): ≥60 mg/kg/day in the lung (prominent alveolar macrophages); 300 mg/kg/day in the mesenteric lymph node (increased cellularity of sinus macrophages) and thymus (macrophage vacuolation; increased thymus weight). Consistent with phospholipid accumulation (phospholipidosis) based on ultrastructural appearance of mesenteric lymph nodes at 300 mg/kg/day. Findings were not associated with degenerative changes. In 13-week studies in rats, these effects were not observed.	**Participant Exposure:** A safety margin of ≥40 fold will be maintained from the no effect dose (60 mg/kg/day) in rats.
Theoretical Risk: Potential effects on vasoregulation.	TRPV4 mediates prostaglandin release from isolated human endothelial cells and in vivo in rats, supporting the potential for TRPV4 blockade to modulate blood pressure via prostaglandin release. No effect of GSK2798745 on blood pressure was observed in preclinical studies.	**Participant Monitoring:** Blood pressure will be monitored throughout the study.
Theoretical Risk: Potential effect on hearing.	Genetic deletion of TRPV4 in mice has been shown to effect hearing. TRPV4 knockout (KO) mice at age 8 weeks exhibited normal hearing thresholds, but at age 24 weeks, had delayed-onset hearing loss; additionally, the cochlea was found to be vulnerable to acoustic injury with sound overexposure [Tabuchi, 2005]. Patients with Charcot-Marie-Tooth Disease Type 2C (CMT2C), an autosomal dominant axonal	**Participant Monitoring:** Despite the very low risk that hearing will be affected, audiometry will be conducted during the study at baseline in each Treatment Period and at the Follow Up Visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	neuropathy related to TRPV4 gene mutations, demonstrate symptoms that include hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss). These are predominantly gain of function TRPV4 abnormalities, in which the hearing loss is sporadic among family members; and relegated to some TRPV4 defects, but not in others. Although the exact mechanism is unclear, it has been suggested that the TRPV4 channel plays an important role in peripheral nerve function and that the alterations in TRPV4 in CMT2C may be due to increased channel activity leading to excessive calcium influx and a calcium overload. However, these findings are academic, and have not been observed in any drug induced model. There is potential for benefit with GSK2798745, in that with cells (HEK293) expressing the CMT2C mutant channel, inhibitors of the TRPV4 channel were found to block the increased intracellular calcium concentrations and resultant cell death [Landouré, 2010].	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at a phlebotomy site may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Risk associated with cough monitoring	Mild contact dermatitis (skin irritation) or redness may be associated at the sites where a microphone is adhered.	Site staff will follow standard approaches for managing events related to application of self-adherent pads.
Risks associated with CXR (if required for participant selection)	The approximate effective radiation dose for a chest X-ray is 0.1 milliSievert (mSv).	If a participant has had chest imaging within the 12 months prior to starting the study, the procedure does not need to be repeated.

3.3.2. Benefit Assessment

- Potential benefit of receiving GSK2798745 that may have clinical utility during study duration.
- Medical evaluations and assessments associated with study procedures, e.g. physical examination, electrocardiogram, laboratory assessments, chest x-ray (CXR) (if applicable).
- Contributing to the process of developing new therapies in idiopathic or treatment resistant chronic cough, an area of unmet medical need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study (e.g. dose selection, careful participant selection and risk monitoring), the potential risks identified in association with GSK2798745 are justified by the anticipated benefits that may be afforded to participants with idiopathic or treatment resistant chronic cough.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary	
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers
Exploratory	
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts over 24 hours following 7 days of dosing
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo at improving patient reported outcomes in participants with idiopathic or treatment-resistant chronic cough	• Change from baseline cough severity and urge to cough visual analogue scale (VAS) • Change from baseline Leicester Cough Questionnaire (LCQ) score
• To evaluate the pharmacokinetics (PK) of GSK2798745 and its M1 metabolite in participants with idiopathic or treatment-resistant chronic cough	• Plasma concentrations of GSK2798745, and derived PK parameters, as data permit

5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, randomised, placebo-controlled, double-blind, two-period crossover study, in participants with chronic cough.

Each participant will have 2 treatment periods, and be randomised to one of the following treatments in each period:

- 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days
- Matching placebo once daily for 7 days

Each participant will:

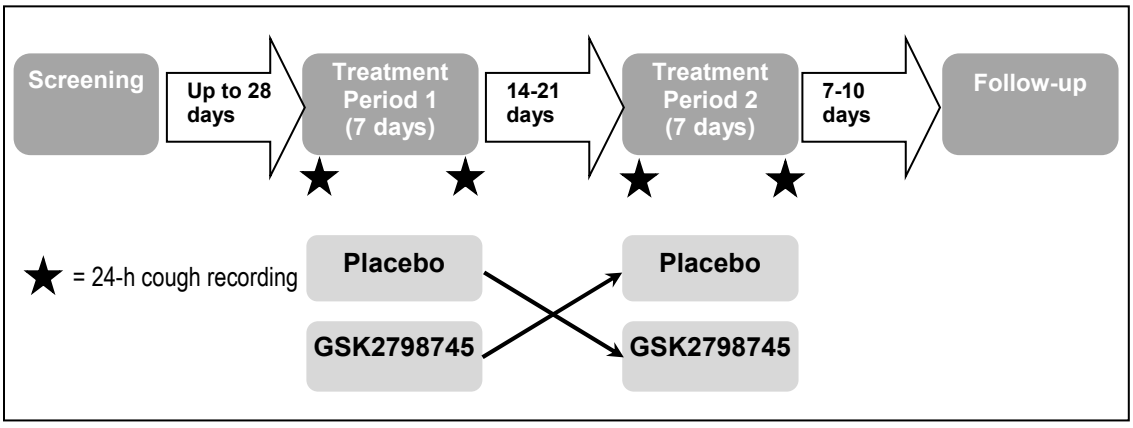
- be screened (screening may be conducted across more than 1 visit);
- have 2 treatment periods (each 7 days) with a washout period of 14 to 21 days between the treatment periods; and
- have a follow-up visit (within 7 to 10 days after their last dose).

