PROJECT NO. / PROTOCOL NO.: AS/BK/OCT-19/0055

Sponsor Code: 212969

TITLE

An oral single-dose, randomized, balanced, open-label, two-sequence, two-treatment, two-period, crossover bioequivalence study of Paroxetine tablets 20 mg of GlaxoSmithKline Pharmaceuticals S.A, with that of PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México S.A. de C.V., in healthy adult male and female subjects under fasting conditions.

Version No.: 02

Date: 12/Oct/2020

CONTRACT RESEARCH ORGANIZATION	SPONSOR
Avant Santé Research Center S.A. de C.V. Av. Lázaro Cárdenas No. 500 Col. Residencial San Agustín San Pedro Garza García, Nuevo León México, C.P. 66260 Tel.: PPD www.avantsante.com	GlaxoSmithKline México, S.A. de C.V. Calzada México Xochimilco No. 4900 Col. San Lorenzo Huipulco 14370 Ciudad de México.

CONTACT INFORMATION OF SPONSOR / INVESTIGATOR

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Primary Study Manager:

PPD

PPD

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Sponsor's Authorized Signatory:

Sigfrido Manuel Rangel Frausto

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Author: This protocol is prepared based on the available literature and applicable regulatory requirements to the best of my knowledge, as well as of previous experience from the sponsor GlaxoSmithKline México, S.A. de C.V.

Name: _____ Signature and Date: _____

STATEMENT OF COMPLIANCE

We, the undersigned have read and understood this protocol and hereby agree to conduct the study in accordance with the same and to comply with all the requirements regarding the obligations of investigators and all other pertinent requirements of the NOM 177-SSA1-2013 (COFEPRIS), the Declaration of Helsinki, the ICH Guidelines on Good Clinical and Laboratory Practices (WHO) of COFEPRIS and all internal relevant SOPs. We further agree to ensure that all the personnel involved in the conduct of this study are duly informed regarding their obligations.

Signature: _____ **Date: _____**
Dr. Javier Jesús Osorio Escobar
Principal Investigator

Signature: _____ **Date: _____**
Dr. José Guillermo Sander Padilla
Clinical Investigator

Signature: _____ **Date:** _____

Biol. PPD

PPD

Signature: _____ **Date:** _____

PPD **, PhD.**

PPD

Signature: _____ **Date:** _____

PPD **, PhD.**

PPD

SANITARY RESPONSIBLE AND QUALITY ASSURANCE

Signature: _____ **Date:** _____

Q.F.B PPD

PPD

Signature: _____ **Date:** _____

M. Sc. PPD

PPD

Signature: _____ **Date:** _____

M.B.A. PPD

PPD (Clinical and Bioanalytical Unit)

SPONSOR'S APPROVAL

I, the undersigned, have read and understood this protocol and agree hereby to have the study conducted in accordance with the same and to comply with all the requirements regarding the obligations of Sponsor and all other pertinent requirements of the current NOM-177-SSA1-2013 (COFEPRIS), of the Declaration of Helsinki, ICH Guidelines on Good Clinical and Laboratory Practices (WHO) and of COFEPRIS.

_____ Date: _____

Authorization Signature

Sigfrido Manuel Rangel Frausto
GlaxoSmithKline México, S.A. de C.V.
Calzada México Xochimilco No. 4900 Col.
San Lorenzo Huipulco 14370 Ciudad de México
Ph. No.: PPD
Email: PPD

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ABBREVIATIONS

ADR(s)	:	Adverse Drug Reaction(s)
AE(s)	:	Adverse Event(s)
ANOVA	:	Analysis of Variance
AUC_{0-inf}	:	Area Under Plasma Concentration-Time Curve from Time 0 to Infinite
AUC_{0-t}	:	Area Under Plasma Concentration-Time Curve from Time Zero to the Last Measurable Concentration
BLOQ	:	Below the Limit of Quantification
BMI	:	Body Mass Index
C_{max}	:	Maximum Concentration Observed in Plasma
COFEPRIS	:	Federal Commission for the Protection against Sanitary Risk (Comisión Federal para la Prevención contra Riesgos Sanitarios)
CNFV	:	Pharmacovigilance National Center (Centro Nacional de Farmacovigilancia)
CNS	:	Central Nervous System
CoA	:	Certificate of Analysis
COVID-19	:	The coronavirus disease
COX-2	:	Cyclooxygenase-2
CRF(s)	:	Case Report Form(s)
CV	:	Coefficient of Variation
CYP	:	Cytochrome P
ECG	:	Electrocardiogram
GCP	:	Good Clinical Practices
GLP	:	Good Laboratory Practices
H	:	Hour
HIV	:	Human Immune Deficiency Virus
ICF	:	Informed Consent Form
ICH	:	International Council for Harmonization
ICU	:	Intensive Care Unit
IP(s)	:	Investigational Product(s)
Kg	:	Kilogram

L	:	Liter
LOQ	:	Limit of quantification
M	:	Missing Sample
m^2	:	Square Meter
MAOIs	:	Monoamine Oxidase Inhibitors
mg	:	Milligram
mL	:	Milliliter
mmHg	:	Millimeter of Mercury
Ng	:	Nanogram
NOM	:	Mexican Official Norm
NSAIDs	:	Nonsteroidal Anti-Inflammatory Drugs
OCD	:	Obsessive Compulsive Disorder
OTC	:	Over-the-counter
pH	:	Potential hydrogen
PI	:	Principal Investigator
QA	:	Quality Assurance
QC	:	Quality Control
QT	:	Q-wave and T-wave
REC/RC	:	Research Ethics Committee / Research Committee
RLS	:	Restless Legs Syndrome
RMF	:	Research Master File
Rpm	:	Revolutions Per Minute
RT-PCR	:	Real time–Polymerase Chain Reaction
SADR(s)	:	Serious Adverse Drug Reaction(s)
SAE(s)	:	Serious Adverse Event(s)
SARS-CoV-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	:	Statistical Analysis System
SGPT/ALT	:	Serum Glutamate Pyruvate Transaminase / Alanine Transferase
SGOT/AST	:	Serum Glutamate Oxaloacetate Transaminase / Aspartate Transferase
SIADH	:	Syndrome of Inappropriate Anti-Diuretic Hormone Secretion
SOP(s)	:	Standard Operating Procedure

SSRIs	:	Selective Serotonin Reuptake Inhibitors
$t_{½}$	:	Half-Life
TCAs	:	Tricyclic Antidepressants
THC	:	Tetra Hydro Cannabinoids
TMF	:	Trial Master File
T_{max}	:	Time of the Maximum measured plasma concentration
UADR(s)	:	Unexpected Adverse Drug Reaction(s)
UPLC	:	Ultra Performance Liquid Chromatography
USFDA	:	United States Food and Drug Administration
VDRL	:	Venereal Disease Research Laboratory
%	:	Percent
^0C	:	Degree Celsius
µg	:	Microgram
5-HT	:	5-hydroxytryptamine

