TITLE PAGE

Protocol Title: A Single Centre, Double Blind (Sponsor Open), Placebo Controlled, 3-Period Crossover, Ascending Dose Study in Japanese Healthy Elderly Male Subjects to Evaluate the Safety, Tolerability and Pharmacokinetics of Danirixin in the Fed State (Part1) and an open label, 2-way crossover to evaluate food effect on the pharmacokinetics of Danirixin (Part2).

Protocol Number: 206817

Short Title: Phase I study of Danirixin in Japanese healthy elderly male subjects

Compound Number: GSK1325756

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1. SYNOPSIS

Protocol Title: A Single Centre, Double Blind (Sponsor Open), Placebo Controlled, 3-Period Crossover, Ascending Dose Study in Japanese Healthy Elderly Male Subjects to Evaluate the Safety, Tolerability and Pharmacokinetics of Danirixin in the Fed State (Part1) and an open label, 2-way crossover to evaluate food effect on the pharmacokinetics of Danirixin (Part2).

Short Title: Phase I study of Danirixin in Japanese healthy elderly male subjects

Rationale: The primary objective of this study is to assess the safety, tolerability and pharmacokinetics (PK) following single doses of GSK1325756H (Hydrobromide Salt Tablet Formulations of Danirixin) 10, 50 and 100 mg, and to investigate a potential food effect on PK of GSK1325756 following a single dose of GSK1325756H 50 mg in healthy Japanese subjects of over 65 years of age inclusive. This is the first study in which GSK1325756 will be administered in a Japanese population.

Objectives and Endpoints:

Objectives	Endpoints
Part 1 • To assess the safety, tolerability and PK following single doses of GSK1325756H 10, 50 and 100 mg in the fed state in healthy Japanese subjects of over 65 years of age inclusive. **Part 2** • To investigate the safety, tolerability and food effect on PK of GSK1325756 following a single dose of 50 mg in the fed and fasted state, in healthy Japanese subjects of over 65 years of age inclusive.	**Part 1 and 2** • Adverse events (AEs) • Change from baseline of clinical laboratory values, vital signs, and electrocardiogram (ECG) parameters • Blood concentration of GSK1325756 • Cmax, AUC(0-t), AUC(0-inf), AUC(0-24), tmax, t1/2, tlag, tlast of the blood concentration of GSK1325756, as data permit

Overall Design: This study consists of two parts; Part 1 is a double blind, placebo-controlled, 3-period crossover, ascending dose, single oral administration in the fed condition and Part 2 is an open label, 2-way crossover, single oral dose in the fed and fasted state. After screening in each Part, subjects will be randomized and receive the treatments. A minimum 7-day wash-out period will occur between each treatment period.

Number of Participants: Sufficient participants will be randomised such that approximately 18 and 16 evaluable participants complete the study of Part 1 and Part 2, respectively.

Treatment Groups and Duration:

Subjects will be divided into the study of Part 1 and 2, and receive the following study treatment doses shown below;

Part 1

This is a double blind, placebo-controlled, 3-period crossover, ascending dose, single oral administration in the fed condition. After screening, during treatment periods 1 to 3, subjects will be randomized to receive:

- GSK1325756H 10 mg , single dose, in the fed state
- GSK1325756H 50 mg, single dose, in the fed state
- GSK1325756H 100 mg, single dose, in the fed state, or
- Placebo, single dose, in the fed state

Subjects will have a screening visit within 30 days prior to the first dose of study. A minimum washout period of 7 days will be required between each treatment period. Subjects will receive three treatment periods in the study. Subjects will be housed in the Clinical Research Unit from Day -1 (the day before dosing) through Day 3 for Period 1 and 2, and from Day -1 (the day before dosing) through Day 4 for Period 3. Subjects will return to the clinic 7 days (at least) after the previous administration day for Period 1 and 2, and subjects will visit the unit on Day 8 (+/- 1 day) of the last dosing for Period 3 for follow-up.

Group	n	Period 1	Washout	Period 2	Washout	Period 3
A	6	10 mg	at least 7 days	50 mg	at least 7 days	Placebo
B	6	10 mg		Placebo		100 mg
C	6	Placebo		50 mg		100 mg

Part 2

This is an open label, 2-way crossover, single oral dose in the fed and fasted state study. After screening, subjects will be randomized and receive the treatments in the fed and fasted condition.

Subjects will have a screening visit within 30 days prior to the first dose of study treatment, two treatment periods separated by at least 7 days, and follow-up. Subjects will be housed in the Clinical Research Unit from Day -1 (the day before dosing) through Day 3 (for Period 1 and 2), and re-visit 7 (±1) days after the last dose of Period 2 for follow-up.

Group	n	Period 1	Washout	Period 2
D	8	50 mg, fed	at least 7 days	50 mg, fasted
E	8	50 mg, fasted		50 mg, fed

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Time and Events Table

Part 1, Period 1-2

Day	Screening	Day-1	Day 1													Day 2	Day 3
Time post-dose			Pre-dose	0 h	0.25 h	0.5 h	0.75 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	48 h
Informed consent	X																
Subject demography /Medical history	X																
Height, Weight, BMI	X																
Urine drug screen	X																
Serological test	X																
Physical examination	X	X	X								X					X	X
Vital signs (PR, BP, temp)	X	X	X								X					X	X
12-lead ECG	X	X	X								X					X	X
Ophthalmic examination	X[3]																
SAEs[2]	<==========																==========>
AEs[2]	<==========																==========>
Con Med review	<==========																==========>
Hematology, clinical chemistry and urinalysis	X	X															X
Administration				X													
PK sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Admission		X															
Discharge																	X

1. Screening visit will occur only prior to the first dosing. Treatment Period 2 will occur after at least 7-days wash-out period. High fat meal will be started and completed before within 30 minutes of GSK1325756H/Placebo dosing.
2. All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified (see Section 9.1 Adverse Events).