Each participant will be involved in the study for a maximum of 10½ weeks.

Coughs will be recorded using the VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period.

A minimum of one interim analysis for futility and possible sample size adjustment will be conducted during the study.

Figure 1 Study Design Overview



5.2. Number of Participants

This is a study in participants with idiopathic or treatment refractory chronic cough. The target number of evaluable participants is 24. A participant will be considered evaluable if they have completed at least one Treatment Period and have evaluable cough counting

data from at least one Treatment Period. A sample-size re-estimation will be conducted when approximately 50% of the target sample size has completed the study. The sample size may be revised upwards or downwards (see Section 10.3.3). Following the sample size re-estimation, the target number of evaluable participants will not exceed 40 and the number of participants randomised will not exceed 48.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up visit.

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

5.4. Scientific Rationale for Study Design

- A multicentre, randomised, double-blind, placebo-controlled crossover trial is a well-established strategy to evaluate efficacy and safety of investigational medicinal products, such as GSK2798745.

- A placebo arm is included to determine the absolute effect of GSK2798745. In addition, the placebo-controlled design is appropriate as there are no effective, currently approved prescription medicines for chronic cough, and over-the-counter cough medicines have generally not shown benefit over placebo.

- Cough will be measured using a VitaloJAK cough device which is a validated, dedicated high fidelity recording device that provides ambulatory objective monitoring of cough with post-recording signal processing and expert systems to analyse coughs. Coughs will be recorded for 24 hours prior to dosing of each treatment period (baseline) and for 24 hours following dosing on Day 7 of each treatment period.

- The crossover design will be employed to minimise, as much as possible, the potential for variability in randomisation in a relatively small sample size.

- As chronic cough can significantly impact physical and emotional wellbeing, patient reported outcomes are important factors in determining the impact of a cough treatment. The Leicester Cough Questionnaire (LCQ) will be utilised as it is an established self-completed health related quality of life measure of chronic cough. The LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change [Birring, 2003].

5.5. Dose Justification

In this study, participants will take a 4.8 mg starting dose on Day 1, followed by a 2.4 mg GSK2798745 (tablet) once daily for remaining 6 days.

In the first time in human study with GSK2798745 (GlaxoSmithKline [GSK] study TR4113787), single doses up to 12.5 mg, and repeat doses of 5 mg once daily for

14 days, were tested in healthy participants. In addition, participants with heart failure were treated for 7 days with once daily doses of 2.4 mg GSK2798745 (as a capsule with food). There were no serious adverse events (SAEs) in study TR4117387. In other studies, with GSK2798745, there has been only one SAE to date. A participant with heart failure (Study 201881) had orthostatic hypotension during the washout period between the 2 treatment periods. The Principal Investigator (PI) deemed it not related to study treatment.

Another healthy participant study was conducted to compare the pharmacokinetics (PK) of different tablet formulations administered with or without food (GSK study 204725). A population PK (POP PK) approach was used to analyse all available clinical PK data (taking into consideration participant weight, formulation, impact of food, and other variables). Trial simulations were performed with this POP PK model with different dosing regimen.

A rat study was conducted assessing the ability of different doses of GSK2798745 infusion to reduce the increased lung-to-bodyweight ratio induced by the TRPV4 agonist, GSK1016790. Based on this study, the estimated human IC_{50} is 2.1–3.2 ng/mL. To evaluate drug activity/efficacy at the intended dosing regimen, TRPV4 blockade was estimated using the population model, and the potency values derived from the rat pulmonary study.

Based on the simulations, the intended dosing scheme for this study with up to 40 evaluable participants is a 4.8 mg dose on Day 1 followed by a 2.4 mg dose once daily for the following 6 days. Table 1 lists the predicted average TRPV4 inhibition over the 24-hour period on Day 7 based on this potency range. The schematic in Figure 2 also depicts the range of GSK2798745 systemic exposure and the predicted percent inhibition of TRPV4 with the intended regimen. With a loading dose of 4.8 mg, both GSK2798745 exposure and TRPV4 inhibition reach steady state from the first dose, compared with after 4 to 6 days without the loading dose.

This dose regimen was selected to ensure that no participant intentionally exceeds the daily AUC of 513 ng*hr/mL and C_{max} of 50 ng/mL while simultaneously providing sufficiently high channel blockade. That is the exposure observed at the no observed adverse effect level (NOAEL) of 3 mg/kg in the 3-month dog safety study with a 30-fold safety margin. The likelihood of one or more participants of the 40 participants to be dosed with this regimen, exceeding the threshold on Day 1 and Day 7 is listed in Table 1.

Food does not significantly impact the predicted exposures of GSK2798745 and the resulting TRPV4 inhibition as displayed in Table 1. So, GSK2798745 can be administered with or without food.

