TITLE PAGE

Protocol Title: Randomized, open label, 2-way crossover, single dose bioequivalence study of Paroxetine IR tablets manufactured in GSKT and Mississauga sites in healthy Chinese participants under fasting and fed conditions.

Protocol Number: 207652 Amendment 1

Short Title: China Paroxetine IR Phase I Healthy Volunteer Single Dose Bioequivalence Study

Compound Number: BRL29060

Sponsor Name and Legal Registered Address:

GlaxoSmithKline (China) Investment Co., LTD.
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Regulatory Agency Identifying Number(s): Not Applicable

Approval Date: 20-JUL-2018

SPONSOR SIGNATORY

PPD

PPD He
VP, Country Medical Director
Worldwide Medical Affairs, GlaxoSmithKline

July. 20, 2018
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1	20-Jul-2018	2017N312753_01
Original Protocol	01-Jun-2017	2017N312753_00

Amendment 1 20-JUL-2018

Overall Rationale for the Amendment: Sponsor change.

Section # and Name	**Description of Change**	**Brief Rationale**
Title page	Sponsor change	Sponsor change
9.4.2 Vital Signs	Add time window for blood pressure and pulse rate assessing	To have better instruction for procedures
10.3.3 Safety Analyses	Change data standard description from IDSL to CDISC.	Data collection strategy changed
Through out	Minor editorial and document formatting revision	Minor, to make the protocol to be consistent

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1. SYNOPSIS

Protocol Title: Randomized, open label, 2-way crossover, single dose bioequivalence study of Paroxetine IR tablets manufactured in GSKT and Mississauga sites in healthy Chinese participants under fasting and fed conditions.

Short Title: China Paroxetine IR Phase I Healthy Volunteer Single Dose Bioequivalence Study

Rationale:

China Food and Drug Administration (CFDA, 2016) has published [Article #106] on May 25,2016--- the Relevant Matters for Facilitating the Opinions of the General Office of the State Council on Conducting Consistency Evaluation for the Quality and Efficacy of Generic Drugs, with a list of 289 products on Essential Drug List Quality consistency evaluation to be completed before the end of 2018. Seroxat IR tablet as localized originator drugs is included in the list.

Paroxetine, as a selective serotonin reuptake inhibitor (SSRI), is registered for use in China since 1995. Paroxetine immediate release (IR) formulation was approved for the treatment of Major Depressive Disorder in 1995 based on a randomized, double blind, amitriptyline controlled study . In 1998, Paroxetine IR (Seroxat IR) was approved for the treatment of three anxiety indications in China: Panic Disorder, Obsessive-Compulsive Disorder and Social Anxiety Disorder. Panic Disorder was approved based on a randomized, double blind, clomipramine controlled, in-parallel study, while Obsessive-Compulsive Disorder was approved based on a randomized, double blind, clomipramine controlled , in-parallel study. Both studies were conducted in Chinese subjects. Social Anxiety Disorder was approved by clinical trial waiver.

The licence of Seroxat IR in China is owned by TSKF(Tianjin SmithKline & French) and toll manufacture is GSKT (Glaxo SmithKline Tianjin). To meet the requirement of quality consistency evaluation, we approached to claim GSKT product as reference standard and waive bioequivalence (BE) study but failed, as GSKT product is WG(wet granulation) formulation, while GSK reference product manufactured by Missisauga is DC(direct compression) formulation. GSKT will do manufacture technical transfer from WG to DC. After the technical transfer successfully completed, we will conduct a BE study between GSKT investigational DC products and Mississauga reference DC products to support the quality consistency evaluation.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To evaluate the bioequivalence of paroxetine IR tablets manufactured in GSKT and Mississauga sites in healthy Chinese participants under fasting and fed conditions.	• $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and Cmax of paroxetine IR tablets

Objectives	Endpoints
Secondary • To assess the safety and tolerability of dosing with paroxetine IR tablets in healthy Chinese participants. • To obtain the pharmacokinetic profile of paroxetine IR tablets in healthy Chinese participants.	• Safety and tolerability as measured by adverse events, vital signs, ECG and clinical laboratory measurements. • Tmax, λz, and t1/2 of paroxetine IR as data permit.

Overall Design:

This is a single dose, open-label, randomized, two-way crossover study to demonstrate the bioequivalence of paroxetine IR tablets manufactured in GSKT(A) and Mississauga(B) sites in healthy Chinese participants under fasting and fed conditions. This study includes a screening period (up to 7 days) and an open-label treatment period. Participants will be followed 7 to14 days after last dosing.

From Day -7 to Day -1

After obtaining the Informed Consent Form signed by the participants, they will be verified against the inclusion and exclusion criteria to confirm his/her eligibility to participate in the study.

From Day 0 to Day 16

On Day 0, participants will be admitted into the study ward to complete vital signs, physical examination; eligibility for enrolment will be confirmed; and the participant's concomitant therapies and adverse reactions will also be collected and recorded.

On Day 1, each enrolled participant will take a single dose of paroxetine IR 40mg A or B (20mg *2 tablets). Blood samples will be collected at a set of timepoints pre- and post-dosing from Day1 to Day 5 for determination of single-dose pharmacokinetics of paroxetine A or B.

Following a washout from Day 6 to Day 11, participants will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1. They will be admitted into the study ward to complete physical examination and confirm eligibility again on Day 11. Eligible participants will take paroxetine IR 40mg A or B (20mg*2 tablets) once on Day 12, and blood samples will be collected at a set of timepoints pre and post dosing from Day12 to Day 16.

Safety data collection includes physical examinations, laboratory tests, electrocardiogram (ECG), vital signs measurements and recording of adverse events. Other clinical assessments will also be performed as appropriate.

Participants will complete follow-up 7 to 14 days after last dosing, and complete monitoring of any adverse events.

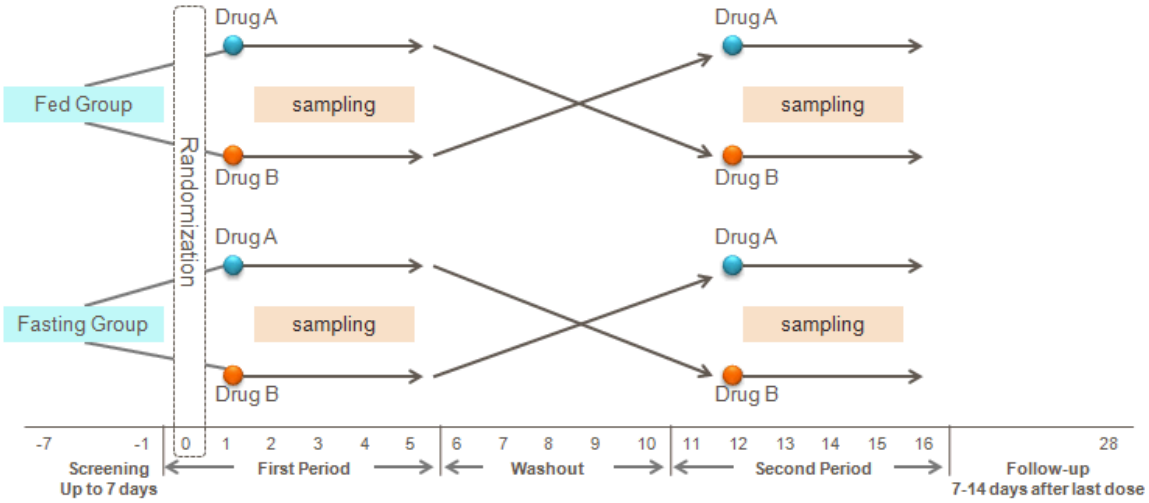
Number of Participants:

A sufficient number of healthy participants (approximately 36 for Fasting group and 44 for Fed group) will be enrolled so that approximately 32 participants in Fasting group and 40 participants in Fed group complete the study.