1.0 PROTOCOL SUMMARY

Study Title	An oral single-dose, randomized, balanced, open-label, two-sequence, two-treatment, two-period, crossover bioequivalence study of Paroxetine tablets 20 mg of GlaxoSmithKline Pharmaceuticals S.A, with that of PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México S.A. de C.V., in healthy adult male and female subjects under fasting conditions.
Regulatory Agency and Country of Submission	COFEPRIS-México.
Study Objective	Primary Objective: To evaluate and compare the single oral dose bioavailability of Paroxetine tablets 20 mg manufactured by GlaxoSmithKline Pharmaceuticals S.A. for GlaxoSmithKline México, S.A. de C.V. with that of PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México, S.A. de C.V. in healthy, adult, male and female subjects under fasting conditions. Secondary Objective: To evaluate safety and tolerability of single oral dose of Paroxetine 20 mg tablets in healthy adult male and female subjects under fasting conditions.
Study Design	An oral single-dose, randomized, balanced, open-label, two-sequence, two-treatment, two-period, crossover bioequivalence study under fasting conditions.
Sample Size	At least 34 healthy adult male and female subjects will be randomized and dosed in this study.

Study Treatments	**Test product (A):** Paroxetine tablets 20 mg. [Paroxetine as Paroxetine hydrochloride]. Manufactured by: GlaxoSmithKline Pharmaceuticals S.A. Manufactured for: GlaxoSmithKline México, S.A. de C.V. **Reference product (B):** PAXIL (Paroxetine as Paroxetine hydrochloride) tablets 20 mg. Manufactured by: GlaxoSmithKline México, S.A. de C.V. Sanitary Registration Number: 008M93SSA IV**.**
Introduction	Paroxetine is an antidepressants drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3$•HCl•1/2H_2O. Paroxetine is indicated for the treatment of: • Major depressive disorder. • Obsessive Compulsive Disorder (OCD). • Panic disorder with and without agoraphobia. • Social anxiety disorders/social phobia. • Generalised anxiety disorder. • Post-traumatic stress disorder.
Screening (selection and enrollment)	Healthy adult male & female volunteers, light or non or ex-smokers, aged between 18 and 55 years (both inclusive), with a weight ≥ 50.00 kg, with a BMI between ≥ 18.0 and ≤ 27.0 kg/m^2 will be selected according to the inclusion and exclusion criteria.

	All the subjects will have a medical history during the selection and enrollment process. Volunteers shall be found healthy according to the physical examination (including vital signs assessment), normal laboratory test results and 12-lead ECG. The physical examination findings, ECG and laboratory tests will be considered valid for a maximum period of 90 days prior to the dosing on the first period of the study. Pregnancy test in urine will be carried out during the screening period and at the time of each period check-in for all female subjects. Real-time (RT-PCR) test for the detection and diagnosis of SARS-COV-2 will be carried out within the 72 hours prior to the first period check-in for all the subjects. Avant Santé Research Center S.A. de C.V. will ensure the volunteer participation history by verifying the COFEPRIS database for bioequivalence studies.
Drug Administration (Dosing)	In each study period, all subjects will be required to fast overnight for at least 10.00 hours prior to dosing until at least 04.00 hours post-dose. In each study period, a single-dose of either the test product (A) or reference product (B) will be orally administered to the subjects in sitting posture along with 250 mL of water at room temperature under fasting conditions. The administration of the test or reference products to each subject will be performed as per a randomization schedule. The subjects will be instructed to swallow the tablet as a whole as mentioned in the prescribing information and not to touch the tablet with their hands, chew or crush the tablet since this can affect the drug release.

	Hands and mouth will be checked after dosing to ensure compliance and also the subject does not touch the IP with hands. Immediately after dosing in each period trained study personnel will evaluate the compliance by supervising the complete administration procedure SOP CP020 (Administration of the Investigational Product). Drug administration will be registered in the respective source documents.
Dietary Plan	Subjects will be provided with standard meals throughout their stay in the facilities. On the check-in day (day -1) they will receive dinner, which will be finished at the latest 10.00 hours prior to dosing at the following day in each study period. Subjects will be required to fast overnight for at least 10.00 hours prior to dosing and until at least 04.00 hours post-dose in each study period. After the dose administration of test or reference product (day 1), lunch, snack and dinner will be provided at 04.00, 08.00 and 12.00 (with a grace period of + 45 minutes) hours post-dose respectively, in each study period. The meal plan will be uniform for all the subjects and same between the study periods. Information on the amount of meal consumed and the time of consumption by each subject will be registered in the respective source documents.
Study Restrictions	All subjects will be instructed to follow the below mentioned restrictions for at least 72.00 hours prior to dosing and till last blood sample collection in each study period: • Smoking of cigarettes or nicotine containing products. • Any food or beverages containing xanthine- (tea, coffee, theobromine, theophylline, chocolates, cola drinks, etc.).

	• Alcohol or related products. • Smoked or carbon cooked food. • Beverages with pomelos or grapefruit juice or products containing grapefruit extract (e.g. soda). Medications All subjects will be asked about their medication history. They will be instructed not to take any medication until the study is completed; particularly during the last 14 days preceding the first dosing for any prescribed medication, the last 7 days before for OTC medicinal or herbal products used for therapeutic purposes, and the last 30 days before for any enzyme inhibiting / inducing drugs preceding the first dosing. Subjects will be specifically reminded that the restriction mentioned above includes analgesics, cold & anti-allergic preparations, vitamins and natural products used for therapeutic benefits and antacid preparations. Vitamins used as nutritional supplements in non-therapeutic doses (as judged by the principal investigator or designee) may be accepted, but their consumption must be stopped from at least 7 days prior to the dosing and until the study is completed. Fluid (water) restriction The subjects will not be allowed to drink water 1 hour before and until 2 hours post-dose except for the 250 mL of water provided for the dosing, unless it is clinically indicated; at all other times water will be provided *ad libitum*. Postural (activity) Restriction The dose will be administered to all subjects at the scheduled time and subjects will be instructed to remain in comfortable sitting position for the first 02.00

	hours following the drug administration except when clinically indicated or protocol specified activity (blood sample collection) or due to natural exigencies. After 02.00 hours post-dose, subjects will be allowed to wander and will be advised to avoid any severe physical exertion. In case of an adverse event (AE), subjects will be maintained in the proper position as per physician's assessment in each study period.
Housing	Subjects will be in the clinical facility from at least 10.50 hours prior to the dosing until the last in-house blood sample collection i.e. 24 hours in each study period. Subjects will visit clinical facility at 36.00, 48.00 and 72.00 hours for the collection of the ambulatory samples in each study period. Subjects will be instructed to self-quarantine during the outpatient period of the study i.e. until 72 h blood sample collection in period-2 or until withdrawal, whichever is earlier, and to monitor at home their daily body temperature.
Washout Period	There will be a washout period of at least 7 days between successive dosing.
Sampling Schedule	In each study period, a total of 24 blood samples (4 mL each) will be collected from each subject as per the following schedule: • The first blood sample will be collected within 1.50 hours prior to the dosing (00.00 hours / pre-dose). • The remaining samples will be collected after the dosing of the test or reference drug at 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 09.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours.