Figure 2 GSK2798745 exposure and % TRPV4 inhibition

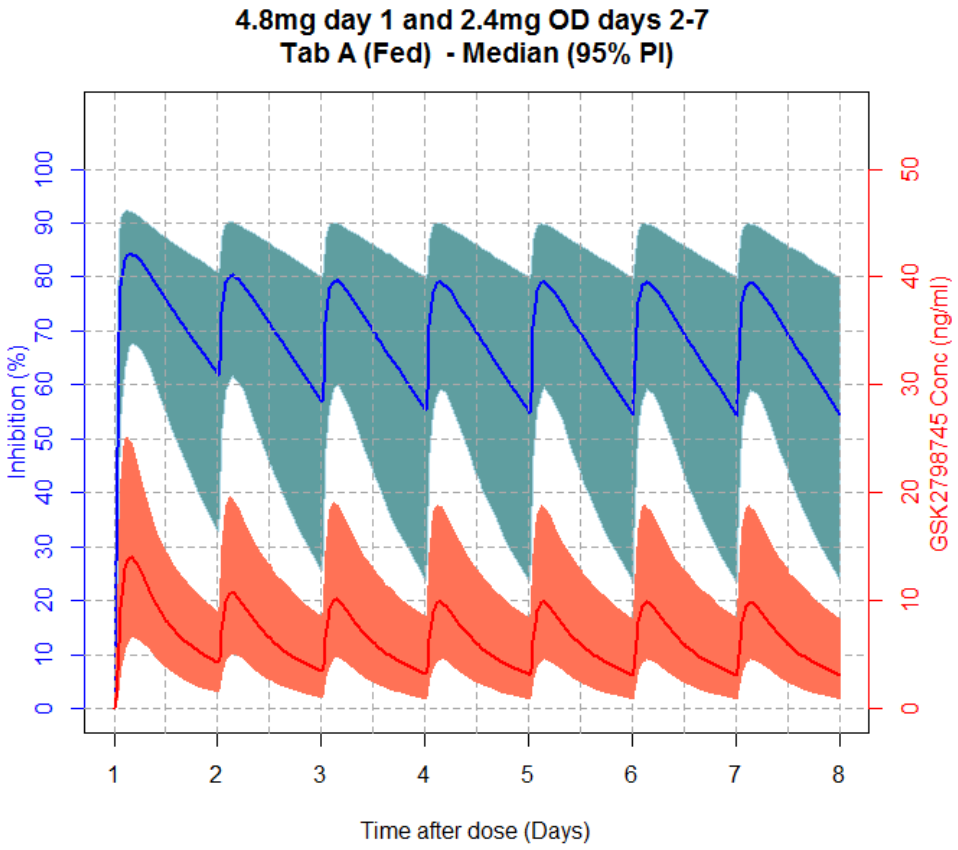


Table 1 Predicted exposure, probability of exceeding threshold and TRPV4 percent inhibition

4.8 mg on Day 1 and 2.4 mg OD Days 2–7	24 h exposure	Median (95% PI)		% Probability that ≥ 1 of 40 participants exceed threshold of		%TRPV4 inhibition over 24-hour period Median (95% PI)
		AUC24 (ng*hr/mL)	C_{max} (ug/mL)	AUC24 (513 ng*hr/mL)	C_{max} (50 ng/mL)	
With food	Day 1	201.5 (127.5 – 302.8)	18.7 (11.2 – 29.8)	0	0	72.0 (56.5 – 82.6)
	Day 7	147.6 (79.4 – 281.1)	13.1 (7.5 – 22.8)	2.0	0.2	67.3 (46.6 – 83.6)
Without food	Day 1	202.0 (128.3 – 303.5)	22.7 (15.3 – 34.2)	0	0.6	72.0 (55.3 – 83.4)
	Day 7	141.5 (76.6 – 269.7)	14.9 (9.1 – 24.8)	1.8	0.4	65.7 (44.2 – 82.7)

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Chronic idiopathic cough for ≥1 year (before screening), defined as: • a cough that is unresponsive to at least 8 weeks of targeted treatment, **or** • a cough for which no objective evidence of an underlying trigger has been determined, despite medical investigations. 3. No significant findings on chest imaging (CXR or CT scan) within 12 months before screening (participants with an abnormal CXR within 12 months, from a temporary process, will be allowed to participate if a repeat CXR is normal). 4. FEV1 ≥80% of the predicted normal value (at screening), or documented evidence of FEV1 ≥80% within the 6 months before screening. 5. Score of ≥40 mm on the Cough Severity VAS at Screening.

WEIGHT
6. Body weight ≥50 kg and body mass index (BMI) within the range 18 to 40 kg/m^2 (inclusive) at screening.

SEX
7. Male or female **a.Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of this protocol from the time of first dose of study treatment until 2 weeks after last dose of study treatment, and refrain from donating sperm during this period. **b.Female participants:** A female participant is eligible to participate if she is **not of childbearing potential** as defined in Appendix 5.

INFORMED CONSENT
8. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or current evidence of any serious or clinically significant gastrointestinal, renal, endocrine, neurologic, hematologic or other condition that is uncontrolled on permitted therapies or that would, in the opinion of the investigator or the medical monitor, make the participant unsuitable for inclusion in this study.
2. History or current evidence of chronic productive cough.
3. History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the 6 months before screening.
4. Active ulcer disease or gastrointestinal bleeding at the time of screening (positive fecal occult blood test [FOBT] at screening).
5. History of stroke or seizure disorder within 5 years of screening.
6. Respiratory tract infection within 6 weeks of screening.
7. Participant who, in the investigator's opinion, poses a significant suicide risk. Evidence of serious suicide risk may include any history of suicidal behaviour and/or any evidence of suicidal ideation on any questionnaires e.g. Type 4 or 5 on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last 6 months (assessed at screening).
8. Alanine transferase (ALT) >2x upper limit of normal (ULN) at screening.
9. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. QTc >450 msec or QTc >480 msec in participants with bundle branch block at screening. *NOTE: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.*

PRIOR/CONCOMITANT THERAPY
12. Use of a listed prohibited medication (Section 7.7) within the restricted timeframe relative to the first dose of study treatment. 13. Use of a strong inhibitors or inducers of cytochrome P450 (CYP) 3A or p-glycoprotein (Section 7.7).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months of screening. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. Current enrollment or past participation within the 3 months before screening in any clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS
17. Positive human immunodeficiency virus (HIV) antibody test at screening. 18. Presence of Hepatitis B surface antigen (HBsAg) at screening. 19. Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. *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.* 20. 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 are not required to also undergo Hepatitis C RNA testing.* 21. Cardiac troponin at screening > ULN for the assay.

OTHER EXCLUSIONS
22. History of alcohol abuse within 6 months of screening, in the opinion of the investigator. 23. Current smoker or history of smoking within the 6 months before screening, or a cumulative history of ≥ 20 pack years. *Pack years = (No. of cigarettes smoked/day/20) x (No. of years smoked)* 24. 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.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants are not permitted to consume red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the start of study treatment until the end of study treatment (in both Treatment Periods).

6.3.2. Alcohol and Tobacco

- During each Treatment Period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample on Day 7.
- Only non-smokers may be recruited into this study.