Treatment Groups and Duration:

The whole study will be divided into two groups, one for fasting condition and another for fed condition. For each group, eligible participants will be randomized to either AB or BA treatment sequence according to 1:1 ratio.

Refer to the schematics for the study.



2. SCHEDULE OF ACTIVITIES (SOA)

	Screening	**First Period**						**Wash out**
Study day	**Up to 7 days**	**D0**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6-10**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Administration			×					
Standard Meal (fed group)			×					
Sampling (hour after dosing)			**Pre, 0.5, 1, 2,3, 4, 5, 6, 7, 8, 10, 12, 16**	**24,36**	**48**	**72**	**96**	
Informed consent	×							
Inclusion/exclusion criteria	×	×						
Demographics and medical history[1]	×							
C-SSRS[2]	×							
Weight/Height	×	×						
Physical examination	×	×						
Vital signs[3]	×	×	×	×	×	×	×	
12-lead ECG	×							
Laboratory tests [5]	×							
Pregnancy test (WOCBP)[4]	×							
Alcohol and drug screen	×							
HIV, Hep B, Hep C, Syphilis	×							
Concomitant medication	→	→	→	→	→	→	→	→
AE			→	→	→	→	→	→
SAE	→	→	→	→	→	→	→	→

	Second Period						Early Withdraw	Follow up[6]
Study day	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**		**7-14 days after last dose**
Visit	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Administration		×						
Standard Meal (fed group)		×						
Sampling (hour after dosing)		**Pre, ,0.5, 1, 2,3, 4, 5, 6, 7, 8, 10, 12, 16**	**24,36**	**48**	**72**	**96**		
Inclusion/exclusion criteria	×							
C-SSRS[2]						×	×	
Weight/Height						×	×	
Physical examination	×					×	×	R
Vital signs[3]	×	×	×	×	×	×	×	R
12-lead ECG						×	×	R
Laboratory tests [5]						×	×	R
Pregnancy test (WOCBP)[4]	×					×	×	
Concomitant medication	→							
AE	→							
SAE	→							

Key: × = Mandatory Assessment; R =Repeated in case of abnormal results from the last visit.

1. Medical history: Medical and medication history and Alcohol/Smoking history
2. C-SSRS: Screening visit use 'baseline' version. The following visit use 'since last visit' version.
3. Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at screening, when admit to unit (Day 0 and Day 11) and as clinically indicated. Blood pressure and pulse rate will be measured pre-dosing and at 2h post-dosing on Day 1 and Day 12; on the Day 2(24h), 3, 4, 5, 13(24h), 14, 15, 16; or early withdraw.
4. WOCBP=Woman of Childbearing Potential. Pregnancy test: either urine or serum test is valid.
5. Clinical laboratory tests including haematology, clinical chemistry and routine urinalysis. Refer to Appendix 5 for more details.
6. The participant will complete follow-up 7-14 days after last dose of medication. The follow-up can be visited by telephone if the participant does not need to receive any examination.

3. INTRODUCTION

3.1. Study Rationale

China Food and Drug Administration (CFDA, 2016) has published [Article #106] on May 25,2016--- the Relevant Matters for Facilitating the Opinions of the General Office of the State Council on Conducting Consistency Evaluation for the Quality and Efficacy of Generic Drugs (http://www.sfda.gov.cn/WS01/CL0087/154042.html), with a list of 289 products on Essential Drug List Quality consistency evaluation to be completed before the end of 2018. Seroxat IR tablet as localized originator drugs is included in the list.

Paroxetine, as a selective serotonin reuptake inhibitor (SSRI), is registered for use in China since 1995. Paroxetine immediate release (IR) formulation was approved for the treatment of Major Depressive Disorder in 1995 based on a randomized, double blind, amitriptyline controlled study [Tian, 1996]. In 1998, Paroxetine IR was approved for the treatment of three anxiety indications in China: Panic Disorder, Obsessive-Compulsive Disorder and Social Anxiety Disorder. Panic Disorder was approved based on a randomized, double blind, clomipramine controlled, in-parallel study [Zhang, 2000] , while Obsessive-Compulsive Disorder was approved based on a randomized, double blind, clomipramine controlled, in-parallel study [Wu, 2004]. Both studies were conducted in Chinese subjects. Social Anxiety Disorder was approved by clinical trial waiver.

The licence of Seroxat IR in China is owned by TSKF(Tianjin SmithKline & French) and toll manufacture is GSKT (Glaxo SmithKline Tianjin). To meet the requirement of quality consistency evaluation, we approached to claim GSKT product as reference standard and waive bioequivalence (BE) study but failed, as GSKT product is WG(wet granulation) formulation, while GSK reference product manufactured by Missisauga is DC(direct compression) formulation. GSKT will do manufacture technical transfer from WG to DC. After the technical transfer successfully completed, we will conduct a BE study between GSKT investigational DC products and Mississauga reference DC products to support the quality consistency evaluation.

3.2. Background

Paroxetine, a phenylpiperidine compound, is a potent and SSRI. Paroxetine IR formulation has been approved in numerous countries for the treatment of depression, panic disorder, social anxiety disorder, obsessive compulsive disorder, generalised anxiety disorder and post-traumatic stress disorder. Paroxetine can be used for maintaining therapy with once daily dosing, with little accumulation of drug over the long-term. Thereby, paroxetine also reduces the maximal duration of unwanted pharmacological effects that are observed with all SSRIs.

Paroxetine is administered as the hydrochloride salt. All doses stated are equivalent to the concentration of paroxetine free base. Comparing oral versus intravenous administration of paroxetine, the terminal phase half-life (t1/2) of paroxetine from intravenous injection averaged 13.8 hours (range 6.9-37.1; n = 9). Plasma half-lives were longer after oral

compared to intravenous injection. This dose-route dependency and pharmacokinetic non-linearity precludes an estimate of absolute bioavailability. An early study suggested that paroxetine available to the systemic circulation is approximately 50%. The effects of food on the bioavailability of paroxetine were studied in participants administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the Cmax was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate are found predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by Cytochrome P450 2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. Therefore pharmacokinetic parameters of paroxetine are not constant resulting in non-linear kinetics. Large inter-individual variability in Cmax, t1/2, and AUC was established in studies. However, the non-linearity in kinetics is generally small and is confined to those participants who achieve low plasma levels at low doses.