	• The samples corresponding to 36.00, 48.00 and 72.00 hours post dose will be collected on separate visits as ambulatory sample in each period of the study. The total blood volume collected from each subject will not exceed 223 mL, which includes about 10 mL for the selection process (selection and enrollment), 21 mL for the discarded heparinized blood and 192 mL for the pharmacokinetic evaluation. If circumstances arise, where more than 223 + 10 mL of blood from each subject needs to be withdrawn the subject will be asked for additional consent and REC / RC will be informed.
Blood Sample Collection, Processing and Storage	Once collected, the blood samples will be placed in an ice-filled container or another cooling device until the centrifugation process is started. Centrifugation process will be started within 45 minutes from the time of blood sample collection and will be performed at 3000 rpm for 10 minutes at 4 ± 2 ºC. The plasma obtained from blood samples will be transferred as soon as possible into two different cryo-tubes (aliquot 1 and aliquot 2), pre-labeled with project number, period number, subject number, sample number and aliquot number. The plasma volume obtained from blood sample will be allocated as follows: Aliquot 1: 1.0 mL of plasma (approximately). Aliquot 2: rest of the plasma. All plasma samples (aliquot 1 for sample analysis and aliquot 2 as back-up) will be stored at a temperature of -50 °C or below.
Safety Assessment	Medical examination will be performed before check-in, prior to the dosing and before the check-out in each study period.

	Nevertheless, it may also be performed at any time during the study conduction if judged necessary by the physician. Physical examination will be performed before check-in of each study period and may also be performed at any time during the study conduction if judged necessary by the physician. Vital signs (sitting blood pressure, pulse rate, respiratory rate and axillary-body temperature) will be measured and registered at the time of check-in, prior to dosing, at 03.00, 05.00 and 12.00 hours (within ±45 minutes) after the dosing, before the check-out and at the time of each ambulatory sample collection in each study period. The subjects' well-being will be asked at the time of the medical examination, during the vital signs recording and at the time of each ambulatory sample collection in each study period; this will be registered in the respective source document. Seven (7) to 9 days after the collection of 72-h blood sample in second period or after the withdrawal, a telephone call will be made to each subject by the personnel designated by the PI to monitor any serious adverse event, specifically, subjects will be questioned about any symptoms related to COVID-19.
Bioanalysis	The concentration of Paroxetine in plasma samples collected during the study will be quantified using a validated bioanalytical UPLC/MS-MS method (LOQ - 0.106 ng/mL) according to COFEPRIS guidelines, GLP and in-house SOPs. Method validation and subject sample analysis will be performed using same anticoagulant (K_2-EDTA) that will be used for blood sample collection in clinical phase.

Pharmacokinetic Parameters	Employing the observed concentration vs. time profiles of Paroxetine and using WinNonlin® software (version 6.4 or higher), the following pharmacokinetic parameters will be calculated: • Primary Variables: C_{max} and $AUC_{0-t.,}$ • Secondary Variables: $AUC_{0-inf,}$ AUC_% Extrap, T_{max}, Kel, $t_{½}$.
Statistical Analysis	Descriptive statistics will be calculated. Statistical analysis will be performed by using ANOVA on ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-t.}$ The statistical model used in this research is a general linear model and the same is covered in protocol section 14.3
BE Criteria	Based on the statistical results of classic 90% confidence interval for the ratio of the geometric least squares means for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Paroxetine conclusion will be drawn for test product (A) vs. the reference product (B) under fasting conditions. The bioequivalence of the test product (A) with that of the reference product (B) under fasting conditions will be concluded, if the 90% Confidence Intervals of the ratio of the test and reference product (test/reference) falls within the acceptance range of 80.00 – 125.00% for the ln-transformed parameters C_{max} and AUC_{0-t} for Paroxetine.
Ethical Considerations	This study will be conducted carried as per NOM-177-SSA1-2013, COFEPRIS guidelines, ICH-GCP and principles of Declaration of Helsinki (Fortaleza, Brazil, October 2013). Protocol, Case Report Form (CRF) and the informed consent form (ICF) approval will be taken from the REC / RC, and COFEPRIS before initiation of the study.

Clinical Study Report	The clinical study report will be prepared as per NOM-177-SSA1-2013 (COFEPRIS) and sponsor requirements, having all the clinical, bioanalytical, pharmacokinetic and statistical data subjected to Quality Assurance audits.
Archiving	The raw data and reports will be filed at Avant Santé Research Center S.A. de C.V, with controlled access for 30 years. Avant Santé Research Center S.A. de C.V. will not destroy/discard any document related to the study without written confirmation from the sponsor.

2.0 STUDY RELATED SERVICES

2.1 Research Ethics Committee

Research Ethics Committee of Avant Santé Research Center S.A. de C.V.,

Av. Lázaro Cárdenas # 500, Col. Residencial San Agustín,

San Pedro Garza García, N. L.,

México, C. P. 66260.Tel: PPD to PPD

2.2 Research Committee

Research Committee of Avant Santé Research Center S.A. de C.V.,

Av. Lázaro Cárdenas # 500, Col. Residencial San Agustín,

San Pedro Garza García, N. L.,

México, C. P. 66260.Tel: PPD to PPD.

2.3 Clinical Diagnostic Laboratory

- Swiss Lab (SwissLab S.A. de C.V.)

  Río San Juan 200, Miravalle, CP 64660.

  Monterrey, N.L. México, Tel. PPD

  and / or

- Grupo Diagnóstico Médico Proa S.A. de C.V. (This lab is considered as a back-up)

  Alfonso Herrera 75, Col. San Rafael, Delegación Cuauhtémoc. Ciudad de México. México. CP 06470. Tel: PPD

2.4 Contract Hospital

Swiss Hospital S.A.P.I. de C.V.,

Río San Juan # 200, Colonia Miravalle, Monterrey, Nuevo León, México,

C.P. 64650, Tel: PPD, Emergencies: PPD

2.5 Ambulance

Emergencia Médica Profesional, S. C.

Calzada San Pedro No. 504-A, Colonia Fuentes del Valle, San Pedro Garza García, Nuevo León. C.P. 66220

Tel: PPD , Emergency: PPD

2.6 Clinical Unit

Avant Santé Research Center S.A. de C.V.

Ave. Lázaro Cárdenas No. 500, Col. Residencial San Agustín, San Pedro Garza García, Nuevo León, México, C.P. 66260

Tel.: PPD to PPD

2.7 Bioanalytical Unit

Avant Santé Research Center S.A. de C.V.

Ave. Lázaro Cárdenas No. 500,

Col. Residencial San Agustín, San Pedro Garza García, Nuevo León, México, C.P. 66260

Tel.: PPD to PPD

2.8 Biostatistics Service

Avant Santé Research Center S.A. de C.V.