6.3.3. 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 (e.g. walking, watching television, reading).
- Participants will be instructed to avoid noisy environments 24 hours before the audiometry assessments.
- Participants will be asked to stay awake for 10 hours after attachment of the cough monitor, and to avoid noisy environments whilst wearing the cough monitor

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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, and any SAEs.

Participants may be rescreened once. If rescreening is performed, participants must be assigned a different unique subject identification number for the rescreening, and all screening procedures must be repeated. See the study reference manual (SRM) for more details.

In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the subject will be considered a screen failure.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK2798745	Matching Placebo
Dosage formulation:	White to almost white, round, film-coated tablet. Tablet A (micronized active pharmaceutical ingredient [API])	White to almost white, round, film-coated tablet
Unit dose strength:	2.4 mg	Not applicable
Route of Administration	Oral	Oral
Dosing instructions:	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).	Two tablets to be taken on Day 1. One tablet to be taken on Days 2 to 7. All doses to be taken with a glass of water (~240 mL) at about the same time each day (±2 hours relative to dosing on Day 1).
Packaging and Labelling	GSK2798745 tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.	Placebo tablets will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures that include induction-seal liners. Each bottle will be labelled as required per country requirement.
Manufacturer	GSK	GSK

7.1.1. Medical Devices

- The VitaloJAK (Model 7100; manufactured by Vitalograph Ltd) will be used to sense and record coughs for up to 24 hours (baseline and Day 7 in each treatment period). The VitaloJAK has a CE mark, indicating compliance to the Medical Devices Directive of the European Community (see Section 9.1.1).
- Instructions for using the VitaloJAK will be provided in a study-specific manual provided by Vitalograph.

7.2. Dose Modification

No dose modifications are permitted without submission of a substantial amendment to the protocol.

7.3. Method of Treatment Assignment

All participants will be centrally randomised using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and instructions for the IWRS will be provided to each site. Participants will be registered using the IWRS, and assigned a unique number (randomisation number). The randomisation number encodes the participant's assignment to one of the 2 treatment sequences shown in Table 2, according to the randomisation schedule generated prior to the study by the Clinical Statistics Department at GSK. In the randomisation, participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months). Each participant will be dispensed blinded study treatment, labelled with his/her unique randomisation number.

Table 2 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2
AB	Placebo tablets for 7 days	GSK2798745 tablets for 7 days
BA	GSK2798745 tablets for 7 days	Placebo tablets for 7 days

Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (SOA) (Section 2.2). Returned study treatment should not be re-dispensed.

7.4. Blinding

This will be a double blind (sponsor open) study. All study staff involved in clinical assessments (which includes the investigator, sub-investigators, other site staff), and the participant will be blinded to the treatment allocated to individual participants. Selected sponsor study team members (and delegates if programming activities are outsourced) will be unblinded to perform the interim analysis. This may include the medical monitor, study statistician, study programmer (and delegates) and study pharmacokineticist; however, only the statistician and programmer (and delegates) will have access to individual participant level data. Access to unblinded data will be kept to the minimum set of individuals required to implement any interim analyses, but may include GSK management/review committees if alterations to the study conduct are required. Details of who were unblinded to what data and when will be included in the clinical study report.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.

The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

A participant will be withdrawn if the participant's treatment 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.

A participant whose treatment sequence assignment is inadvertently unblinded (either to investigative staff or the participant themselves) will be permitted to remain in the study, although the accidental unblinding will be recorded as a protocol deviation and hence the participant will be subject to review as to their inclusion in analyses.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. 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.

7.6. Treatment Compliance

Participants will take the study treatment at home on Day 2 to 6. Compliance will be assessed at the end of each Treatment Period by reviewing the participant diary card and questioning the participant. A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance

records. Treatment start and stop dates will be recorded in the CRF for Day 1, 6 and 7 of each Treatment Period.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), approved by the investigator, in consultation with the GSK Medical Monitor, that the participant is receiving at the time of enrolment, or receives during the study, must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications

Paracetamol at doses of ≤3 grams/day is permitted for use any time during the study.

Other concomitant medication will be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

Stable use of some medications may be permitted if the dose is stable for at least 3 months prior to Day 1, and the medication was prescribed for an indication other than cough. The dose should remain constant throughout the study. Changes in dose are not permitted, unless required for safety or tolerability. These willl be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

7.7.2. Prohibited Medications

Except for the permitted medication noted above and those approved by the investigator in consultation with the GSK Medical Monitor (Section 7.7.1), participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) or 30 days for ACE inhibitors, before the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study.

During the study, participants should not use drugs that are strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp), because they may alter GSK2798745 concentrations. The list of background therapy/drugs may be modified based on emerging data. These include, but are not limited to, those listed in Table 3.

Table 3 Strong inducers/inhibitors of CYP3A4 and P-gp

Antiretrovirals:	atazanavir, danoprevir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir
Antibiotics:	clarithromycin, telithromycin, troleandomycin, rifampin
Oral antifungals:	ketoconazole, itraconazole, voriconazole
Antidepressant	nefazadone
Immunosuppressant	cyclosporine
Anti-Epileptic	carbamazepine, phenytoin

GSK2798745 has weak CYP3A4 inhibition potential. It is possible that concentrations of drugs that are substrates of CYP3A4 may be increased. HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, are examples of CYP3A4 substrates that might be taken by the eligible participants. Participants being treated with simvastatin will be allowed to participate in the study, as long as their dose is ≤20 mg once daily. Participants being treated with >20 mg once daily simvastatin will be considered on a case basis by the investigator in consultation with the GSK Medical Monitor. Participants being treated with atorvastatin of any therapeutic dose are allowed to participate in the study. The concentration of atorvastatin may be evaluated after the study. The investigators may also consider substitutions of these medications.

It is strongly recommended that participants avoid using drugs that are sensitive substrates of Cytochrome P450 (CYP) 3A4 and/or P-gp or that have a low therapeutic index because concentrations of these substrates may be increased by GSK2798745. If co-administration of medications with interaction potential with GSK2798745 is necessary, investigators should monitor participants for loss of efficacy or consider substitutions of these medications.