3. Ophthalmic examinations are conducted on the day between Screening and Day-1. However, it is not carried out for those who are ineligible due to other screening criteria.

Part 1, Period 3

Day	Day-1	Day 1													Day 2	Day 3		Day 4	Follow up [2,3]
Time post-dose		Pre-dose	0 h	0.25 h	0.5 h	0.75 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	48 h	60 h	72 h	
Physical examination	X	X								X					X	X		X	X
Vital signs (PR, BP, temp)	X	X								X					X	X		X	X
12-lead ECG	X	X								X					X	X		X	X
Ophthaimic examination																			X
SAEs	<==========>																		
AEs	<==========>																		
Con Med review	<==========>																		
Hematology, clinical chemistry and urinalysis	X																	X	X
Administration			X																
PK sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Admission	X																		
Discharge																		X	

1. Treatment Period 3 will occur after at least 7-days wash-out period. High fat meal will be started and completed before within 30 minutes of GSK1325756/Placebo dosing.
2. Follow up visit will occur after 7 days (+/- 1day) of the last dosing.
3. In the case where the subject has discontinued the study prematurely, the assessments for follow up will be carried out.

Part 2, Period 1-2

Day	Screening	Day-1	Day 1													Day 2	Day 3	Follow up[3,5]
Time post-dose			Pre-dose	0 h	0.25 h	0.5 h	0.75 h	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	48 h	
Informed consent	X																	
Subject demography /Medical history	X																	
Height, Weight, BMI	X																	
Urine drug screen	X																	
Serological test	X																	
Physical examination	X	X	X								X					X	X	X
Vital signs (PR, BP, temp)	X	X	X								X					X	X	X
12-lead ECG	X	X	X								X					X	X	X
Ophthalmic examination	X[6]																	X
SAEs[4]	<==========																	==========>
AEs[4]	<==========																	==========>
Con Med review	<==========																	==========>
Hematology, clinical chemistry and urinalysis	X	X															X	X
Administration				X														
PK sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Admission		X																
Discharge																	X	

1. Screening visit will occur only prior to the first dosing. Treatment Period 2 will occur after at least 7-days wash-out period.
2. For the fed condition, meal will be started and completed before within 30 minutes of GSK1325756H dosing.
3. Follow up visit will occur after 7-days (+/- 1day) of the last dosing.
4. All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified. All AEs will be collected from the start of treatment until the follow-up visit at the time points specified (see Section 9.1.Adverse Events).
5. In the case where the subject has discontinued the study prematurely, the assessments for follow up will be carried out.
6. Ophthalmic examinations are conducted on the day between Screening and Day-1. However, it is not carried out for those who are ineligible due to other screening criteria.

- The timing and number of planned study assessments, including safety, tolerability, and PK 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 blood 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 Institutional Review Board (IRB) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF).

3. INTRODUCTION

GSK1325756 is a selective CXC chemokine receptor 2 (CXCR2) antagonist being developed as a potential anti-inflammatory agent for the treatment of chronic obstructive pulmonary disease (COPD) and evaluated for its potential to reduce pulmonary morbidity in hospitalized patients with viral respiratory tract infections.

3.1. Study Rationale

The primary objective of this study is to assess the safety, tolerability and PK following single doses of GSK1325756H 10, 50 and 100 mg (Part 1), and to investigate a potential food effect on PK of GSK1325756 following a single dose of GSK1325756H 50 mg in healthy Japanese subjects of over 65 years of age inclusive (Part 2). This is the first study in which GSK1325756 will be administered in a Japanese population.

The current study will provide an understanding of the PK of the hydrobromide salt of GSK1325756 in a population of healthy elderly subjects. The effect of food on the PK of the GSK1325756H will also be addressed in this population based on PMDA's advice. The outcome of this study will contribute to the selection of the most appropriate dosing regimen for Phase IIa study in Japan.

3.2. Background

GSK1325756 is a non-peptide, high affinity, selective, and reversible CXCR2 antagonist, which has demonstrated potent antagonism of CXCR2 activity both in vitro and in vivo in preclinical studies. There is a large body of evidence indicating that the chemokine receptor CXCR2 plays a pivotal role in neutrophil recruitment to the lung [Chapman, 2009]. Expressed on the surface of neutrophils and several other cell types of hematopoietic and non-hematopoietic origin, the CXCR2 receptor binds ELR^+ cytokines such as CXC chemokine ligand 8 (CXCL8) or interleukin-8 (IL-8). For neutrophils, chemokine binding to CXCR2 results in chemotaxis and cell activation, releasing of a number of inflammatory mediators and proteinases thought to contribute to the progressive fibrosis, airway stenosis, and destruction of the lung parenchyma characteristic of COPD. Lazaar and colleagues [Lazaar, 2011] demonstrated the ability for the CXCR2 antagonist, SB-656933, to reduce neutrophil recruitment into the lung in an experimental human model of lung inflammation. This evidence supports the strategy for selective antagonism of the interaction between CXCR2 and its various chemokine ligands as a mechanism for reducing neutrophil migration into the lung.

As reported in the Investigator's Brochure [GlaxoSmithKline Document Number YM2010/00163/07], in six completed studies using GSK1325756, 210 healthy non-Japanese subjects have received either single doses of GSK1325756 up to 400 mg or repeat doses of 50 mg and 200 mg (once daily for 14 days). GSK1325756 has been well-tolerated and most AEs were mild to moderate in intensity. The most commonly observed AEs were headache and diarrhea. There were no clinically significant changes in vital signs, ECG parameters or laboratory assessments at any oral or intravenous dose of GSK1325756. There were no severe or serious adverse events (SAE) reported.