Ave. Lázaro Cárdenas No. 500, Col. Residencial San Agustín,

San Pedro Garza García, Nuevo León, México, C.P. 66260

Tel.: PPD to PPD

2.9 Biological Waste Management

Veolia Soluciones Industriales México, S.A de C.V

Av. Lázaro Cárdenas No. 435, PISO 10, Col. Zona Loma Larga Oriente

San Pedro Garza García, Nuevo León C.P 66266

Tel.: PPD Fax PPD

e-mail: PPD www.veolia.com.mx

3.0 BACKGROUND INFORMATION

Paroxetine is an antidepressant drug [1]. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'fluorophenyl)-3S- [(3',4' methylene di oxy phenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3$•HCl•1/2H_2O. Its molecular weight is 374.8 g/mol. and its structural formula is: [2]

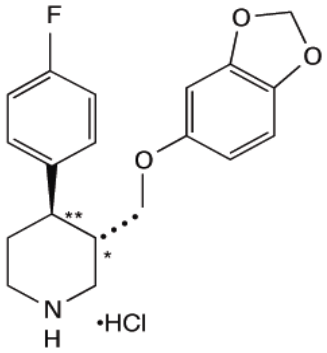

Figure 1 Paroxetine hydrochloride structural formula

3.1 Mechanism of Action

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) reuptake and is thought to be related to its specific inhibition of 5-HT reuptake in brain neurons.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for alpha1, alpha2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) receptors. This lack

of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS depressant and hypotensive properties. [1]

3.2 Therapeutic Indications

Paroxetine is indicated for the treatment of:

- Major depressive disorder.
- Obsessive Compulsive Disorder (OCD).
- Panic disorder with and without agoraphobia.
- Social anxiety disorders/social phobia.
- Generalised anxiety disorder.
- Post-traumatic stress disorder. [1]

3.3 Pharmacokinetics

3.3.1 Absorption

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases with higher single doses or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non-linear kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.

Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy. [1]

3.3.2 Distribution

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma. Approximately 95% of the paroxetine present is protein bound at therapeutic concentrations.

No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy). [1]

3.3.3 Metabolism

The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.

Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake. [1]

3.3.4 Excretion

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus, paroxetine is eliminated almost entirely by metabolism.

Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine.

[1]

Table 1 Pharmacokinetic Parameters of Paroxetine

Reference	Drug	Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
3 (In-house data (Avant Santé) **AS/AO/ABR-17/0012**	Paroxetine tablets	20 mg	6.884	4.806	11.4
4	Paroxetine tablets	20 mg	5.396 (µg/L)	5.35	11.98

Special Populations:

Elderly: Increased plasma concentrations of paroxetine occur in elderly subjects. [1]

3.4 Dosage and Administration:

The recommended initial dose is 20 mg daily.

Administration: Paroxetine tablets can be administered with or without food. [2]

3.5 Interactions

Interaction with other medicinal products and other forms of interaction:

Serotonergic drugs:

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects. Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, linezolid, methyl thioninium chloride (methylene blue)), SSRIs, lithium, pethidine and St. John's Wort – *Hypericum perforatum* – preparations) are combined with paroxetine. Caution is also advised with fentanyl used in general anesthesia or in the treatment of chronic pain.

Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome.

Pimozide

Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated.

Drug metabolizing enzymes

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

When paroxetine is to be co-administered with a known drug metabolizing enzyme inhibitor, consideration should be given to using paroxetine doses at the lower end of the range.

No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolizing enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin) or with fosamprenavir/ritonavir. Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).

Neuromuscular Blockers:

SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium and suxamethonium.

Fosamprenavir/ritonavir:

Co-administration of fosamprenavir/ritonavir 700/100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir/ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had

no significant effect on metabolism of fosamprenavir/ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir/ritonavir exceeding 10 days.

Procyclidine: Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Anticonvulsants: carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

CYP2D6 inhibitory potency of paroxetine:

As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. clomipramine, nortriptyline, and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including paroxetine) should whenever possible be avoided.

Alcohol:

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking paroxetine.

Oral anticoagulants:

A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants.

NSAIDs and acetylsalicylic acid, and other antiplatelet agents:

A pharmacodynamic interaction between paroxetine and NSAIDs/acetylsalicylic acid may occur. Concomitant use of paroxetine and NSAIDs/acetylsalicylic acid can lead to an increased haemorrhagic risk.

Caution is advised in patients taking SSRIs, concomitantly with oral anticoagulants, drugs known to affect platelet function or increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions that may predispose to bleeding.

Pravastatin:

An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels. Patients with diabetes mellitus receiving both paroxetine and pravastatin may require dosage adjustment of oral hypoglycaemic agents and/or insulin.

Drugs affecting gastric pH:

In vitro data have shown that dissociation of paroxetine from the oral suspension is pH-dependant. Therefore, drugs that alter gastric pH (such as antacid drugs, proton pump inhibitors or histamine H2-receptor antagonists) may affect plasma paroxetine concentrations in patients taking the oral suspension. [1]

3.6 Adverse Drug Reactions

Some of the adverse drug reactions listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports. [1]

Table 2 Adverse reactions of Paroxetine

System organ class	Frequency	Adverse Reaction
Blood and lymphatic disorders	Uncommon	Abnormal bleeding, predominantly of the skin and mucous membranes (including ecchymosis and gynecological bleeding).
	Very rare	Thrombocytopenia.
Immune system disorders	Very rare	Severe and potentially fatal allergic reactions (including anaphylactoid reactions and angioedema).
Endocrine disorders	Very rare	Syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
Metabolism and nutrition disorders	Common	Increases in cholesterol levels, decreased appetite.
	Uncommon	Altered glycaemic control has been reported in diabetic patients.
	Rare	Hyponatraemia.
Psychiatric disorders	Common	Somnolence, insomnia, agitation, abnormal dreams (including nightmares).
	Uncommon	Confusion, hallucinations.
	Rare	Manic reactions, anxiety, depersonalization, panic attacks, akathisia.
Nervous system disorders	Common	Dizziness, tremor, headache, concentration impaired.
	Uncommon	Extrapiramidal disorders.
	Rare	Convulsions, restless legs syndrome (RLS).
	Very rare	Serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor).
Eye disorders	Common	Blurred vision.
	Uncommon	Mydriasis.
	Very rare	Acute glaucoma.
Cardiac disorders	Uncommon	Sinus tachycardia.
	Rare	Bradycardia.

System organ class	Frequency	Adverse Reaction
Vascular disorders	Uncommon	Transient increases or decreases in blood pressure, postural hypotension.
Respiratory, thoracic and mediastinal disorders	Common	Yawning.
Gastrointestinal disorders	Very common	Nausea.
	Common	Constipation, diarrhoea, vomiting and dry mouth.
	Very rare	Gastrointestinal bleeding.
Hepatobiliary disorders	Rare	Elevation of hepatic enzymes.
	Very rare	Hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).
Skin and subcutaneous tissue disorders	Common	Sweating.
	Uncommon	Skin rashes, pruritus.
	Very rare	Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions.
Renal and urinary disorders	Uncommon	Urinary retention, urinary incontinence.
Reproductive system and breast disorders	Very common	Sexual dysfunction.
	Rare	Hyperprolactinaemia/galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia, amenorrhoea, menstruation delayed and menstruation irregular).
	Very rare	Priapism.
Musculoskeletal and connective tissue disorders	Rare	Arthralgia, myalgia.
General disorders and administration site conditions	Common	Asthenia, body weight gain.
	Very rare	Peripheral oedema.