All concomitant medications may be reviewed by the Medical Monitor and it will be up to the discretion of the Investigator in consultation with the GSK Medical Monitor, whether the medication can be continued and/or the participant can participate in the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study, because the indication being studied is not life threatening or seriously debilitating.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who withdraw or who are withdrawn from study treatment will be withdrawn from the study. See the SoA (Section 2.1) for assessments to be performed at early withdrawal.

Participants who start taking a prohibited medication during the study will be withdrawn, unless approved by the investigator in consultation with the GSK Medical Monitor.

8.1.1. Adverse Event Stopping Criteria

Participants who experience an adverse event, which in the opinion of the investigator could jeopardise the participant's safety, will be withdrawn from the study.

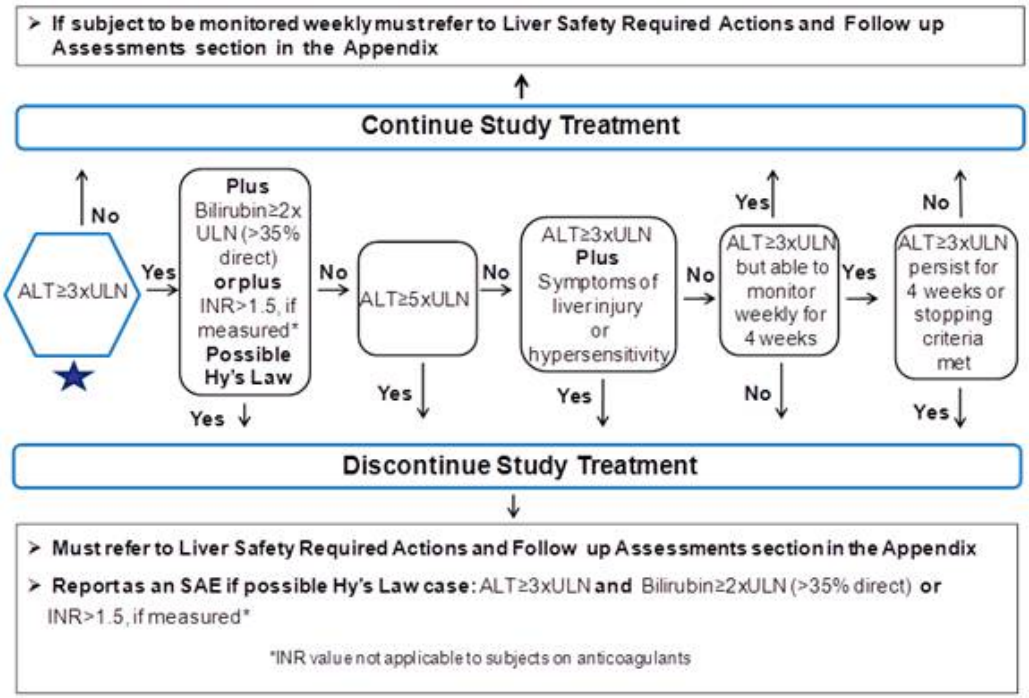
8.1.2. Liver Chemistry Stopping Criteria

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, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 3 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.2.1. Rechallenge

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

8.1.3. QTc Stopping Criteria

If a participant meets either bulleted criterion below, two further ECG recordings should be done (obtained over a brief [e.g. 5 to 10 minute] recording period). A participant who meets either bulleted criterion, based on the average of the triplicate ECG readings, will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

8.1.4. Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria

8.1.4.1. Symptomatic Participant:

If a participant experiences symptoms of cardiac ischemia (e.g. chest pain, increased shortness of breath, and diaphoresis), cardiology consultation should be obtained immediately. GSK2798745 should be discontinued permanently. The participant should be evaluated by a cardiologist and undergo any clinically appropriate testing. The participant should be followed up until symptoms are resolved.

8.1.4.2. Asymptomatic Participant:

Cardiac troponin will be measured pre-dose and at the end of dosing, in each Treatment Period. If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (Day -1, Treatment Period 1), the participant should be assessed for symptoms of cardiac ischemia (as above). If the participant is asymptomatic, the participant can continue in the study after discussion with the Medical Monitor and close monitoring for symptoms.

8.2. 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, behavioural, compliance or administrative reasons.
- 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.
- Refer to the SoA for data to be collected at the time of withdrawal (early withdrawal visit).

8.3. 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 with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA.
- Protocol waivers or exemptions are not allowed
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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.

9.1. Efficacy Assessments

9.1.1. Cough Counting

Cough monitoring will be conducted at the beginning and end of each treatment period, as shown in Section 2 (SOA).

The VitaloJAK cough monitor will be used. The VitaloJAK cough monitor was developed by Prof PPD Dr PPD and Prof PPD at University Hospital of South Manchester NHS Foundation Trust (UHSM), and has been fully validated in clinical studies. The VitaloJAK cough monitor has CE registration and Food and Drug Administration (FDA) 510K clearance.

The VitaloJAK Cough Monitor requires a disposable, single use chest sensor that is attached to the participant's chest, and a 'lapel microphone' that is attached to the participant's clothing. The monitor collects high fidelity recordings, recording all sound frequencies required for the semi-automated analysis of cough. The recording automatically stops at 24 hours.

Kits will be supplied by Vitalograph to the site containing all items required for each 24-hour recording, including the monitor, memory card and battery packs.

Recordings from the VitaloJAK Cough Monitor will be sent to Vitalograph for analysis via the Vitalograph Web Portal. Recordings will be processed through the semi-automated cough analysis system developed by UHSM. Vitalograph will QC check the recordings on receipt. The recording will then be processed to remove non-cough sounds

and silences, leaving a set of segmented files for analysis by a Cough Analyst at Vitalograph.

9.1.2. Cough Visual Analogue Scale (VAS)

Participants will be asked to complete 2 VAS forms, one each to rate the severity of their cough, and their urge to cough (see SRM).

The VAS forms should be completed before other clinical assessments (and before the LCQ), and participants should be given instructions on how to complete the form. The forms will be provided by GSK – the site should **not** make photocopies of the forms, or print from the PDF file.