The clinical trial in patients with COPD (200163) has been completed dosing but has not been reported. In Part A of the 200163 study, 9 COPD patients received GSK1325756 50 mg or placebo bis in die (BID) for 14 days. One subject reported an SAE of worsening arthrosis that was not attributed to study drug by the investigator and the subject was not withdrawn from the study. No vital sign, ECG or safety laboratory abnormalities were reported as an AE in Part A. Part B of the COPD study has completed dosing. Subjects have received GSK1325756 75 mg (n = 45) or placebo (n = 48) BID for 52 weeks. Twenty subjects in Part B (10 in each treatment group) have reported 49 SAEs, the majority of which have been COPD exacerbations. Only two SAEs (both COPD exacerbations in subjects on placebo) were attributed to study drug by the investigator. There has been one death, in a subject who developed liver failure on placebo; this event was not attributed to the study drug by the investigator.

GSK1325756 is in Phase II development as a novel, oral anti-inflammatory agent for the maintenance treatment of COPD and as a treatment for hospitalized influenza infection.

More information about the non-clinical and clinical studies is available in the IB, including its Supplement [GlaxoSmithKline Document Number YM2010/00163/07].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK1325756 may be found in the IB. The following section outlines the risk assessment and mitigation strategy for this protocol:

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Impact – eligibility criteria	Mitigation Strategy
Investigational Product (IP) [e.g., GSK1325756]			
Reduction in peripheral blood neutrophil count	Observed with other molecules with CXCR2 antagonist activity, including after single doses; has not been observed with GSK competitive reversible CXCR2 antagonists elubrixin [Lazaar, 2011] and GSK1325756 in healthy volunteers or COPD subjects, including elderly subjects, dosed with GSK1325756 up to one year.	A subject's peripheral blood neutrophil count must be within the normal range.	Refer to Time and Events Table Section 2 for neutrophil monitoring. Any subject that has a peripheral blood neutrophil count of < 1.0 x 10^9 cells/L that is confirmed with repeat testing will be withdrawn from the study and monitored daily until the neutrophil count returns to the pre-dose value.
Infection Risk	Neutrophils are an important component of host defense and innate immunity. Inhibition of neutrophil migration and activation could impact host defense and innate immunity. No increase in pneumonia has been observed in COPD patients dosed for one year or in patients with influenza.	A subject's peripheral blood neutrophil count must be within the normal range.	Careful monitoring of adverse events
Testicular toxicity	Testis and epididymal effects occurred in dogs following 6 or 7 non-tolerated oral doses of 300 or 1000 mg/kg/day following suspension dosing and at doses of	Subjects who are able to follow the contraceptive guidance are eligible.	Contraceptive guidance and collection of pregnancy information will be implemented as in Appendix 5. Subjects who are unable to follow

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Impact – eligibility criteria	Mitigation Strategy
	30 mg/kg/day following 39 weeks of dosing. In rats, testicular changes and secondary effects on the epididymis occurred after administration of GSK1325756H at oral doses of 500 mg/kg/day following 4 weeks of dosing which were similar to those seen previously with GSK1325756B at equivalent exposures. There have been no reported testicular effects in clinical studies up to one year in duration.		the contraceptive guidance are ineligible. Standard safety monitoring will be implemented. The potential risk of testicular injury is described in the ICF. From PK modeling, it is predicted that the risk of the exposure in subjects receiving 50 mg of GSK1325756H twice daily to exceed twice the AUC(0-24) of NOAEL for testicular influence is low.
Photosensitivity	The UV/visible spectrum for GSK1325756, exhibits an absorbance maximum at 323 nm, which is within the range of natural sunlight (290 – 700 nm). Concentrations of drug-related material observed in the uveal tract/retina and pigmented skin were highest at 6 hours after dosing (i.e., 13.1 and 3.59 µg equiv/g tissue, respectively), representing tissue:plasma radioactivity concentrations of 3.29 and 0.9, respectively. In addition there was evidence of retention of drug-related material in the uveal	Subjects who are able to avoid direct exposure to sunlight are eligible.	Avoid direct exposure to sunlight for as long as possible using a hat appropriate sunscreen treatment etc.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Impact – eligibility criteria	Mitigation Strategy
	tract/retina at 35 days following a single dose.		
Gastrointestinal (GI) effects (abdominal pain, diarrhoea)	GI effects (e.g., erosion or ulceration) were observed in animal toxicology studies with GSK1325756B but not hydrobromide salt formulation. In one study CX3114922, 7 events of mild, self-limiting diarrhea were reported in 5 subjects receiving GSK1325756B.	The safety margins between nonclinical NOAEL exposure levels and clinical exposure levels are currently considered sufficient to support long term clinical studies up to 75 mg BID.	Closely monitor, paying particular attention to a possible association with GI effects, and collect information on and characterize GI effects.

3.3.2. Benefit Assessment

There is no direct medical benefit to the subjects from taking part in this study. The information obtained from this study will contribute to the development of GSK1325756 and may benefit patients in the future. The overall risk benefit balance is considered to be acceptable.