Although the overall safety of paroxetine IR has been well established in numerous clinical trials, it can produce side effects which can be a discomfort to the patient and may result in termination of treatment. Data from paroxetine IR clinical trials in major depression show that nausea is the most frequently reported adverse event associated with discontinuation of therapy. Although usually transient and mild, nausea may ultimately compromise the patient's recovery by causing noncompliance or treatment discontinuation.

Trials of patients with major depressive disorder (MDD), panic disorder (PD), social anxiety disorder (SAD), and obsessive compulsive disorder (OCD) have shown paroxetine to be of clinical benefit. Therefore, paroxetine has been shown to be a valuable agent for the treatment of these disorders. A detailed description of the chemistry, pharmacology, efficacy, and safety of paroxetine is provided in the Investigator’s Brochure/package insert.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Paroxetine IR may be found in the Paroxetine IR Prescription information, Investigator’s Brochure and Periodic Benefit Risk Evaluation Report.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [BRL 29060]		
Serotonin syndrome/Neuroleptic malignant syndrome-like events	Overstimulation of the serotonergic system can lead to serotonin syndrome. This is most likely to occur through the combined use of various serotonergic drugs. Source: Spontaneous data and evidence from published medical literature provide evidence of paroxetine induced serotonin syndrome.	Warning patients to be alert for symptoms, Warning prescribers of risk in patients in whom paroxetine is coadministered with other serotonergic drugs and recommending prompt discontinuation of paroxetine should symptoms develop. Paroxetine is contraindicated with monoamine oxidase inhibitors (MAOIs) due to this risk.
Bone Fracture	Serotonin receptors are found in all major types of bone cell (osteoblasts, osteocytes, and osteoclasts), indicating an important role of the neuroendocrine system in bone. Source: Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association with fractures.	Warning prescribers of risk which is greatest in the early stages of therapy.
Hyponatraemia	It has been suggested that SSRI-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) is multifactorial and there are three potential mechanism involving antidiuretic hormone (ADH): an increase in the secretion of ADH centrally, augmentation of the effect of ADH in the renal medulla and a resetting of the osmostat that lowers the threshold for secretion. Source: Paroxetine clinical studies, scientific and medical literature, spontaneous case reports.	Warning prescribers of risk (in particular elderly patients) for the development of SIADH and/or hyponatraemia.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Bleeding disorders, predominantly of the skin and mucous membranes	SSRIs are antagonists of the serotonin transporter system which can lead to a lower concentration of serotonin in platelets. Serotonin mediates vasoconstriction, platelet aggregation and platelet activation following injury, and because platelets cannot synthesize serotonin, treatment with SSRIs can lead to a reduction of platelet serotonin and therefore impair haemostasis. Source: Clinical study data, medical literature and spontaneous case reports provide evidence of paroxetine induced bleeding.	The risk of bleeding related adverse events may be minimised by observing caution when using paroxetine in patients concomitantly using medications that may increase the risk for bleeding and in those patients with a known tendency for bleeding or those with predisposing conditions.
Glaucoma	The serotonin receptors that have been found to be involved in eye functioning are 5-HT1A, 5-HT2A, 5-HT2C and 5-HT7 and there are a number of potential mechanisms, by which paroxetine may induce glaucoma in certain patients. Source: Medical literature and spontaneous data provide evidence of paroxetine induced acute glaucoma.	Observing caution in patients with narrow angle glaucoma.
Interaction with CYP2D6 substrates	As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Source: Clinical pharmacology/pharmacokinetic studies / In vitro assays / Literature.	Warning prescribers of risk of taking paroxetine with other medications and the need to exercise caution when prescribing paroxetine to patients already receiving known substrates or vice versa.
Akathisia	The mechanism for akathisia is not completely understood but it is postulated to be related to a decrease in dopaminergic neurotransmission and it has been suggested that SSRIs induce akathisia (and parkinsonism) by indirectly stimulating serotonin (5-	Warning prescribers of risk, informing patients regarding signs/symptoms to be aware of.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	HT)2A receptors, which results in inhibition of dopamine release. Source: Medical literature and spontaneous case reports provide evidence of SSRI induced akathisia.	
Symptoms seen on discontinuation of paroxetine	Although there are several hypotheses the exact mechanism of antidepressant discontinuation syndrome remains unknown. Source: Clinical studies, medical literature and spontaneous case reports provide evidence of discontinuation related adverse events.	Informing patients regarding signs / symptoms to be aware of. Advice to prescribers to gradually taper paroxetine when discontinuing treatment.

3.3.2. Benefit Assessment

MAJOR DEPRESSIVE DISORDER
Paroxetine is indicated for MDD, including reactive and severe depression and MDD accompanied by anxiety. In the treatment of depressive disorders, paroxetine exhibits comparable efficacy to standard (e.g., tricyclic) antidepressants. Results of studies in which patients received paroxetine treatment for up to one year indicate that paroxetine is effective in preventing the relapse and also recurrence of depressive symptoms.

OBSESSIVE COMPULSIVE DISORDER
Paroxetine has been shown to be effective in the treatment of OCD. In a placebo-controlled trial, the efficacy of paroxetine in the treatment of OCD has been maintained for at least 1 year. Paroxetine was also effective in preventing the relapse of OCD.

PANIC DISORDER
Paroxetine has been shown to be effective in the treatment of PD with and without agoraphobia. The combination of paroxetine and cognitive-behavioural therapy has been shown to be significantly more effective than cognitive-behavioural therapy alone in the treatment of PD.
In a placebo-controlled trial, the efficacy of paroxetine in the treatment of PD has been maintained for up to 1 year. Paroxetine has also been shown to be effective in the prevention of relapse of PD.

SOCIAL ANXIETY DISORDER/SOCIAL PHOBIA
Paroxetine has been shown to be effective in the treatment of SAD/Social Phobia. The maintained efficacy of paroxetine in the long term treatment of SAD/Social Phobia has been demonstrated in a Relapse Prevention Study.

3.3.3. Overall Benefit: Risk Conclusion

Paroxetine has a well-characterised safety profile supported by over 20 years on the market globally, across a number of indications, and with a large cumulative post-marketing exposure.
The benefit/risk profile of paroxetine remains favourable, therefore the Sponsor considers that investigation of Paroxetine IR is justified in study 207652.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the bioequivalence of paroxetine IR tablets manufactured in GSKT and Mississauga sites in healthy Chinese participants under fasting and fed conditions.	• $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and Cmax of paroxetine IR tablets

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of dosing with paroxetine IR tablets in healthy Chinese participants.	• Safety and tolerability as measured by adverse events, vital signs, ECG and clinical laboratory measurements.
• To obtain the pharmacokinetic profile of with paroxetine IR tablets in healthy Chinese participants.	• T_{max}, λz, and $t_{1/2}$ of paroxetine IR as data permit.

5. STUDY DESIGN

5.1. Overall Design

This is a single dose, open-label, randomized, two-period crossover study to demonstrate the bioequivalence of paroxetine IR tablets Manufactured in GSKT (A) and Mississauga (B) sites in healthy Chinese participants under fasting and fed conditions. This study includes a screening period (up to 7 days) and two open-label treatment periods. Participants will be followed up 7 to 14 days after last dosing.