9.1.2.1. Cough Severity VAS

The participant will be asked: '*How severe was your cough today?*'

The participant will place a mark on a 100 mm horizontal line, rating the severity of their cough from 'Not at all' to 'Extremely'.

9.1.2.2. Urge to Cough VAS

The participant will be asked: '*Please rate the intensity of your urge to cough today*'

The participant will place a mark on a 100 mm horizontal line, rating their urge to cough from 'No urge' to 'Severe urge'.

9.1.3. Leicester Cough Questionnaire (LCQ)

The LCQ is a validated, self-completed, quality of life measure of chronic cough [Birring, 2003]. The questionnaire is designed to assess the impact of cough on various aspects of the participant's life.

The LCQ should be completed after the Cough VAS, but before other clinical assessments, and participants should be given instructions on how to complete the questionnaire. The participant will be asked to read 19 statements, and rate their answer on a 7 point Likert response scale (see SRM).

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the start of treatment until the follow-up visit. However, any SAEs assessed as related to study participation (e.g. study treatment, 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 AEs will be collected from the start of treatment until the follow-up visit.
- Medical occurrences that begin before the start of study treatment, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.
- 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 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- 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 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. 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 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor, will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 Medical Dictionary for Regulatory Activities (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.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

9.3. Treatment of Overdose

For this study, any dose of GSK2798745 greater than the planned dose in the protocol, will be considered an overdose.

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

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

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2798745 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 24 h from the date of the last dose of study treatment 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 will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A full physical examination will include, at a minimum, measuring weight, and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, measuring weight, and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height will be measured at screening only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate.
- At screening, three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. At all other time-points, single measurements will be taken.

9.4.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At screening, triplicate ECG are required: 3 individual ECG tracings should be obtained over a brief (e.g. 5 to 10 minute) recording period.

9.4.4. Audiometry

Audiometry will be performed by authorised, trained staff using standard audiometry techniques. Participants will be instructed to avoid noisy environments 24 h prior to the audiometry assessments. Only air conductance will be performed. It will be at the discretion of the Investigator, Medical Monitor and/or the audiologist to determine if significant changes from baseline are seen and if a bone conductance test should be performed. Details of the audiometry testing are in the SRM.

9.4.5. Chest X-ray

CXR is only required if a participant has not had chest imaging within 12 months of screening. If a participant has had an abnormal CXR within 12 months, from a temporary process, the CXR may be repeated to determine eligibility.

CXR will be performed by authorised, trained staff.

9.4.6. FEV_1

- FEV1 will be measured to assess eligibility. It does not need to be repeated if there is documented evidence of FEV1 ≥80% within the 6 months before screening.
- Spirometry assessments will be performed whilst the subject is in a seated position (if the assessment is done on a bed, the subject's legs should be over the edge).
- Spirometry assessments will be repeated until 3 technically acceptable measurements have been made. To confirm eligibility, 1 or more of the 3 measurements is required to be ≥80%.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 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 7 to 10 days after the last dose of study treatment 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 aetiology 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.

9.4.8. Faecal Occult Blood Test

Based on the preclinical finding of gastric erosions (See Section 3.3.1), FOBT will be performed to determine eligibility and assess any possible study treatment-related GI blood loss.

At each time-point, participants will be given 2 FOBT cards with instructions for completing (using 2 different bowel movements) and returning the tests (in person or by post).

9.4.9. Columbia Suicidality Severity Rating Scale (CSSRS)

Based on preclinical studies that have been conducted, GSK2798745 is considered to be a central nervous system (CNS)-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although GSK2798745 has not been shown to be associated with an increased risk of suicidal thinking or behaviour, GSK considers it important to monitor for such events.

Participants being treated with GSK2798745 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour. Consideration should be given to discontinuing GSK2798745 in participants who experience signs of suicidal ideation or behaviour. Families of participants being treated with GSK2798745 should be alerted about the need to monitor subjects for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour, and to report such symptoms immediately to the study investigator.

The CSSRS is a measure of suicidal ideation and behaviour, with demonstrated predictive validity and reliability. Sections of the CSSRS include suicidal ideation, intensity of ideation, suicidal behaviour, and actual suicide attempt(s). The CSSRS assesses lifetime and current suicidal thoughts and behaviours across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the Principal Investigator or a sub-investigator for the study. See SRM for details of the scale.

At screening, the ‘Baseline’ CSSRS questionnaire will be completed. At all other time-points, the ‘Since Last Visit’ CSSRS questionnaire will be used (see Section 2, SOA).

9.4.10. Diary card

In each Treatment Period, a diary card will be used to collect:

- dosing information for Days 2 to 6 (Date and Time of Dose);
- AEs; and
- concomitant medications.

Between Treatment Periods 1 and 2 (the 'Washout Period'), a diary card will be used to collect AEs and concomitant medications.

Paper diary cards will be used (see SRM).

9.5. Pharmacokinetics

- Blood samples for pharmacokinetic analysis of GSK2798745 will be collected at the timepoints indicated in the SOA (Section 2).
- Blood will be collected in ethylenediaminetetraacetic acid (EDTA) tubes. The actual date and time of each blood sample collection will be recorded.
- The timing and volume of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring of GSK2798745 and, if possible, any relevant GSK2798745 metabolites.
- Additional collection, processing, storage and shipping procedures are provided in the laboratory manual.
- PK analysis will be performed under the control of Platform Technologies and Science-In Vitro/In Vivo Translation (PTS-IVIVT)/ and Third Party Resourcing (TPR) GlaxoSmithKline. Plasma concentrations of GSK2798745 will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).
- Plasma samples may be analyzed for the metabolite M1. GSK may store the remaining plasma from the PK plasma samples for future possible additional metabolite analysis. Additional analysis of compound-related metabolites may be reported under a separate protocol.
- For participants taking atorvastatin, an extra sample will be taken at each PK time-point for analysis of atorvastatin concentration, and possible analysis of atorvastatin metabolites.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Laboratory Manual.