3.3.3. Overall Benefit:Risk Conclusion

Appropriate measures have been taken to minimize the risk to subjects in this study through eligibility criteria and consideration of burden relative to study procedures. It is acceptable to conduct this study in healthy elderly volunteers, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical research unit with access to hospital emergency facilities.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1 • To assess the safety, tolerability and PK following single doses of GSK1325756H 10, 50 and 100 mg in the fed state in healthy Japanese subjects of over 65 years of age inclusive. **Part 2** • To investigate the safety, tolerability and food effect on PK of GSK1325756 following a single dose of 50 mg in the fed and fasted state, in healthy Japanese subjects of over 65 years of age inclusive.	**Part 1 and 2** • AEs • Change from baseline of clinical laboratory values, vital signs, and ECG parameters • Blood concentration of GSK1325756 • Cmax, AUC(0-t), AUC(0-inf), AUC(0-24), tmax, t1/2, tlag, tlast of the blood concentration of GSK1325756, as data permit

5. STUDY DESIGN

5.1. Overall Design

This study consists of two parts;

Part 1

This is a double blind, placebo-controlled, 3-period crossover, ascending dose, single oral administration in the fed condition (high fat meal). During treatment periods 1 to 3, subjects will be randomized and receive the treatments:

- GSK1325756H 10 mg, single dose, in the fed state
- GSK1325756H 50 mg, single dose, in the fed state
- GSK1325756H 100 mg, single dose, in the fed state, or
- Placebo, single dose, in the fed state

Subjects will have a screening visit within 30 days prior to the first dose of study treatment. A minimum washout period of 7 days from the dose of GSK1325756 will be required between each treatment period. Subjects will receive three treatment periods in the study. Subjects will be housed in the Clinical Research Unit from Day -1 (the day before dosing) through Day 3 for Period 1 and 2, from Day -1 (the day before dosing) through Day 4 for Period 3. Subjects will return to the clinic 7 days (at least) after the previous administration day for Period 1 and 2, and subjects will visit the unit on Day 8 (+/- 1 day) of the last dosing for Part 3 for follow-up.

For each dosing period, the progress to the next period will be determined by GSK medical monitor and investigator based on the blinded safety profiles (AE, clinical laboratory values, vital signs and 12-lead ECG). Furthermore, for the progresses Period 2 to Period 3, GSK medical monitor will determine the appropriateness of the progresses Period 2 to Period 3 based on the result of blood concentration of GSK1325756 assessed by the sponsor's person who is responsible for confirmation of concentration under unblind.

Table 2 Dose regimen for GSK1325756H or placebo

Group	n	Period 1	Washout	Period 2	Washout	Period 3
A	6	10 mg	at least 7 days	50 mg	at least 7 days	Placebo
B	6	10 mg		Placebo		100 mg
C	6	Placebo		50 mg		100 mg

Part 2

This is an open label, 2-way crossover, single oral dose in the fed (low fat meal) and fasted states.

Subjects will have a screening visit within 30 days prior to the first dose of study treatment, two treatment periods separated by at least 7 days, and follow-up. Subjects will be housed in the Clinical Research Unit from Day -1 (the day before dosing) through Day 3 (for Period 1 and 2), and re-visit 7 (±1) days after the last dose of Period 2 for follow-up.

The initiation of Part 2 will be determined by GSK medical monitor and investigator based on the review of the blinded safety (AE, clinical laboratory values, vital signs and 12-lead ECG). Furthermore, GSK medical monitor will determine the appropriateness of the initiation of Part 2 based on the result of blood concentration of GSK1325756

assessed by the sponsor's person who is responsible for confirmation of concentration under unblind..

Table 3 Dose regimen for GSK1325756H

Group	n	Period 1	Washout	Period 2
D	8	50 mg, fed	at least 7 days	50 mg, fasted
E	8	50 mg, fasted		50 mg, fed

5.2. Number of Participants

Part 1 and Part 2

Sufficient participants will be randomised such that approximately 18 and 16 evaluable participants complete the study of each part. If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence, if applicable, at the discretion of the sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he has completed all sessions of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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

Part 1

This part is a double-blind, randomized, placebo-controlled, dose escalating, crossover design to characterize the safety, tolerability, PK following single dose of GSK1325756H in healthy Japanese elders. This part will include a placebo control study, to allow for evaluation of adverse events attributable to treatment versus those independent of treatment. In this part, high fat meal will be given 30 minutes prior to dosing.

With consideration for that it has been reported that majority of COPD population are elders [Fukuchi Y, 2004], healthy Japanese elders will be enrolled in this study to evaluate safety, tolerability and PK of GSK1325756, which enable comparison to the non-Japanese data in healthy elders from Study 201037.

In previous clinical studies GSK1325756 was very well tolerated. Since this study is the first study in Japanese subjects, this study adopts a cautious approach starting with a single administration of low dose level (10 mg) and will include rigorous safety monitoring to confirm the safety profile prior to moving to the next dose level.

Since the terminal half-life was approximately 11-12 hours after 50 mg GSK1325756H both in fast and fed condition in the past study in non-Japanese (Study 201037), 3 days is considered to be sufficient for the evaluation of PK and safety in Period 1 and 2 (10 and 50 mg) of Part 1 and 4 days in Period 3 (100 mg) of Part 1. The study plans follow up until at least 7 (±1) days after the last dose of each part. Assuming the half-life conservatively, 7 days is sufficient duration for the washout and the following up.

Period 3 will occur based on the review of the blinded safety and PK concentration data from Period 2 of Part 1 (i.e., 50 mg single dose after intake of high fat meal) in consideration of safety.

Since high fat meal was given in previously conducted study (Study 201037), high fat meal is also given in this study in order to enable to make a comparison between the exposure of Study 201037 and this study.

Part 2

Part 2 is 2 way complete crossover design to evaluate the food effect on PK of GSK1325756. In this part, low fat meal will be given 30 minutes prior to dosing.

This part will occur based on the review of the blinded safety and PK concentration data from Period 2 of Part 1 (i.e., 50 mg single dose after intake of low fat meal) in consideration of safety.