3.7 Contraindications

Paroxetine is contraindicated with following:

- Hypersensitivity to the active substance or to any of the excipients.
- In combination with monoamine oxidase inhibitors (MAOIs including linezolid and methylene blue).

- Paroxetine should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine. Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsade's de pointes, and sudden death.
- Paroxetine should not be used in combination with pimozide. [1]

4.0 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate and compare the single oral dose bioavailability of Paroxetine tablets 20 mg manufactured by GlaxoSmithKline Pharmaceuticals S.A. for GlaxoSmithKline México, S.A. de C.V. with that of PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México, S.A. de C.V. in healthy, adult, male and female subjects under fasting conditions.

4.2 Secondary Objective

To evaluate the safety and tolerability of single oral dose of Paroxetine 20 mg tablets in healthy adult male and female subjects under fasting conditions.

5.0 HYPOTHESIS OF THE STUDY

Null hypothesis: H_0: mean test / mean reference < L or mean test / mean reference > U

Paroxetine tablets 20 mg manufactured by GlaxoSmithKline Pharmaceuticals S.A. and PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México, S.A de C.V. are not bioequivalent.

Alternative hypothesis: H_1: L ≤ mean test / mean reference ≤ U

Paroxetine tablets 20 mg manufactured by GlaxoSmithKline Pharmaceuticals S.A. and PAXIL (Paroxetine) tablets 20 mg of GlaxoSmithKline México, S.A. de C.V. are bioequivalent.

Two one-sided t-tests will be carried out on each PK parameter of Paroxetine using least squares means (LSM) values for geometric LSMs of the primary PK parameters (mean test or mean reference = LSM value of the corresponding PK parameter for test or reference product). The type I error will be set to $\alpha = 5\%$ and therefore 90% (two-tailed) confidence intervals will be provided together with the indication whether the null hypothesis of nonequivalence for the appropriate parameter can be rejected.

Probabilities p(t) of Schuirmann, left tail (t_l) and right tail (t_r) values will be calculated for the lower limit L = 0.80 and upper limit +U = 1 / 0.80 = 1.25 for geometric LSM of pharmacokinetic parameters C_{max} and $AUC_{0-t.}$

6.0 STUDY RATIONALE

Paxil (Paroxetine) tablets 20 mg of GlaxoSmithKline México, S.A. de C.V. is listed as a reference product by COFEPRIS. Currently, the drug product is manufactured at Xochimilco, México site using wet granulation process and Xochimilco, México site will exit GSK network in 2021.

Considering the same, Paroxetine tablets 20 mg manufactured using direct compression process at GlaxoSmithKline Pharmaceuticals S.A. site was selected as new supplier. Additionally, formulation composition is modified with respect to in-active ingredients.

To register the above mentioned changes [change in the drug product manufacturing site, differences in the formulations and process] in the marketing registration application for México, a bioequivalence study is required as per Oficio Circular CAS/OR/01/868/2013 [5] to establish similarity between the test product (new) manufactured at GlaxoSmithKline Pharmaceuticals S.A. and reference product manufactured at Xochimilco, México site.

México.

This product is an immediate release product and can be administered with or without food; hence, the test product (to be marketed) should be bioequivalent to the reference product under fasting conditions determined by C_{max} and AUC_{0-t} values of Paroxetine

Hence, the test product PAXIL (Paroxetine) tablets 20 mg manufactured by GlaxoSmithKline Pharmaceuticals S.A. manufactured for GlaxoSmithKline México S.A. de C.V. will be compared with that of Paxil (Paroxetine) tablets 20 mg GlaxoSmithKline México, S.A. de C.V. to evaluate bioequivalence.

6.1 Dose Rationale

The recommended initial dose of Paroxetine is 20 mg/ day. Hence, 20 mg dose of Paroxetine is within the dose range, which is expected to be tolerable in healthy adult volunteers. [2]

7.0 STUDY DESIGN

Each period will have identical procedures. For a detailed schedule of events, see Attachment-II.

7.1 Study Design

An oral single-dose, randomized, balanced, open-label, two-sequence, two-treatment, two-period, crossover bioequivalence study under fasting conditions.

The study design is presented in Figure 2 below.

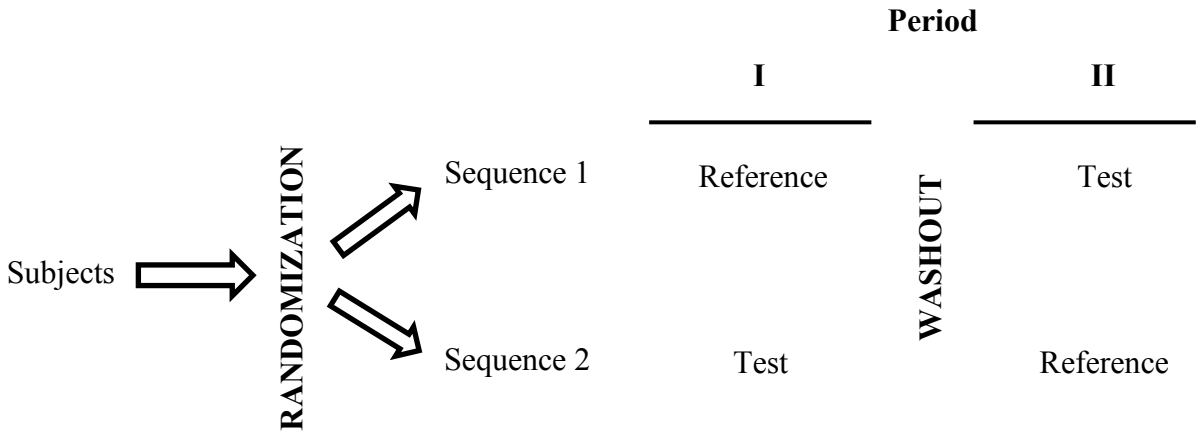

Figure 2 Study Design Diagram

7.2 Rationale for Study Design and Blood Sampling Points

Generally, bioequivalence studies are conducted in healthy adult volunteers. As this product is indicated for men and women, this bioequivalence study is planned in healthy adult human male and female volunteers. These products are an immediate release formulation and it can be administered with or without food, fasting bioequivalence study is required.

In this study two formulations are being compared, a randomised, two-period, two-sequence single dose crossover fasting study design is planned in healthy subjects to assess bioequivalence.