10. STATISTICAL CONSIDERATIONS

This study is designed to estimate the effect of GSK2798745 relative to placebo on day-time cough count totals following seven days of dosing. Day-time cough count totals will be derived from the total number of coughs during the first 10 hours following dosing, during which time the participant is expected to be awake.

The inference to be carried out will be with respect to the following hypothesis:

- Treatment with GSK2798745 leads to an improvement in day-time 10-hour cough count totals compared with placebo.

The above hypothesis will be investigated in this study by means of a Bayesian approach, which will assume a non-informative prior distribution. It is anticipated that the day-time 10-hour cough count totals will be log-transformed before statistical analysis, and hence the treatment effect will be evaluated in terms of a ratio of day-time cough count totals (GSK2798745 / placebo). A day-time cough count total of at least 30% less for GSK2798745 than for placebo is of interest. The posterior probability that the true ratio of the mean effect size of the test treatment and the mean effect size of the reference treatment μ(test) / μ(reference), is less than 0.7, and corresponding 90% credible intervals, will be obtained. The posterior probability that the true ratio is less than 0.7 will be referred to as PP (ratio<0.7).

10.1. Sample Size Determination

A simulation approach has been employed to investigate the chance of correctly determining a positive study with the planned number of participants. An estimate of 0.28 for the within subject variability in cough count totals was obtained from previous studies and this estimate was used in the simulations.

A treatment ratio (active:placebo) of 0.7 is considered to indicate an effective treatment. A treatment ratio of 0.5 is considered to represent a very effective treatment.

A positive study will be declared if the posterior probability that the true treatment ratio is less than 0.7 is more than 70% (PP(ratio <0.7) >70%). Given the planned sample size of 24 participants, if our variability assumptions are correct, then if the true treatment ratio is 0.5, there is a 95.3% probability of correctly declaring success. Conversely, if the true treatment ratio is 1, there is a 0.2% probability of declaring success at the end of the study.

An unblinded sample size re-estimation is planned in addition to the final analysis. This will be performed when at least 12 participants have completed both dosing periods and key assessment data is available. Cleaned efficacy data will be provided by Data Management to the unblinded study statistician.

Estimated treatment ratio of day-time cough counts between GSK2798745 and placebo will be calculated together with 90% credible intervals assuming a non-informative prior. This analysis will be supplemented by deriving predictive and/or conditional power in order to support sample size re-estimation. As a result of the sample size re-estimation, the sample size could be revised either upwards or downwards from the planned sample size of 24 evaluable participants, but the target number of evaluable participants will not exceed 40 participants.

Full details of the plan for the sample size re-estimation will be described in the Reporting and Analysis Plan (RAP).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants screened and for whom a record exists on the study database.
All Subjects	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	All randomised participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Day-time 10-hour cough counts following seven days' dosing of GSK2798745 as compared with placebo will be analysed by first log transforming the day-time 10-hour cough counts recorded on day 7 of each dosing period. The difference between GSK2798745 and placebo in log-transformed count rates will be investigated using a mixed effects model with fixed effects terms for treatment and period. Centre effects and the effect of whether or not the participant has participated in a cough clinical trial (which will be included as a stratification factor in the randomisation) in the previous 12 months will also be investigated. Baseline cough counts may be included in the model as a covariate. Participant will be treated as a random effect in the model. The posterior probability and corresponding 90% credible intervals that the ratio of the mean effect size of the test treatment and the mean effect size of the placebo treatment μ(test) - μ(placebo), is less than 1 will be constructed. In addition, the posterior probability true effect size distribution will be used to obtain estimates for the probabilities that the true effect size falls below thresholds of interest (e.g. what is the probability the true ratio is less than 0.7 and less than 0.5). The presence of carryover effects or treatment by period interaction will also be investigated and, if deemed appropriate, an analysis by period will be undertaken.
Exploratory	Will be described in the reporting and analysis plan.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	For the safety data, no formal hypotheses are being tested and no statistical analyses will be performed. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) will be summarized by treatment and time-point.

10.3.3. Interim Analyses

At least one interim analysis will be conducted during the course of the study. The treatment level results will be made available to the GSK study team who will review the available cough count data before making a decision on whether to:

i) stop the study on the grounds of futility
ii) adjust the sample size, in the event that futility criteria have not been met.

The interim analysis will also include a preliminary assessment of whether there is any evidence for the presence of carryover effects or treatment by period interaction.

Following the interim analysis, any adjustment to the sample size will be communicated to the sites.

The interim analysis will be conducted after at least 12 participants have completed both dosing periods and will look at day-time 10-hour cough count data, as well as supporting PK data, if required.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statisticians (including QC statistician) and programmers will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.3.4. Exploratory Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacokinetics Modelling & Simulation Department within GlaxoSmithKline. Calculations will be based on the actual sampling times recorded during the study. The systemic concentrations of GSK2798745, any metabolites, and atorvastatin will be summarised, as data permit. The details of the PK analysis will be listed in the RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
C_{max}	Maximum observed plasma concentration
CMT2C	Charcot-Marie-Tooth Disease Type 2C
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CSSRS	Columbia Suicidality Severity Rating Scale
CT	Computed tomography
CXR	Chest X-ray
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FOBT	Faecal Occult Blood Test
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
IC_{50}	50% maximal inhibitory concentration
ICF	Informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IVIVT	In Vitro/In Vivo Translations
IWRS	Interactive Web Response System
kg	kilogram
KO	Knockout
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemogloin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSV	MilliSievert
NOAEL	No observed adverse effect level
nM	Nano Molar
P2X3	P2X purinoceptor 3
P-gp	p-glycoprotein
PK	Pharmacokinetic
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPR	Third Party Resourcing
TRPV4	Transient receptor potential vanilloid 4
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White blood cells
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Vitalograph
VitaloJAK

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (Fasting not required)	Calcium	Alkaline phosphatase	Creatinine phosphokinase (CPK)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Cardiac troponin			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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 8.1.2 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and 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 as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

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 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 substantial 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.
- 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.

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative 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 centre.
- 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 multi-centre 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.