The whole study will be divided into two groups, one for fasting condition and another for fed condition. For each group, eligible participants will be randomized to either AB or BA treatment sequence according to 1:1 ratio.

From Day -7 to Day -1

After obtaining the Informed Consent Form signed by the participants, they will be verified against the inclusion and exclusion criteria to confirm his/her eligibility to participate in the study.

From Day 0 to Day 16

On Day 0, participants will be admitted into the study ward to complete vital signs, physical examination; eligibility for enrolment will be confirmed; and the participant's concomitant therapies and adverse reactions will also be collected and recorded.

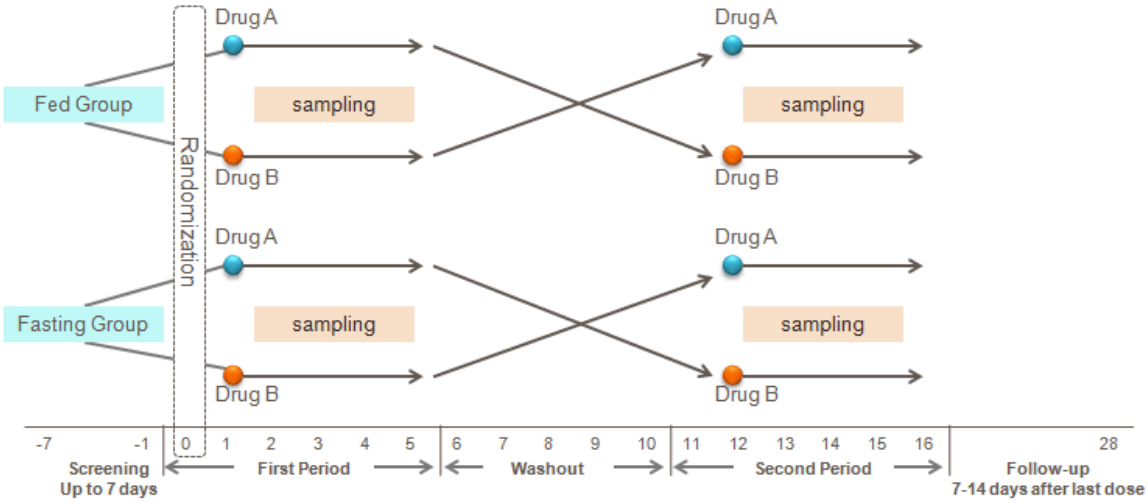
On Day 1, each enrolled participant will take a single dose of paroxetine IR 40mg (20mg*2 tablets) A or B once. Blood samples will be collected at a set of timepoints (refer to SoA) pre and post dosing from Day1 to Day 5 for determination of single-dose pharmacokinetics of paroxetine A or B.

Following a washout from Day 6 to Day 11, participants will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1. They will be admitted into the study ward to complete physical examination and confirm eligibility again on Day 11. Eligible participants will take paroxetine IR 40mg (20mg*2 tablets) A or B once on Day 12 and blood samples will be collected at a set of timepoints (refer to SoA) pre and post dosing from Day12 to Day 16.

Safety data collection includes physical examinations, laboratory tests, electrocardiogram (ECG), vital signs measurements and recording of adverse events. Other clinical assessments will also be performed as appropriate.

Participants will complete follow-up 7 to 14 days after last dosing, and complete monitoring of any adverse events.

Figure 1 Study Schematics



5.2. Number of Participants

A sufficient number of healthy participants (approximately 36 for Fasting group and 44 for Fed group) will be enrolled so that approximately 32 participants in Fasting group and 40 participants in Fed group complete the study. Either gender of evaluable participants should be no less than one-third of the total evaluable participants. Participant and Study Completion

A completed participant is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last participant's last visit.

5.3. Scientific Rationale for Study Design

This is a single dose, open-label, randomized, two-period crossover study in healthy Chinese participants to demonstrate the bioequivalence of 40mg paroxetine IR (20mg *2 tablets) made by GSKT (investigational drug, DC formulation) and Mississauga (reference drug, DC formulation) under fasting and fed conditions.

Both the investigational and the reference drugs are provided by GlaxoSmithKline (GSK). A two-period cross-over design was selected for this study so that within participant comparisons can be utilized and the number of participants required for the study can be reduced. Both fasting and fed BE studies are designed according to the China bioequivalence guideline. The Pharmacokinetic (PK) sampling and washout period

are designed to ensure that PK parameters are well-estimated and pre-dose concentrations are completely negligible in Period 2.

Sampling time points were decided based on the pharmacokinetic parameters of DC formulation in past successful global BE studies under both fasting and fed conditions and the CFDA bioequivalence study guideline. The last sampling time point was selected as 96 hours considering the elimination half-life of around 16 hours.

5.4. Dose Justification

Paroxetine IR has been approved in China for the treatment of MDD, PD, OCD and SAD. In the clinic, Chinese patients receive flexible Paroxetine IR doses that are the same as the doses approved in the US, starting from 10 mg/day up to 50-60 mg/day. Nonlinearity of paroxetine kinetics has been observed in the past clinical pharmacology studies. From the "Product-Specific Guidances for Generic Drug Development", bioequivalence study at 40 mg dose level (both fasting and fed conditions) was suggested for paroxetine IR, (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089264.pdf). Since the highest strength of GSK paroxetine IR approved in China is 20 mg, in the current study, 2*20 mg paroxetine IR will be compared to evaluate the bioequivalence of paroxetine IR manufactured between two sites.

The effects of food on the bioavailability of paroxetine were studied in participants administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the Cmax was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours. Paroxetine IR should be administered as a single daily dose with or without food under the same dose level. Thus the same dose levels are used for fasting and fed cohorts.

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:

1. Able to actively communicate with the investigator and to complete the study-related documents; able to understand the contents of the Informed consent form (ICF) and to sign a written ICF prior to any study-specific procedures.
2. Males and females aged between 18 and 45 years inclusive, at the time of signing the informed consent.
3. Non-smoking healthy males and females as assessed by medical history and physical examination. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A participant with a clinical abnormality or laboratory parameters which 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 GSK Medical Monitor if necessary) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

4. Body weight≥50kg(male) or 45kg(female) and Body mass index (BMI) 19.0 to 26.0 kg/m2 (inclusive).
5. A female participant is eligible to participate if she is of:
    - Child-bearing potential with negative pregnancy test as determined by serum or urine human chorionic gonadotropin (hCG) test at screening or prior to dosing AND
    - Agrees to use one of the contraception methods listed in Appendix 2 during the study and until follow up contact.
6. Male participants with female partners of child-bearing potential must agree to use one of the contraception methods listed in Appendix 2 during the study and until follow up contact.
7. Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and total bilirubin ≤1.5x upper limit of normal (ULN) (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. Based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period:
    - QTc < 450 msec; or
    - QTc < 480 msec in participants with bundlebranch block.