Since the terminal half-life was approximately 11-12 hours after 50 mg GSK1325756H both in fast and fed condition in the past study in non-Japanese (Study 201037), 3 days is considered to be sufficient for the evaluation of PK and safety of Part 2 (50 mg). The study plans follow up until at least 7 (±1) days after the last dose of each part. Assuming the half-life conservatively, 7 days is sufficient duration for the washout and the following up.

5.5. Dose Justification

Part 1

To date, dose range of 10 to 400 mg of GSK1235756 including all proposed doses for this study are within the safe and well tolerated from previously investigated across the GSK1325756 programme in non-Japanese population. Study 201037 showed that systemic GSK1325756 exposure was higher following oral 50 mg GSK1325756H compared to GSK1325756B (free base of Danirixin) in fed conditions (84% increase in area under the concentration-time curve from time 0 to infinity [AUC(0-inf)], 92% increase in area under the concentration-time curve from time 0 to t [AUC(0-t)] and 76% increase in Maximum observed concentration [Cmax]). The oral 10 mg GSK1325756H dose is approximately equivalent to oral 20 mg GSK1325756B, based on the results of

Study 201037. The oral 50 mg GSK1325756H dose is selected to enable comparison with the non-Japanese PK data in Study 201037 and will be proposed dose level for Phase II study (Study 206818). In addition, since the oral 50 mg GSK1325756H is to be administrated twice daily in Phase II study, the 100 mg dose is selected as a top dose to investigate the higher systemic exposure than that of following 50 mg twice daily.

The middle dose in this study, 50 mg will be 1/70 of the no observable adverse effect level (NOAEL) of 4 week rat study based on systemic blood exposure (Table below). The starting and top dose in this study (10 mg and 100 mg) is 1/5 and double of the middle dose (1/140 and 1/35 of the NOAEL), and has a sufficient safety margin.

Species (Duration)	Dose	Sex	Cmax	AUC	Exposure Ratio	
Rat (4 week)	150 mg/kg/day [NOAEL]	M	61.9	491	71.7	67.7
		F	58.3	567	67.5	78.2
Human	Single 50 mg	M/F	0.863	7.248	-	-

Part 2

Since the food effect was evaluated using 50 mg in the previous study (Study 201037), 50 mg is chosen for the dose to evaluate the food effect on the single dose PK in Japanese population.

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. Participant must be over 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECG. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

3. Participants whose peripheral blood neutrophil counts and hematocrit values are within normal range at screening visit.

Weight

4. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5 – 24.9 kg/m^2 (inclusive).

Sex

5. Japanese Male

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and until follow up visit.

Informed Consent

6. Capable of giving signed informed consent as described in restrictions listed in the informed consent form (ICF).

6.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigator
3. Alanine Aminotransferase (ALT) > 1.5x upper limit of normal (ULN)
4. Bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. QTcF > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

- For purposes of data analysis, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication including herbal medications and proton pump inhibitor (PPI) within 14 days prior to dosing. Specific medications listed in Section 7.7 may be allowed

Prior/Concurrent Clinical Study Experience

8. History of donation of blood or blood products ≥ 400 mL within 3 months or ≥ 200 mL within 1 month prior to screening
9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
10. Current enrollment or past participation within the last 30 days before signing of consent in this clinical study involving an investigational study treatment or any other type of medical research

Diagnostic assessments

11. The subject with positive Serological test for syphilis (Rapid Plasma Reagin [RPR] and Treponema pallidum hemagglutination test [TPHA]), Human immunodeficiency virus (HIV) Antigen/Antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibody, or Human T-cell lymphotropic virus type 1 (HTLV-1) antibody at screening
12. Positive pre-study drug screen

Other Exclusions

13. Regular alcohol consumption within 6 months prior to the study defined as:
    - For an average weekly intake of > 14 units for males. One unit is equivalent to 350 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits
14. Smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening
15. 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

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to

the first dose of study medication until completion of all study procedures in each study period after the final dose.

- No water is allowed at least 2 hours before and after dosing. Also, keep resting as much as possible in sitting or semi-sitting position. Water is allowed ad libitum at all other times.
- Once in the clinical unit subjects will not be allowed to eat or drink anything other than provided by the study centre.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until collection of the final PK and clinical laboratory sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until collection of the final PK and clinical laboratory sample.
- Participants will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted from the screening until collection of the final PK sample.

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 during studies (e.g., watching television, reading).
- Participants will avoid a long direct exposure to sunlight for as long as possible using a appropriate sunscreen treatment etc. from the initiation of dosing to follow-up visit when participants will go outside.

6.4. Screen Failures

Screen failures are defined as participants who are screened 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.

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:	GSK1325756H	Placebo
Dosage formulation:	GSK1325756H Tablets,10 mg are white film coated, round tablets intended for oral administration. GSK1325756H Tablets, 50 mg are white film coated, oval-shaped tablets intended for oral administration,	White oval-shaped tablets which does not include GSK1325756H.
Unit dose strength(s)/Dosage level(s):	10 mg, 50 mg	Not applicable
Route of Administration:	oral	oral
Dosing instructions:	With food and 240 mL (8 oz) water, unless explicitly defined by protocol	With food and 240 mL (8 oz) water, unless explicitly defined by protocol
Manufacturer:	GlaxoSmithKline	GlaxoSmithKline

Note: When 100 mg strength is administrated, subjects receive two doses of 50 mg strength.

7.2. Dose Modification

No dose modification is planned.

7.3. Method of Treatment Assignment

On Day 1 of each Part, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 3 sequences in Part 1 and one of the 2 sequences in Part 2, according to the randomization schedule generated prior to the study by the Biomedical Data Sciences Department at GSK. Participants will be randomized in a 1:1:1 ratio to receive sequence (A:B:C) for Part 1, or will be randomized in a 1:1 ratio to receive sequence (D:E) for Part 2. Each participant will be dispensed blinded study treatment, labeled with his unique randomization number, throughout the study.