Sampling points have been placed with sufficient frequency to characterize C_{max} and AUC parameters adequately, considering the T_{max} and half-life of Paroxetine. The T_{max} occurs approximately 5.00 hours after the drug administration and the mean elimination half-life is approximately 12 hours [3].

A minimum of seven times the mean half-life will be considered as wash-out period between consecutive treatments to avoid carry-over effects, hence a wash-out period of at least 7 days

is considered. The duration of blood sampling is planned till 72.00 hours to cover at-least four half-lives for Paroxetine.

7.3 Sample Size

At least 34 healthy adult male and female subjects are required to meet at least a statistical power of 90% at 5% level of significance to achieve the bioequivalence results within 80.00-125.00% in this study. In addition, a maximum of 4 subjects will be dosed in account for withdrawal and dropouts.

Hence, a maximum of 38 subjects will be randomized and dosed. No subjects should be replaced after administered with the study treatment.

If possible, a maximum of two additional standby subjects (Stand by-I, Stand by-II) will be enrolled to replace any subject, who is withdrawn or dropped due to any reason prior to administration of study medication in period-1.

7.4 Justification of the Sample Size

Based on the in-house study data [3], a maximum intra subject variability of coefficient of variation (ISCV %) of 23.1 was observed for C_{max} of Paroxetine. According to NOM-177-SSA1-2013, section 8.5.1.1, the statistical power must not be less than 80%. Based on the observed maximum ISCV% of 23.1% and assuming the test/reference ratio of 95%, the inclusion of 34 subjects in the study is required to meet at least a statistical power of 80% at 5% level of significance to achieve the results within 80.00-125.00% for 2-way crossover study.

Using the intra-subject variability and the expected test/reference ratio from above paragraph, the sample size is estimated from the following equation:

$$n_i \geq 2\,[t_{1-\alpha,\,n-2}+t_{1-\beta,\,n-2}]^2[CV/(-\ln(\theta_L)-(-\ln(\theta))]^2 \text{ where } \theta \leq 1$$

α: Probability of Type I error (0.05)

β: Probability of Type II error (0.1)

CV: Intra Subject Variability (0.231)

θ: Expected T/R ratio (0.95)

θL: Lower bioequivalence limit (0.80)

Assuming the minimum sample size required (n) as 12, the sample size is estimated as follows:

$$n_i \geq 2\,[t_{1\text{-}0.05,\,12\text{-}2} + t_{1\text{-}0.1,\,12\text{-}2}]^2\,[0.231/\,(-\ln(0.8) - (-\ln(0.95))]^2$$

$$n_i \geq 37$$

Using the estimated sample size form previous iteration (n=37) from the above estimation, the sample size is again estimated as follows:

$$n_i \geq 2\,[t_{1\text{-}0.05,\,37\text{-}2} + t_{1\text{-}0.1,\,37\text{-}2}]^2\,[0.231/\,(-\ln(0.8) - (-\ln(0.95))]^2$$

$$n_i \geq 32$$

Using the estimated sample size form previous iteration (n=32) from the above estimation, the sample size is again estimated as follows:

$$n_i \geq 2\,[t_{1\text{-}0.05,\,32\text{-}2} + t_{1\text{-}0.1,\,32\text{-}2}]^2\,[0.231/\,(-\ln(0.8) - (-\ln(0.95))]^2$$

$$n_i \geq 33$$

Using the estimated sample size form previous iteration (n=33) from the above estimation, the sample size is again estimated as follows:

$$n_i \geq 2\,[t_{1\text{-}0.05,\,33\text{-}2} + t_{1\text{-}0.1,\,33\text{-}2}]^2\,[0.231/\,(-\ln(0.8) - (-\ln(0.95))]^2$$

$$n_i \geq 33$$

Convergence has reached and the estimated sample size is at least 34 (round to equal number) subjects to meet at least a statistical power of 80% at 5% level of significance to achieve the results within 80.00-125.00% for 2-way crossover study.

7.5 Washout Period

There will be a washout period of at least 7 days between successive dosing.

7.6 Duration of the Study

The expected duration of the subjects' participation in the study will be at-least 12 days, including a wash-out period of 7 days between each dosing.

7.7 Randomization

The order of receiving the test and reference products for each subject during each period of the study will be determined according to a randomization, generated by using SAS® software (version 9.4 or higher). This randomization will be balanced for the test product (A) and reference product (B). All the subjects should be divided into blocks of equal size and two-sequence "AB" and "BA" will be used for assignment of treatment in the respective study period (refer Figure-2). Analysts will not have access to the period randomization schedule. Randomization will be performed according to the procedure PB009 (Procedure for Randomization Schedule Generation).

7.8 Blinding

This study is an open label study; the subjects and the investigators will not be blinded towards the identity of the study treatments. Analysts (bioanalytical personnel) will be blinded with regard to the sequence of administration of test and reference products.

7.9 Test and Reference Products

Table 3 Investigational Product Details

IP Details	Reference Product (B)	Test Product (A)
Distinctive Name	PAXIL	N/A
Generic name	Paroxetine hydrochloride	Paroxetine hydrochloride
Pharmaceutical form	Tablets	Tablets
Formulation	Immediate release	Immediate release
Strength	20 mg	20 mg

IP Details	Reference Product (B)	Test Product (A)
Dose	20 mg	20 mg
Lot / Batch No. (1)	To be designated	To be designated
Expiry date / Re-test date (1)	To be designated	To be designated
Storage Conditions	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F).	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F).
Name of the manufacturer	GlaxoSmithKline México, S.A. de C.V.	Manufactured by: GlaxoSmithKline Pharmaceuticals S.A. Manufactured for: GlaxoSmithKline México, S.A. de C.V.
Sanitary Registration Number	008M93SSA	Not applicable (2)

1: Research Ethics Committee and Research Committee shall be notified on the lot / batch number and the expiry/retest date of the study drugs before conducting the clinical stage. The same information shall be notified to COFEPRIS in the final report of the study.

2: The Test drug will be evaluated for obtaining COFEPRIS registration.

7.10 Reception and Storage of Investigational Products

In accordance to the NOM-177-SSA1-2013, a sufficient quantity of the investigational products (test and reference) will be supplied to the research center by the sponsor in its original marketing package (applicable for reference product) or in a sealed package along with its Certificate of Analysis (CoA) for the conduct of the study as well as for retention (once the study is completed). Therefore, at least 80 tablets of reference product and 80 tablets of test product will be supplied and stored at Avant Santé facilities, in order to guarantee the

necessary resources for dosing the product of investigation at least once and also for its retention (once the study is concluded to be able to repeat the study).

The study drug reception, handling and storage of investigational products will be performed according to SOP CP017 (Study Drug Reception and Storage).

The test and reference products will be supplied in sealed packages.

Once received, both investigational products (test and reference) will be kept in separate boxes (labeled with project number, IP name, IP type, batch number, manufacturing date and / or expiration date, and storage conditions along with "For clinical research use only" statement) and stored in pharmacy as per the storage conditions mentioned on the label.

If the aforementioned conditions are not specified, the IPs will be stored as per the conditions specified by the sponsor or the available literature.