6.2. Exclusion Criteria

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

Medical Conditions

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
2. Drug or alcohol abuse or dependency within one year prior to enrolment. History of regular alcohol consumption within one year of the study defined as: an average weekly intake of >14 drinks. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.
3. Unstable disease conditions; any laboratory measurements assessed by the investigator as clinically relevant (including ECG, haematology, biochemistry and urine analysis, etc.)； any disorder that might interfere with the absorption, distribution, metabolism or excretion of the study drug; or in the investigator’s opinion the disease may lead to safety concerns or interfere with the pharmacokinetics assessment.

4. Participants with concurrent or previous neuropsychological disorders, as assessed by Columbia Suicide Severity Rating Scale or by the investigator, have suicidal tendency, or have committed suicidal behavior/attempt.
5. Known history of cerebral trauma, previous cerebral disorders, seizures or eating disorder, and other conditions that in the investigator's opinion may increase the risk of seizures.

Prior/Concomitant Therapy

6. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
7. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study medication.
8. In subjects with concomitant use of MAOIs (including linezolid, an antibiotic which is a reversible non-selective MAOIs and methylthioninium chloride (methylene blue)) or within two weeks of terminating treatment with MAOIs.
9. In participants with concomitant use of thioridazine or pimozide.

Prior/Concurrent Clinical Study Experience

10. The participant has participated in a clinical trial and has received an investigational product within 90 days prior to the first dosing day in the current study, or has participated in a clinical trial without receiving any investigational product within 30 days prior to the first dosing day in the current study.

Diagnostic assessments

11. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months.
12. Serum HIV antibody or Syphilis antibody positive.
13. A positive pre-study drug/alcohol screen.

Other Exclusions

14. Known allergy to paroxetine IR Tablets or any of its components.
15. Blood donation in excess of 400 mL in the 3 months prior to enrolment.
16. Obvious evidence of active haematological diseases, or significant blood loss in the last 3 months. History of sensitivity to heparin or heparin-induced thrombocytopenia.
17. Lactating females or women of child bearing potential used oral or implanted contraceptives within the 30 days prior to enrolment, or received injections of chronically acting contraceptives in the 1 year prior to study initiation.
18. Other conditions which, in the Investigator's judgment, render participants unsuitable for the clinical study.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- In fasting group, the participants should be on fasting overnight for 10 hours prior to Day 1 and Day 12 administration. No food can be taken until 4 hours post dose.

  In fed group, the participants should be on fasting overnight for 10 hours prior to Day 1 and Day 12, and eat standard breakfast within 30 minutes on Day 1 and Day 12. The dose should be administered at 30 minutes after the start of the breakfast.
- No liquids other than water for drug intake should be taken in the 1 hour pre-dose and the 2 hours post-dose.
- Refrain from consumption of red wine, juice, grape fruit, barbecue or cruciferous vegetables (broccoli, cauliflower) from 7 days prior to the first dose of study medication until collection of the final pharmacokinetic samples.
- Unless permitted by the sponsor, any prescription or over the counter (OTC) is prohibited during the study.

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 48 hours prior to the start of dosing until collection of the final pharmacokinetic samples.
- During each dosing session, participants will abstain from alcohol for 48 hours prior to the start of dosing until collection of the final pharmacokinetic samples.
- Participants are non-smokers and will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted for 48 hours prior to the start of dosing until collection of the final pharmacokinetic samples.

6.3.3. Activity

Participants will abstain from strenuous exercises for 48 hours prior to each blood collection occasion for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watch television, read*).* Ultraviolet radiation, e.g., sun bath, is prohibited during the study.

Participants will be admitted to the study ward in the nights before PK assessments. The participants may leave the study ward, if judged as appropriate by the investigator, after certain times for PK sampling, but will need to return to the study ward for other scheduled times to complete PK blood sampling and adverse event assessments.

6.4. Screen Failures

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

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), investigational drug(s), reference drug(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 Drug Name:	Paroxetine IR tablets A (Investigational drug)	Paroxetine IR tablets B (Reference drug)
Dosage formulation:	film-coated tablet	film-coated tablet
Unit dose strength:	20mg/tablet	20mg/tablet
Route of Administration	oral	oral
Dosing instructions:	2 tablets once daily	2 tablets once daily
Packaging and Labelling	Study Treatment will be provided in blister. Each container will be labelled as required per country requirement.	Study Treatment will be provided in bottle. Each container will be labelled as required per country requirement.
Manufacturer	TSKF (toll manufacture GSKT)	Mississauga

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

Participants will be randomly assigned to either regimen sequence (AB or BA) in a balanced manner to ensure similar proportions of participants on each sequence, according to a randomization schedule prepared in advance of the study by Statistics, GlaxoSmithKline, using internal validated software (i.e. RandAll).

7.4. Blinding

It is not applicable because this will be an open-label study.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of investigational product is required.

Investigational product must be dispensed or administered according to procedures described herein. Only participants enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All investigational product must be stored in a secure area with access limited to the investigator and authorized site staff. Investigational product is to be stored up to 25°C/protected from moisture and light. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from and returned to GSK and the amount administered to participants. The required counting unit for this study will be tablet. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused investigational product are listed in the Study Reference Manual (SRM).

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. 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 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.

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 nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) 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.

Concomitant medication may be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

7.8. Treatment after the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be stopped **for a participant** if the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

NOTE: Refer to Appendix 5 for details of the required assessments if a participant meets the above criteria**.**

8.1.2. QTc Stopping Criteria

- The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

- A participant that meets either criterion below will be withdrawn from the study. The same QT correction formula (e.g QTcB, QTcF) should be used to determine inclusion and discontinuation for any individual participant throughout the study.

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. Some of the possible reasons for withdrawing are:

  1. In the investigator's opinion, the participant has experienced serious adverse event or significant changes in laboratory measurements that necessitate discontinuation from the study and appropriate treatment measures. In this case the sponsor should be immediately informed.
  2. The participant or the physician in charge requires or the investigator decides that the participant should be discontinued from the study.
  3. The investigator or GSK terminate the entire study for any reason, or discontinue further participation of the participant in the study.
  4. Enrolment error, i.e., the participant fails to fulfil the inclusion/exclusion criteria for this study.
  5. Any situation meeting the exclusion criteria during study.
  6. Use of concomitant medications prohibited in the protocol. If possible, it is recommended to contact GSK before withdrawing.
  7. The participant is unable to tolerate the assigned doses. (Refer to Section 8.1. for participant specific dose adaptation/stopping criteria including Liver Chemistry and QTc.).
  8. The participant becomes pregnant.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- Refer to the SoA for data to be collected at the time of 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 or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are 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 (eg, 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 timing and number of planned study assessments, including safety, pharmacokinetic, assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IEC will be informed of

any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

9.1. Efficacy Assessments

No efficacy assessment will be conducted in this Bioequivalence study.

9.2. Adverse Events

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

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

9.2.1. 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.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee 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.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3.). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until follow up.
- 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 2.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of Paroxetine IR > 40mg/day will be considered an overdose.

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

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until Paroxetine IR can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 5 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.

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- A complete physical examination should be performed at screening. A brief physical examination should be made at the beginning/end of the study (Day 0, Day 11, Day 16 or early withdraw). Other routine medical assessments may also be performed during the study as clinically indicated.
- Height and weight will also be measured and recorded. The body weight and height measured at screening and Day 0 will be used for determining the inclusion criteria body mass index (BMI).