7.4. Blinding

Participants for Part 1 will be randomized to one of the treatment sequences, A, B or C. Participants for Part 2 will be randomized to one of the two sequences, D or E. Investigators, participants and sponsor will remain blinded to each participant's assigned study treatment throughout the course of the study. Although investigational product administering physician will be able to know information on assignment of investigational product, the physician do not inform site staff who are not involved in investigational drug administration about the information of assignment. Also, he/she does not get involved in safety evaluation under blind.

The sponsor's person who is responsible for confirmation of concentration will review blood drug concentration data under unblind.

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 case report form (CRF).

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

No special preparation of study treatment is required.

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 authorized site staff may supply or administer study treatment. All study treatments

must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized 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 Study Reference Manual (SRM).

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- The investigator nominates an investigational product administering physician, and the physician gives the study drug directly to the subject according to the administration instructions of the protocol.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the start of study

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

7.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study, because only healthy subjects are eligible for study participation.

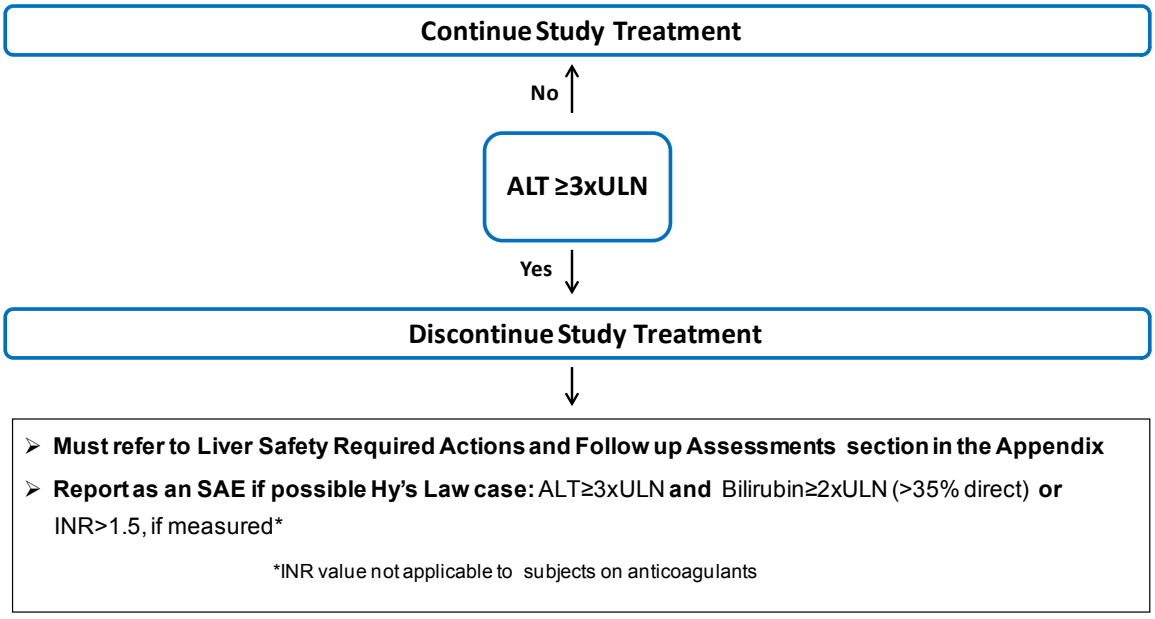
8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

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

8.1.3. Other criteria

A subject that meets the bulleted criterion based on neutrophil counts will be withdrawn from study treatment.

- Neutrophil count < 1.0 * 10^9/L

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, 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 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 study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he 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 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 summarized in the SoA.
- Protocol waivers or exemptions are not allowed

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study 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.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
    - 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 400 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. 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).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- 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 CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 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.

9.1.2. 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.

9.1.3. 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 (as defined in Section 12.4) 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.

9.1.4. 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, IRB, 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 IB and will notify the IRB, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the end of the follow-up period.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of GSK1325756H greater than 100 mg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK1325756 can no longer be detected systemically (at least 14 days).
3. Obtain a blood sample for PK analysis within 14 days 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 or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- Physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Vital Signs

- Axillary temperature, pulse rate and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed (specify participant's position, if applicable) with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

- Single vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

9.3.3. Electrocardiograms

- Single 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.

9.3.4. Ophthalmic Examinations

- Fundus and slit-lamp examinations will be implemented as outlined in the SoA (see Section 2).

9.3.5. 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 should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology 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.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4. Pharmacokinetics

Whole blood samples of approximately 1 mL will be collected for measurement of blood concentrations of GSK1325756 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the SRM by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

10. STATISTICAL CONSIDERATIONS

This is a Phase I study and the primary objective of this study is to assess the safety, tolerability and PK profile of single dose of GSK1325756H in healthy Japanese elderly subjects (Part 1). Also other primary objective of this study is to investigate food effect on PK of GSK1325756H 50 mg single dose in fed state and fasted state in healthy Japanese elderly subjects (Part 2). Where appropriate, the PK parameters will be summarized descriptively.

10.1. Sample Size Determination

10.1.1. Sample Size Assumptions

Given that this is the first time for Japanese subjects that GSK1325756 has been administered, the primary objective of the study is to obtain a preliminary assessment of safety, tolerability and PK profile of the dose range selected and food effect. The sample size is based on feasibility where 18 healthy Japanese elderly subjects will be enrolled in Part 1, and 16 healthy Japanese elderly subjects will be enrolled in Part 2. Consideration has been given to the level of precision we would expect to achieve for the main PK parameters assuming the variability is the same as seen the previous GSK1325756 study.