Upon completion or termination of the study, the investigational products will be stored in Avant Santé Research Center, S.A. de C.V. for at least 1 year after completion of the study or until test product / reference product expiry date is due, whichever occurs first. Test and reference products return or disposal will be followed according to respective in-house procedures. [6,7]

- The test and reference products shall be in the valid expiry date at the time of the study conduction.
- The percentage of assay content of the test product must be within the limits established in the relevant pharmacopeias and it should not differ by more than 5% with that of the reference product.
- Criteria for acceptance or rejection of drugs are followed according to SOP CP017 (Study Drug Reception and Storage).

7.11 Accounting of Investigational Products

The recording of the total quantity of investigational products received, dispensed, used, retained, disposed or returned to the sponsor, will be performed in the respective forms and kept in the pharmacy of Avant Santé Research Center, S.A. de C.V. The investigational products balance will be included in the clinical study report. This activity will be performed according to SOPs CP018 (Study Drug Dispensing and Retention) and CP019 (Investigational Products Return or Disposal).

7.12 Dispensing

The pharmacist will dispense required units of the test and reference products at least a day prior the dosing in each period of the study under the supervision of a person from Clinical Pharmacology department and a person from Quality Assurance. The doses will be transferred to the dispensing containers as per the randomization schedule and properly labeled with the project number, period number, subject number, IP type (test/reference) and storage conditions, along with the following statement: “For clinical research use only”.

At least one dose of each test and reference product will be dispensed as “standby” in order to handle any unexpected loss or damage of the medications during their administration. This activity will be performed according to CP018 (Study Drug Dispensing and Retention)

The test and reference product tablet will be removed from blister pack / package only at the time of dosing.

8.0 SELECTION AND WITHDRAWL OF SUBJECTS

8.1 Screening (selection and enrollment)

Healthy adult male & female volunteers, light or non or ex-smokers, aged between 18 and 55 years (both inclusive), with a weight ≥ 50.00 kg, with a BMI between ≥ 18.0 and ≤ 27.0 kg/m^2 will be selected according to the inclusion and exclusion criteria.

All the subjects will have a medical history during the selection and enrollment process.

Volunteers shall be found healthy according to the physical examination (including vital signs assessment), normal laboratory test results and 12-lead ECG.

The physical examination findings, ECG and laboratory tests will be considered valid for a maximum period of 90 days prior to the dosing on the first period of the study.

Pregnancy test in urine will be carried out during the screening period and at the time of each period check-in for all female subjects.

The process of selection and enrollment or withdrawal of subjects who will participate will be done according to the present protocol and as per the procedures CP002 (Volunteer Registration and Screening) and CP003 (Screening-Failing volunteers).

Real-time (RT-PCR) test for the detection and diagnosis of SARS-COV-2 will be carried out within the 72 hours prior to the first period check-in for all the subjects.

Avant Santé Research Center S.A. de C.V. will ensure the volunteer participation history by verifying the COFEPRIS database for bioequivalence studies.

8.2 Clinical Laboratory Tests

As part of the selection process the following laboratory tests will be performed to each subject.

Table 4 Laboratory Tests

<table>
<tr><th colspan="2">Blood tests</th><th rowspan="2">Urine analysis</th></tr>
<tr><th>Hematology</th><th>Biochemistry</th></tr>
<tr><td>Red blood cell count
White blood cell count
Differential white blood cell count
Hemoglobin estimation
Hematocrit
Platelet count
MCH,
MCV,
Mean Platelet Volume</td><td rowspan="3">Blood glucose (Random)
Blood urea, Blood urea nitrogen (BUN)
Serum creatinine
Serum sodium, potassium and Chloride
Serum uric acid
<u>Liver Function Tests:</u>
Total bilirubin
Direct bilirubin
Indirect bilirubin
SGOT (AST)
SGPT (ALT)
Serum alkaline phosphatase
Total protein
Serum albumin
Serum Globulin
Lipid profile</td><td>pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood / Red blood cells
Nitrites
Microscopic examination
Pregnancy test (female subjects)</td></tr>
<tr><td>Serology</td><td>Urine drug screen</td></tr>
<tr><td>HIV (1 & 2) antibodies
HBsAg (Hepatitis B surface antigen)
HCV (Hepatitis C virus) antibodies) and VDRL</td><td>Cannabinoids (Marijuana / Tetrahydrocannabinol-THC), Cocaine, Opiates, Amphetamine, Methamphetamine and Benzodiazepines</td></tr>
<tr><td colspan="3">Alcohol breath analysis test for all the subjects will be performed before check-in of each study period.
Urine drug screen for all the subjects and pregnancy test in urine for female subjects will be performed before check-in of each period.
Real-time (RT-PCR) test for the detection and diagnosis of SARS-COV-2 will be carried out within the 72 hours prior to the first period check-in for all the subjects.</td></tr>
</table>

8.3 Inclusion Criteria

Subjects must fulfill all of the following criteria to be considered for their inclusion in this study:

1. Healthy adult male or female subjects aged between 18 and 55 years (both inclusive).
2. Subjects is a light or non- or ex-smoker (A light* smoker is defined as someone who smoke 9 or less cigarettes per day and an ex-smoker being defined as someone who completely stopped smoking for at least 6 months before day 1 of this study).

   *: If any subjects stop smoking during last 6 months before day 1 of the study and smoke 9 or less cigarettes per day, the subject will also be considered as a light-smoker.
3. With a weight ≥ 50.00 kg.
4. With a body mass index (BMI) ≥ 18.0 kg/m^2 and ≤ 27.0 kg/m^2.
5. Found healthy according to the clinical laboratory results and physical examination (performed within 90 days prior to the dosing on period-1).
6. Have a normal 12 lead ECG and vital signs.
7. Have laboratory test results within the laboratory's stated normal range; if not within this range, they must lack of no clinical significance as judged by the PI or responsible physician.
8. Willing to avoid sexual contact or use an acceptable contraceptive method during the study including the washout period (for females). In case of male subjects, they should avoid sexual contact or use a latex or synthetic condom each time they have sex with a woman while taking Paroxetine and during 7 days after the end of the study.
9. If study subject is a female and is of child bearing potential, she shall practice a method of birth control for the duration of the study as judged by the investigator (s), like combined short acting (estrogen and progestogen containing) hormonal contraception e.g. oral, intravaginal, and progestogen-only hormonal contraception e.g. oral, intrauterine device

(IUD), intrauterine hormone-releasing system (IUS), condoms, foams, jellies and diaphragm

Or

Abstinence

Or

If study subject is a female and is postmenopausal for at-least 1 year

Or

Is surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy has been performed on the study subject).

10. Have a negative test for active COVID-19, within 72 hours prior to the first period check-in. The testing should be done using a molecular (RT-PCR) approved by the country regulatory authorities.
11. Subject is able to communicate effectively and voluntarily agreed to participate in this study by signing written informed consent after being informed sufficiently about study aspects like objectives, study procedures, characteristics of the investigational drug, expected adverse events.
12. Subject willing to adhere to protocol requirements as described in informed consent (written) approved by REC / RC.