9.4.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at screening, when admitted to unit (Day 0 and Day 11) and as clinically indicated.
- Blood pressure and pulse rate will be measured pre-dosing (60 minutes pre-dosing to dosing time) and at 2h±60 minutes post-dosing on Day 1 and Day 12; on Days 2 (24h±60 minutes post-dosing), Days 3 (48h±60 minutes post-dosing), Day 4 (72h±60 minutes post-dosing), Days 5 (96h±60 minutes post-dosing), Days 13 (24h±60 minutes post-dosing), Day 14 (48h±60 minutes post-dosing), Days 15 (72h±60 minutes post-dosing), Days 16 (96h±60 minutes post-dosing); or early withdraw.
- Other vital signs may also be measured during the study as clinically indicated.

9.4.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA 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.
- If triplicate ECG is required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 5 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 Day 16 or early withdraw should be repeated in follow up visit.
- All protocol-required laboratory assessments, as defined in Appendix 5, 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 (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4.5. Suicidal Risk Monitoring

As an antidepressant, Paroxetine may increase the risk of suicidal ideation or behavior in some participants. Although there has been no evidence of Paroxetine and other antidepressants being associated with increased risk of suicidal ideation or behavior in healthy volunteers, GSK considers it as vital to closely monitor these events prior to and during the conduct of a clinical study.

The participants should receive appropriate assessments to be closely monitored (suicidal ideation/behavior, abnormal behavior changes). Withdrawal of Paroxetine should be considered in the occurrence of these conditions.

Columbia Suicide Severity Rating Scale (C-SSRS) will be used in this study for baseline assessment and for monitoring during the treamtent course.

The C-SSRS is a measure of suicidal ideation and behavior, with demonstrated predictive validity and reliability. Improved assessments of suicidal ideation and behavior are necessary to better understand the relationship between suicidal AEs and medication

treatment. The US FDA recommends the use of suicidality assessment instruments that map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). One such instrument is the C-SSRS. Sections of the C-SSRS include suicidal ideation, intensity of ideation, suicidal behavior, and actual suicide attempt(s). The C-SSRS assesses lifetime and current suicidal thoughts and behaviors across these categories based on an increasing severity of a 1- to 5-rating scale. The semi-structured questionnaire is completed by a trained and experienced neurologist, psychiatrist, or neuropsychologist, or another trained and experienced person approved by the Sponsor, who may be the principal investigator or a sub-investigator for the study. The interview is expected to take approximately 20 to 30 minutes to administer to the participant.

For any adverse events assessed by the investigator as related to suicidality, in addition to reporting in accordance with the adverse event and serious adverse event reporting procedures, the investigator will also need to complete the Possible Suicidality-related Adverse Event Form (PSRAE Form).

9.5. Pharmacokinetics

A vacuum tube pre-filled with ethylenediaminetetraacetic acid (EDTA) will be used to collect 3mL of whole blood for measurement of plasma concentrations of paroxetine as specified in the SoA. Sampling points are planned to be Immediately before and 0.5, 1, 2,3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hour after administration .Instructions for the collection and handling of biological samples will bespecified in SRM. The actual date and time (24-hour clock time) of each sample collection will be recorded. Refer to Appendix 6 for summary of blood sampling.

All plasma samples will be sent to Wuxi AppTec for bioanalysis. Paroxetine plasma concentrations will be determined using a validated method. The detailed information and results from sample analysis will be documented in the final sample analysis report.

Pharmacokinetic (PK) analyses will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) department in China. PK parameters will be determined from the paroxetine plasma concentration-time data and calculated by standard non-compartmental analysis according to current working practices and using WinNonlin 6.3 or higher version.

The main pharmacokinetic parameters include:

- $AUC_{0-\infty}$: Area under the concentration-time curve from time zero extrapolated to infinite time.
- AUC0-t: Area under the concentration-time curve from administration extrapolated to the last time of quantifiable concentration, calculated as logarithm of trapezoid area.
- Cmax: The observed maximum serum drug concentration
- Tmax: Time to reach Cmax
- t1/2: Terminal elimination half-time

- λz: Terminal elimination rate constant
- CL/F: Oral clearance
- Vd/F: Apparent volume of distribution
- MRT: Mean residence time

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

A sufficient number of participants (approximately36 for Fasting group and 44 for Fed group) will be enrolled so that approximately 32 participants in Fasting group and 40 participants in Fed group complete the study. The sample size was primarily determined by calculations as follows.

10.1.1. Sample Size Assumptions

Sample size calculations were based on within-participant estimates of variability (CV_W %) from two previous clinical pharmacology studies of **paroxetine** in healthy volunteers [data on file: Fasting study 973133 and Fed study 973134].

Fasting group: using the highest of the estimates of variability (21.4% for Cmax) in study 973133, it is estimated that a total sample size of 28 will provide at least 90% power to demonstrate equivalence of AUC and Cmax for paroxetine assuming a true ratio of 1.05. Based on the sample size sensitivity analysis, the sample size is further increased to **32** participants, which will provide at least 90% power if the CV_W% is **23.5%** (*which indicates an increase of 10% for the variability estimates in the reference study*).

Fed group: using the highest of the estimates of variability (24% for AUC) in study 973134, it is estimated that a total sample size of 34 will provide at least 90% power to demonstrate equivalence of AUC and Cmax for paroxetine assuming a true ratio of 1.05. Based on the sample size sensitivity analysis, the sample size is further increased to **40** participants, which will provide at least 90% power if the CV_W% is **26.4%** (*which indicates an increase of 10% for the variability estimates in the reference study*).

Equivalence is considered being demonstrated when the 90% confidence interval for the ratio of Test (A): Reference (B) (*A= paroxetine IR 20 mg GSKT tablet , B= paroxetine IR 20 mg Mississauga tablet*) of AUC, and of Cmax, each separately, is completely contained within the range (0.80, 1.25) [Schuirmann, 1987]. This range represents a symmetric 20% range on the log-scale. This calculation was based on a two one-sided testing procedure, each with a type I error rate of 5%.

10.1.2. Sample Size Sensitivity

The sensitivity analyses were conducted based on different scenarios. The power to demonstrate equivalence for AUC and Cmax between the test drug (A) and reference drug (B) given the final determined sample size (32 participants for fasting group and 40

participants for fed group) is provided below. This calculation was also based on a two one-sided testing procedure, each with a type I error rate of 5%.