Part 1:

Assuming a between subject coefficient of variance (CVb%) has been obtained from CX3114922 study that administered single dose of GSK1325756 100 mg in age of 65 to 80 in fed state. The between subject CVb% observed for Cmax was estimated to be 30.1% and AUC(0-t) was estimated to be 30.2%. Based on sample size of 12 subjects of GSK1325756 (10 mg, 50 mg, 100 mg), the CVb% of 30.2% provides a precision estimate for the upper limit value and lower limit value of a mean of 90% confidence interval (CI) of 16.6%

Part 2:

Based on sample size of 16 subjects, assuming a within-subject CVw% of 44.7% for ACU(0-t) and Cmax as observed in Study 201037, it is estimated that the lower and upper bounds of the 90% CI for the ratio of the food effect will be within +/- 30%. Hence, 90% CI would be approximately (0.77, 1.30) if the estimated ratio of food effect is 1.0.

10.1.2. Sample Size Sensitivity

Part 1:

Based on sample size of 12, if the between subject CVb% observed in the PK parameters is 10% and 20% greater between subject CVb% (33.2%, 36.2%), the precision estimate for the upper limit value and lower limit value of a mean of 90% CI will be 18.3% and 20.0% respectively.

Part 2:

Based on sample size of 16, assuming a 10% and 20% greater within subject CVw% (49.2%, 53.6%), the half-width of the 90% CI for the ratio of food effect means should be no more than 33% and 37% of the point estimates. Assuming an observed ratio of one, the corresponding 90% CI for the ratio of food effect means would be (0.75, 1.33) and (0.73, 1.37) respectively.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	Consisting of all subjects screened in the study.
Screening Failure	Subjects who screened in the study but are never subsequently randomised. All participants who sign the ICF have the screening test in the study.
Safety	All randomised participants who take at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received. This population will be defined for each Part.
PK	This population is defined as all subjects administered at least one dose of study treatment and who have PK sample taken and analyzed. Participants will be analyzed according to the treatment they actually received. This population will be defined for each Part.

10.3. Statistical Analyses

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

Complete details of the planned statistical analyses will be provided in the RAP.

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Statistical Analysis Methods
AEs, clinical laboratory values, vital signs and ECG will be summarized by dose group by dose group in Part 1 and by fed state in Part 2. No formal statistical comparisons will be made for the safety data.

10.3.2. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population.

Statistical Analysis Methods
Blood GSK1325756 concentration-time data will be analysed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the blood concentration-time data, the following PK parameters will be determined, as data permit: AUC(0-t), AUC(0-24), AUC(0-inf), Cmax, tmax, apparent t1/2, Tlag and tlast. PK data will be presented in graphical and/or tabular form and will be summarised descriptively. Listings will be generated and summary statistics (n, arithmetic mean with associated 95% CI, standard deviation, minimum, median, maximum, geometric mean with associated 95% CI, SD on log-scale and %CVb or %CVw) will be calculated for each derived blood PK parameter for each group dose in each Part. Part 1: The PK-dose relationship will be examined graphically by plotting derived blood PK parameters (AUC(0-t) and Cmax) for each group dose. Dose proportionality for PK parameters (AUC(0-t) and Cmax) will be assessed by using a power model as described below: log (PK parameter) = $\beta_0 + \beta_1 \cdot \log(\text{dose})$ where β_0 is the intercept and β_1 is the slope. Following loge-transformation, AUC(0-t) and Cmax will be separately analyzed using a power model with fixed effect terms for log-dose, as data permitted. Subjects will be assessed in model as random effect, and degree of freedom will use Kenward-Roger. Point estimates for the slopes of PK parameters and their associated 90% CIs will be constructed. Part 2: An estimation approach will be used to assess the food effect of GSK1325756 on primary PK parameters, where point estimates and corresponding 90% CIs will be constructed to provide a plausible range of values for the true comparisons of interest. To estimate the food effect on the primary PK endpoints, data from Period 1 and Period 2 will be used. Following loge-transformation, AUC(0-t) and Cmax of GSK1325756 will be separately analysed using a mixed effects model with fixed effect terms for regimen (the treatment variable can be applied as this contains whether the subject is on fed or fasted for that particular period) and period. Subject will be treated as a random effect in the model. The point estimates and their associated 90% CIs will then be backtransformed to provide point estimates (ratio) and 90% CIs for the adjusted geometric means of fed and fasted.

10.3.3. Interim Analyses

No formal statistical analysis is planned.

A blind review of preliminary safety data (AE, clinical laboratory values, vital signs, ECG) will be conducted after Period 1 and Period 2 in Part 1 Furthermore, .the sponsor's person who is responsible for confirmation of concentration will review blood concentration of GSK1325756 under unblind.

After completion of Part 1, formal analysis for Part 1 is to be conducted.