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 the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

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 can be found in the source document agreement (to be signed by the investigator (or delegate) at each site).

Study and Site Closure

GSK or its 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:

- 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 treatment development.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> 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 (eg, 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 /AE/SAE CRF page.
- 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 sufficiently 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) **within 72 hours** of SAE entry into the eCRF.
- 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 (who is also the SAE coordinator) by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF (only necessary when electronic data collection tool is not available)
• The SAE paper CRF should be emailed to the medical monitor (who is also the SAE coordinator). • In rare circumstances, if email is not possible, 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of 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) and estradiol 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, a single FSH and estradiol measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 6.1.

- In addition, male participants must refrain from donating sperm from the time of first dose of study treatment until 2 weeks after last dose of study treatment.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*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 drug. 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.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- 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 2 weeks of learning of the partner's pregnancy.
- 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.

12.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2798745 or chronic cough and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2798745 (or study treatments of this drug class), and chronic cough. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analysed if it is hypothesised that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2798745 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2798745 (or study treatments of this class) or chronic cough continues, but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II 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 ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</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 chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (defined as Day -1; Treatment Period 1) (see MONITORING below)
• Do not restart/rechallenge participant with study treatment (not allowed under this protocol)
• Permanently discontinue study treatment and continue any protocol specified follow up assessments</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis, within 24 hours after last dose[5]
• 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</td></tr>
</table>

MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 h** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in 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 pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) 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
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant'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 laboratory manual.

References

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

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Protocol Amendment 2 (22-NOV-2017)

Overall Rationale for the Amendment: The protocol was amended in response to comments from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Section # and Name	Description of Change	Brief Rationale
Section 2.1 (Screening and Follow-up Schedule of Activities)	Addition of the Columbia Suicidality Severity Rating Scale (CSSRS) at Follow-up.	Requested by the MHRA.
Section 7.4 (Blinding)	The following change was made*: In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. ~~If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.~~ If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.*	Requested by the MHRA.
Section 8.1.1 (Adverse Event Stopping Criteria)	Addition of the following section: ***8.1.1 Adverse Event Stopping Criteria*** *Participants who experience an adverse event, which in the opinion of the investigator could jeopardise the participant's safety, will be withdrawn from the study.*	Requested by the MHRA.

Protocol Amendment 1 09-OCT-2017

Overall Rationale for the Amendment: The primary reason for amending the protocol is the removal of the Simplified Nutritional Appetite Questionnaire (SNAQ). The

original protocol included the SNAQ, because of the preclinical finding of reduced food consumption in dogs (30 mg/kg/day) and rats (300 mg/kg/day). Since the publication of the original protocol, data has been reviewed from a study of GSK2798745 in heart failure patients. Participants took 2.4 mg GSK2798745 (n=10) or placebo (n=12) for 7 days. As shown in the table below, there was no observable difference in weight and appetite in participants receiving GSK2798745 and placebo. Therefore, the GSK Global Safety Board agreed to the removal of the SNAQ from future protocols. Weight will be measured at screening, follow-up, and the beginning and end of each Treatment Period, and adverse events that may be associated with low food consumption will be reviewed.

	Baseline (mean ± SD)	**Day 7 (mean ± SD)**	**Change from Baseline**
Weight (kg)			
2.4 mg	87.44 ± 18.54	87.67± 17.50	0.23
Placebo	83.58 ± 10.46	83.33 ± 10.56	-0.25
SNAQ Score (Maximum = 20)			
2.4 mg	16.2 ± 1.69	16.7 ± 1.95	0.5 ± 1.18
Placebo	15.3 ± 1.83	16.2 ± 1.53	0.8 ± 1.11

Section # and Name	**Description of Change**	**Brief Rationale**
Section 2.1 (Screening and Follow-up Schedule of Activities)	Removal of the SNAQ at the follow-up visit. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. The option for a CT scan at screening was included in the original protocol, in error. If chest imaging (chest x-ray or CT scan) has not been conducted within 12 months of screening, a chest x-ray will be conducted.
Section 2.2 (Treatment Period 1 and 2 Schedule of Activities)	Removal of the SNAQ at Day -1 and Day 8, in each Treatment Period.	Rationale for removal of the SNAQ described above.
Section 3.3.1 (Risk Assessment)	Removal of the SNAQ. Removal of the option for a CT scan at screening.	Rationale for removal of the SNAQ described above. Rationale for removal of CT scan at screening described above.

Section # and Name	Description of Change	Brief Rationale
Section 7.7.1 (Permitted Medications)	The following change was made: *Stable use of some medications may be permitted if the dose is stable for at least ~~28 days~~ **3 months** prior to Day 1.*	Time period of stable dose changed from 28 days to 3 months, because 28 days might not be sufficient to achieve stable dosing of some permitted medications.
Section 8.1.3.2 (Symptoms of Cardiac Ischemia and Cardiac Troponin Stopping Criteria: Asymptomatic Participant)	The following change was made: *If any cardiac troponin assessment is >ULN or >2 times the participant's baseline value (~~Screening~~ **Day -1, Treatment Period 1**), the participant should be assessed for symptoms of cardiac ischemia (as above).*	Definition of baseline changed from Screening to Treatment Period 1, Day -1 to be consistent with the baseline used for other laboratory tests.
Section 9.4.5 (Simplified Nutritional Appetite Questionnaire)	Removal of complete section.	Rationale for removal of the SNAQ described above.
Section 9.4.6 (Chest Imaging)	Removal of the option for a CT scan at screening.	Rationale for removal of CT scan at screening described above.
Section 9.4.9 (Columbia Suicidality Severity Rating Scale (CSSRS)	Addition of text stating that families of participants should be alerted about monitoring for emergence of suicidal ideation and behaviour.	New text added to ensure compliance with GSK's *Global Safety Board-Approved Recommendations for Prospective Assessment of Suicidal Ideation and Behaviour in Relevant Clinical Studies*.
Section 9.5 (Pharmacokinetics)	Blood sample volume removed.	Blood volume of sample removed, as this is still to be confirmed. Sample collection instructions to be provided in the laboratory manual.