True Ratio	Fasting group (32 participants)		Fed group (40 participants)	
	CV_W %	Power	CV_W %	Power
1	21.4%	98.67%	24%	98.74%
1.05	21.4%	94.2%	24%	94.38%
1.1	21.4%	76.31%	24%	76.65%
1	23.5% (10% inflated)	96.57%	26.4% (10% inflated)	96.68%
1.05	23.5% (10% inflated)	90.06%	26.4% (10% inflated)	90.25%
1.1	23.5% (10% inflated)	69.5%	26.4% (10% inflated)	69.77%
1	24.6% (15% inflated)	94.91%	27.6% (15% inflated)	95.13%
1.05	24.6% (15% inflated)	87.52%	27.6% (15% inflated)	87.83%
1.1	24.6% (15% inflated)	66.13%	27.6% (15% inflated)	66.52%
1	25.7% (20% inflated)	92.86%	28.8% (20% inflated)	93.22%
1.05	25.7% (20% inflated)	84.78%	28.8% (20% inflated)	85.23%
1.1	25.7% (20% inflated)	62.92%	28.8% (20% inflated)	63.42%

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All participants	All participants who signed the ICF
PK population	All randomized participants who take at least 1 dose of study treatment and provide valid pharmacokinetic data.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

Data will be displayed separately for each group (Fasting or Fed).

10.3.1. Efficacy Analyses

No efficacy analysis is planned in this Bioequivalence study.

10.3.2. Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Primary	Mixed effect model with period and treatment as fixed effects and participant as random effect.
Secondary	Will be summarized with descriptive methods

Pharmacokinetic parameter of paroxetine will be analyzed by non-compartmental methods with WinNonlin Phoenix [version 6.3 or higher version]. Calculations will be based on the actual sampling times recorded during the study. From the serum concentration-time data, the pharmacokinetic parameters in Section 9.5. will be calculated.

The focus of the statistical analysis of the pharmacokinetic data is to demonstrate bioequivalence of paroxetine IR 20 mg GSKT tablet and paroxetine IR 20 mg Mississauga tablet.

After $\log_e$-transformation, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and C_{max} will be analyzed, each separately, using mixed effect model. The model will include period and treatment as fixed effects, and participant as random effects. Point estimates and their associated adjusted 90% confidence interval of difference between A and B will be provided for the above mentioned PK parameters in log scale. The point estimates and their associated adjusted 90% confidence intervals will then be back-transformed to provide point estimates and adjusted 90% confidence intervals for the ratios of A : B. If the 90% confidence interval of $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ ($AUC_{(0-t)}$ only if $AUC_{(0-\infty)}$ can't be accurately determined) and C_{max} fall in the range of 0.80-1.25, it can be stated that the two formulations are bioequivalent.

All pharmacokinetic parameters will be presented in graphical and/or tabular form and will be summarized descriptively in PK population. Details will be provided in Reporting and Analysis Plan (RAP).

10.3.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary	Will be summarized with descriptive methods

All safety analyses will be performed on the Safety Population. All the subjects who have taken study drug will be included in safety population.

No formal statistical analysis of safety data will be performed.

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ classes (SOCs) and preferred term (PT). All adverse events will be listed. A summary of the number and percentage of participants reporting each AE at least once will be produced for all AEs and also for drug-related AEs. A listing showing the relationship of AE verbatim text to group terms and body systems will also be produced.

Vital signs, ECG and clinical laboratory data will be reviewed and summarized during the study to evaluate the safety of subjects. Any clinically relevant abnormalities or values of potential clinical concern will be described.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to the Clinical Data Interchange Standard Consortium (CDISC). More details will be specified in RAP.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

λz	Terminal elimination rate constant
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinite time
AUC_{0-t}	Area under the concentration-time curve from administration extrapolated to the last time of quantifiable concentration
BE	bioequivalence
BMI	body mass index
CFDA	China Food and Drug Administration
CL/F	Oral clearance
Cmax	The observed maximum serum drug concentration
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DC	direct compression
ECG	Electrocardiogram
GSK	GlaxoSmithKline
GSKT	GlaxoSmithKline Tianjin
hCG	human chorionic gonadotropin
ICF	informed consent form
IDSL	Integral Data Standard Library
IEC	Independent Ethics Committees
IR	immediate release
IRB	Institutional Review Boards
MAOIs	monoamine oxidase inhibitors
MDD	major depressive disorder
MRT	mean residence time
MSDS	Material Safety Data Sheet
OCD	obsessive compulsive disorder
OTC	over the counter
PD	panic disorder
PK	pharmacokinetic
PSRAE	Possible Suicidality-related Adverse Event
PT	preferred term
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan

SAD	social anxiety disorder
SAE	serious adverse event
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SOA	Schedule of Activities
SOC	system organ class
SRM	Study Reference Manual
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reactions
t1/2	Terminal elimination half-time
Tmax	Time to reach Cmax
TSKF	Tianjin SmithKline & French
ULN	upper limit of normal
Vd/F	Apparent volume of distribution
WG	wet granulation

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the study and until follow up contact:
    - 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 following when having penile-vaginal intercourse with a woman of childbearing potential:
  - Oral contraceptive, either combined or progestogen alone
  - Injectable progestogen
  - Implants of etonogestrel or levonorgestrel
  - Estrogenic vaginal ring
  - Percutaneous contraceptive patches
  - Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
  - Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).
- 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 study and until follow up contact
- Refrain from donating sperm for duration of study and until follow up.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the following Highly Effective Contraceptive Methods:

- 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.)
- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).
- 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.)

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is

responsible for ensuring subjects understand how to properly use these methods of contraception.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 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.

Female Participants who become pregnant

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

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue the study treatment.

12.3. Appendix 3: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN

If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor 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
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:

• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma</td></tr>
</table>

liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	globulins. • 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 IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

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

Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- 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.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study 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 Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the project contact for SAE receipt. • 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 Sponsor information page.

12.5. Appendix 5: Clinical Laboratory Tests

Haematology, clinical chemistry, urinalysis and additional parameters will be tested at local laboratory.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Haematology

Platelet Count	*Red Blood Cell (RBC Indice)s*:	*Automated White Blood Cell (WBC) Differential:*
RBC Count	Mean corpuscular volume (MCV)	Neutrophils
WBC Count (absolute)	Mean corpuscular haemoglobin (MCH)	Lymphocytes
Hematocrit	Mean corpuscular haemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
		Basophils

Clinical Chemistry

Blood urea nitrogen (BUN)	Sodium	AST (SGOT)	Total and direct bilirubin
Creatinine	Potassium	ALT (SGPT)	Uric Acid
LDH	Chloride	Alkaline phosphatase	Albumin
Gamma-glutamyl transferase (GGT)	Calcium	Total cholesterol	Total Protein
Glucose, fasting			

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other screening tests

Pregnancy test
HIV,Syphilis
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

12.6. Appendix 6: Summary of Blood Sampling

This table summarizes the estimated number of venipunctures and blood volumes required for PK sample collection during the study. Blood volumes required for screening, safety laboratory tests will be determined according to local lab requirement. The frequencies of venipuncture and blood sample collection can be increased for safety considerations without amending the protocol.