11. REFERENCES

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Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C. COPD in Japan: the Nippon COPD Epidemiology study. Respirology 2004; 9: 458-465.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC(0-24)	Area under the concentration-time curve from time 0 to 24 hours
AUC(0-inf)	Area under the concentration-time curve from time 0 to infinity
AUC(0-t)	Area under the concentration-time curve from time 0 to t
BID	Bis in die
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CK (CPK)	Creatine phosphokinase
(e)CRF	(electronic) Case report form
CSR	Clinical Study Report
CV	Coefficient of variance
CXCL8	CXC chemokine ligand 8
CXCR2	CXC chemokine receptor 2
ECG	Electrocardiogram
e.g.	exempli gratia
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GSK	GlaxoSmithKline
h/hrs	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPLC	high performance liquid chromatography
HTLV-1	Human T-cell lymphotropic virus type 1
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
i.e.	id est
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-8	Interleukin-8
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	Kilogram
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
log	Logarithm
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
µg	Microgram
mg	Milligram
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Millisecond
nm	Nanometer
NOAEL	No observable adverse effect level
oz	ounce
pH	Pondus Hydrogenii
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Proton pump inhibitor
PR	Pulse rate
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate by Friderician formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	ribonucleic acid
RPR	Rapid Plasma Reagin
SAE	Serious adverse event
SD	Standard Deviation
SoA	Schedule of Activities
SRM	Study reference manual
SUSAR	suspected unexpected serious adverse reactions
t1/2	Terminal half-life
TG	Triglyceride
tlag	Lag time before observable concentration
tlast	Time to last quantifiable concentration
tmax	Time to maximum observed concentration

TPHA	Treponema pallidum hemagglutination test
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cells
WOCBP	Women of Childbearing Potential

Trademark Information

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WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 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 RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Uric acid	TG	Total Cholesterol	LDL-cholesterol
	HDL-cholesterol	LDH	GGT	CK (CPK)
	Amylase	Chloride	Phosphorus	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine drug screen (to include at minimum: Phencyclidines, Benzodiazepines, Cocaine, Amphetamines, Tetrahydrocannabinol, Opiates, Barbiturates and Trycyclic antidepressants • Serology (Syphilis [RPR & TPHA], HIV antigen/antibody, HBsAg, HCV antibody and HTLV-1 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 and Appendix 6. All events of ALT ≥ 3 × 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).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 (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 by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
    - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, 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 will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB 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 authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- 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 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 medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB 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 multicentre 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.

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 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 authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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 list of the source documents.

Study and Site Closure

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 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • 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.

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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 (e.g., 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 (e.g., 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.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK/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 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 makes an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any 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 for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • 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. • Contacts for SAE reporting can be found in Section 12.7.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Section 12.7.

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

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
- Refrain from donating sperm for duration of study and until follow up visit

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[b] • oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
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.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until follow up visit corresponding to time needed to eliminate study treatment

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- 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: Liver Safety: Required Actions and Follow up Assessments

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

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

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

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.

12.7. Appendix 7: Country-specific requirements

SPONSOR INFORMATION

Sponsor Legal Registered Address:

GlaxoSmithKline K.K.
6-15, Sendagaya 4-chome Shibuya-ku, Tokyo 151-8566 Japan
Study Director: PPD Head, Medicines Development, Clinical Pharmacology & Science Promotion Office

Sponsor Contact Address:

Lead Author: PPD
Medicines Development, Clinical Pharmacology & Science Promotion Office
GlaxoSmithKline K.K.
TEL: PPD
FAX: PPD

Monitoring Leader: PPD
Manager, Medicines Development, Clinical Pharmacology & Science Promotion Office
GlaxoSmithKline K.K.
TEL: PPD
FAX: PPD

Sponsor's Emergency Contact Information (10:00~18:00, Monday to Friday, except national holidays and year-end and new-year holidays);
Medicines Development (Clinical Pharmacology), GlaxoSmithKline K.K.
TEL: PPD (direct dialling)
FAX: PPD

Contact Information at Night and on Holidays (Monday to Friday: 18:00~10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)
PPD (Cell Phone: PPD
PPD (Cell Phone: PPD

Sponsor's Medical Monitor/Medical Expert

PPD
GlaxoSmithKline K.K. (GSK)
6-15, Sendagaya 4-chome Shibuya-ku, Tokyo 151-8566 Japan
TEL: PPD
FAX: PPD

Sponsor's person who is responsible for concentration confirmation

PPD
GlaxoSmithKline

Stockley Partk, West, Uxbridge, Middleesex, UB11 1BT, UK
TEL: PPD

Medical Institution and Investigator

Koichi Nakamura, MD
Clinical Research Tokyo Hospital
87-4 Haramachi 3-chome, NT Bldg. 3F, Shinjuku-ku, Tokyo 162-0053 Japan
TEL: PPD
FAX: PPD

Laboratories

Clinical Laboratory Measurement Facilities
Role: Clinical Laboratory Tests (except for infectious diseases)
Person in charge: PPD
Clinical Research Tokyo Hospital
87-4 Haramachi 3-chome, NT Bldg. 3F Shinjuku-ku, Tokyo 162-0053 Japan
TEL: PPD
FAX: PPD

Role: Clinical Laboratory Tests (infectious diseases)
Person in charge: PPD
Health Sciences Research Institute, Inc.
106 Godo-cho, Hodogaya-ku, Yokohama, Kanagawa 240-0005 Japan
TEL: PPD
FAX: PPD

Role: Ophthalmic Examinations
Person in charge: PPD MD
Yakuoji I Clinic
70 Ichigayayakuoji-machi, Arusu Ichigayayakuoji 1F, Shinjuku-ku, Tokyo 162-0063 Japan
TEL: PPD
FAX: PPD

Pharmacokinetics Measurement Facilities
Person in charge: PPD
Covance Laboratories Limited
Otley Road, Harrogate, North Yorkshire, HG3 1PY, UK
TEL: PPD

Contract research organization

Role: Study Monitoring
Person in charge: PPD
Mediscience Planning Inc.
Toranomon 15 Mori Building, 2-8-10 Toranomon, Minato-ku, Tokyo 105-0001 Japan

TEL: PPD
FAX: PPD

Role: Medical Writing (Protocol & Informed Consent Form)
Person in charge: PPD
Mediscience Planning Inc.
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12.8. Appendix 8: Protocol Amendment History

Not applicable