Objectives	Estimated blood volume taken for each sampling (mL)	Estimated number of blood samples	Estimated total volume of blood samples (mL)
Paroxetine assay	3	36	108

Sampling time window

Sampling point	Pre dose-3 h	4-16 h	24-36h	48-96h
Window	± 5 min	± 15 min	± 30 min	± 60 min

12.7. Appendix 7: 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 ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative 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 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

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

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by 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 SDV agreement and addendum to SDV agreement.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.8. Appendix 8: Protocol Amendment History

Amendment 1 20-JUL-2018

Overall Rational for the Amendment

The amendment of this protocol including:

Section # and Name	Description of Change	Brief Rationale
Title page	Sponsor change	Sponsor change
9.4.2 Vital Signs	Add time window for blood pressure and pulse rate assessing	To have better instruction for procedures
10.3.3 Safety Analyses	Change data standard description from IDSL to CDISC.	Data collection strategy changed
Through out	Minor editorial and document formatting revision	Minor, to make the protocol to be consistent

TITLE PAGE

 # Change 1:

Reason for change: Sponsor change

From:

Sponsor Name and Legal Registered Address:

GlaxoSmithKline (China) Research & Development Limited
No. 1 building, 917 Halei Road
Zhangjiang Hi-tech Park, Pudong

Shanghai, 201203, China

To:

Sponsor Name and Legal Registered Address:

GlaxoSmithKline (China) Investment Co., LTD.
9/F Tower A, Ocean International Centre
Mid 4thEast Ring Rd, Chaoyang District
Beijing, 200025, China

9.4.2. Vital Signs

#Change 2:

Reason for change: Add time window for blood pressure and pulse rate to have better instruction for procedures.

From:

Blood pressure and pulse rate will be measured pre-dosing and at 2h post-dosing on Day 1 and Day 12; on Days 2(24h), 3, 4, 5, 13(24h), 14, 15, 16; or early withdraw.

To:

Blood pressure and pulse rate will be measured pre-dosing (60 minutes pre-dosing to dosing time) and at 2h ±60 minutes post-dosing on Day 1 and Day 12; on Days 2 (24h±60 minutes post-dosing), Days 3 (48h±60 minutes post-dosing), Day 4 (72h±60 minutes post-dosing), Days 5 (96h±60 minutes post-dosing), Days 13 (24h±60 minutes post-dosing), Day 14 (48h±60 minutes post-dosing), Days 15 (72h±60 minutes post-dosing), Days 16 (96h±60 minutes post-dosing); or early withdraw.

10.3.3. Safety Analyses

 # Change 3:

Reason for change: Data collection strategy changed.

From:

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK Integral Data Standard Library (IDSL).

To:

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to the Clinical Data Interchange Standard Consortium (CDISC).

Through out

 # Change 4:

2. Schedule of activities (SOA)

Reason for change: to make the protocol be consistent as per ‘9.4.2 Vital Signs’, vital signs should be assessed at Day 11.

From:

	Second Period						**Early Withdraw**	**Follow up[5]**
Study day	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**		**7-14 days after last dose**
Visit	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Administration		×						
Standard Meal (fed group)		×						
Sampling (hour after dosing)		**Pre, ,0.5, 1, 2,3, 4, 5, 6, 7, 8, 10, 12, 16**	**24,36**	**48**	**72**	**96**		
Inclusion/exclusion criteria	×							
C-SSRS[2]						×	×	
Weight/Height						×	×	
Physical examination	×					×	×	R
Vital signs[3]		×	×	×	×	×	×	R
12-lead ECG						×	×	R
Laboratory tests [5]						×	×	R
Pregnancy test (WOCBP)[4]	×					×	×	
Concomitant medication	→							
AE	→							
SAE	→							

Key: × = Mandatory Assessment; R =Repeated in case of abnormal results from the last visit.

7. Medical history: Medical and medication history and Alcohol/Smoking history
8. C-SSRS: Screening visit use 'baseline' version. The following visit use 'since last visit' version.
9. Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at screening, when admit to unit (Day 0 and Day 11) and as clinically indicated. Blood pressure and pulse rate will be measured pre-dosing and at 2h post-dosing on Day 1 and Day 12; on the Day 2(24h), 3, 4, 5, 13(24h), 14, 15, 16; or early withdraw.
10. WOCBP=Woman of Childbearing Potential. Pregnancy test: either urine or serum test is valid.
11. Clinical laboratory tests including haematology, clinical chemistry and routine urinalysis. Refer to Appendix 5 for more details.
12. The participant will complete follow-up 7-14 days after last dose of medication. The follow-up can be visited by telephone if the participant does not need to receive any examination.

To:

	Second Period						**Early Withdraw**	**Follow up[5]**
Study day	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**		**7-14 days after last dose**
Visit	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Administration		×						

Standard Meal (fed group)		×						
Sampling (hour after dosing)		**Pre, ,0.5, 1, 2,3, 4, 5, 6, 7, 8, 10, 12, 16**	**24,36**	**48**	**72**	**96**		
Inclusion/exclusion criteria	×							
C-SSRS[2]						×	×	
Weight/Height						×	×	
Physical examination	×					×	×	R
Vital signs[3]	×	×	×	×	×	×	×	R
12-lead ECG						×	×	R
Laboratory tests [5]						×	×	R
Pregnancy test (WOCBP)[4]	×					×	×	
Concomitant medication	→							
AE	→							
SAE	→							

Key: × = Mandatory Assessment; R =Repeated in case of abnormal results from the last visit.

13. Medical history: Medical and medication history and Alcohol/Smoking history
14. C-SSRS: Screening visit use 'baseline' version. The following visit use 'since last visit' version.
15. Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at screening, when admit to unit (Day 0 and Day 11) and as clinically indicated. Blood pressure and pulse rate will be measured pre-dosing and at 2h post-dosing on Day 1 and Day 12; on the Day 2(24h), 3, 4, 5, 13(24h), 14, 15, 16; or early withdraw.
16. WOCBP=Woman of Childbearing Potential. Pregnancy test: either urine or serum test is valid.
17. Clinical laboratory tests including haematology, clinical chemistry and routine urinalysis. Refer to Appendix 5 for more details.
18. The participant will complete follow-up 7-14 days after last dose of medication. The follow-up can be visited by telephone if the participant does not need to receive any examination.

 # Change 5:

5.2. Number of Participants

Reason for change: to make the protocol be consistent as early withdraw participants could be replaced according to Section 5.2.

From:

A sufficient number of healthy participants (approximately 36 for Fasting group and 44 for Fed group) will be enrolled so that approximately 32 participants in Fasting group and 40 participants in Fed group complete the study. Either gender of evaluable participants should be no less than one-third of the total evaluable participants. The early withdrawn participants will not be replaced.

To:

A sufficient number of healthy participants (approximately 36 for Fasting group and 44 for Fed group) will be enrolled so that approximately 32 participants in Fasting group and 40 participants in Fed group complete the study. Either gender of evaluable participants should be no less than one-third of the total evaluable participants.

 # Change 6:

9.4.1 Physical Examination

Reason for change: to make the protocol be consistent as per Section '2 Schedule of activities (SOA)', physical examination should be performed at Day 11.

From:

A complete physical examination should be performed at screening. A brief physical examination should be made at the beginning/end of the study (Day 0, Day 16 or early withdraw). Other routine medical assessments may also be performed during the study as clinically indicated.

To:

A complete physical examination should be performed at screening. A brief physical examination should be made at the beginning/end of the study (Day 0, Day 11, Day 16 or early withdraw). Other routine medical assessments may also be performed during the study as clinically indicated.

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1	20-Jul-2018	2017N312753_01
Original Protocol	01-Jun-2017	2017N312753_00