8.4 Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

a. If subject's age is less than 18 or older than 55 years.
b. Have any history of allergy or hypersensitivity to Paroxetine or to any of its metabolites/derivatives or related drugs or excipients.
c. Have a positive test result for hepatitis B surface antigen (HBs Ag) or hepatitis C virus antibody (HCV Ab) or HIV antibodies (types 1 and 2) or VDRL.

d. Subjects with symptoms suggestive of active COVID-19 infection (i.e. fever, cough, respiratory difficulties) within 14 days of inpatient admission.
e. Subjects with known COVID-19 positive contacts* within the past 14 days prior to the first period check-in.

   *Positive Contact; this means, if the subject has been living, providing, care, being within 1.5 m for at least 15 min or having exposure to respiratory secretions with/to a person who has COVID-19.
f. Study drug is contraindicated for medical reasons to the subject as per protocol section 3.7.
g. Have any history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, seizures, endocrine, dermatological, neurological or psychiatric disease or disorder (e.g. Subjects with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder and acute confusional states).
h. Presence of significant gastrointestinal, hepatic or kidney disease, or surgery or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects.

   Or

   Subjects with a history of gastrointestinal disorder or surgery which may affect the absorption of investigational drug.
i. Have a history of alcohol abuse or drug abuse during the last 1 year prior to period-1 dosing.
j. Have a history of smoking ≥ 10 cigarettes per day during the last 6 months prior to period-1 dosing.
k. Have history or presence of cancer.
l. Have any history of gastrointestinal ulcers / intestinal bleeding.
m. Have difficulty in swallowing solid medications such as tablet.
n. Have history of difficulty for donating blood.

o. Have clinically significant abnormal laboratory tests results.

p. Have a systolic blood pressure < 90 or > 140 mmHg or diastolic blood pressure is < 60 or > 90 mmHg.

q. Have a pulse rate < 60 beats/minute or > 100 beats/minute (Lower range of pulse range will be accepted up to 45 beats/minute in case of athlete).

r. Have used any prescribed medication during the last 14 days preceding the first dosing, or use OTC, medicinal or herbal products during the last 7 days or use medicinal enzyme inhibitors / inducers during last 30 days preceding the first dosing.

s. Have participated in a drug research study or donated blood within the last 3 months.

t. Have a positive result for drugs of abuse test [Cannabinoids (Marijuana/Tetrahydrocannabinol-THC), Cocaine, Opiates/Morphine, Amphetamine, Methamphetamine and Benzodiazepines] performed during screening.

u. Female subject, who is currently breast feeding or a who is pregnant or who is likely to become pregnant during the study.

v. Female subject has a positive pregnancy test results.

w. Unwillingness or inability to comply with the instructions on the lifestyle described in this Protocol.

x. If the PI considers, for any reason, that the volunteer is not a suitable candidate to receive the study drug.

8.5 Criteria for Subject Withdrawal from the Study

Subjects have the right to withdraw their consent from the study at any time and for any reason without facing any related prejudice. The Principal Investigator may withdraw a subject from the study if:

a. The subject wishes to withdraw consent (In case the subject request to disposal of the collected samples, the same shall be documented and will be informed to sponsor and REC/RC).
b. The subject suffers from significant inter-current illness or undergoes surgery during the study. In case a subject is positive for COVID-19 or has a related symptom (i.e. fever, cough, respiratory difficulties), they shall be isolated for 14 days and they shall be discontinued In case any other subject was exposed to a COVID-19 patient, they must report this to Avant Santé, GSK and/or their primary care provider.
c. Subject fails to comply with the requirements of the protocol section 9.3 Restrictions.
d. Subject experiences an adverse event and it is not in the subject's best interest to continue in the study (as judged by the PI).
e. Subject has a positive result for the breath alcohol test or urine drugs of abuse test [Cannabinoids (Marijuana/Tetrahydrocannabinol-THC), Cocaine, Opiates/Morphine, Amphetamine, Methamphetamine and Benzodiazepines] prior to check-in of each study period.
f. The subject vomits at the time of the drug administration or vomiting / diarrhea occurs within 10 hours of drug administration (representing twice the median T_{max} of 5 hours).
g. In case of a female subject a positive result for the pregnancy test.
h. Subjects who miss 4 or more consecutive blood draws in any of the study periods.
   According to NOM-177-SSA1-2013, section 8.9.5, frequent sampling points are needed around the T_{max} and also at least four samples during the log-terminal phase to obtain the extraction rate constant. If any subject misses 4 or more consecutive sampling points during the absorption phase or the extraction phase, it will have an impact on the precise accuracy of the C_{max} and AUC curve.
i. The study is suspended or terminated by the sponsor or PI or EC/REC.

It should be noted that any subject that is not discontinued or withdrawn from the study will be considered as a subject who finishes the study.

9.0 TREATMENT OF SUBJECTS

9.1 Drug Administration

In each study period, all subjects will be required to fast overnight for at least 10.00 hours prior to dosing until at least 04.00 hours post-dose.

In each study period, a single-dose of either the test product (A) or reference product (B) will be orally administered to the subjects in sitting posture along with 250 mL of water at room temperature under fasting conditions.

The administration of the test or reference products to each subject will be performed as per a randomization schedule.

The subjects will be instructed to swallow the tablet as a whole as mentioned in the prescribing information and not to touch the tablet with their hands, chew or crush the tablet since this can affect the drug release.

Subject's hands and mouth will be checked after dosing to ensure compliance with dosing.

Immediately after dosing in each period trained study personnel will evaluate the compliance by supervising the complete administration procedure (SOP CP020, Administration of the Investigational Product).

Drug administration will be registered in the respective source documents.

9.2 Dietary Plan

Subjects will be provided with standard meals throughout their stay in the facilities.

On the check-in day (day -1) they will receive dinner, which will be finished at the latest 10.00 hours prior to dosing at the following day in each study period.

Subjects will be required to fast overnight for at least 10.00 hours prior to dosing and until at least 04.00 hours post-dose in each study period.

After the dose administration of test or reference product (day 1), lunch, snack and dinner will be provided at 04.00, 08.00 and 12.00 (with a grace period of + 45 minutes) hours post-dose respectively, in each study period.

The meal plan will be uniform for all the subjects and same between the study periods.

Information on the amount of meal consumed and the time of consumption by each subject will be registered in the respective source documents. The nutritional value of the meals is presented in the following table.

Table 5 Nutritional value of diet on study day 1

Nutritional Value of meals	
2000 kcal ± 10%	**Calories (%)**
Proteins	15-20%
Lipids	25-30%
Carbohydrates	50-60%
Total	*100%

*% of kilocalories is within its adequate distribution of 90–110%.

9.3 Restrictions

- **Smoking**

  All subjects will be instructed to refrain from smoking of cigarettes / nicotine containing products for at least 72.00 hours prior to the dosing and until the last sample collection in each period and will be prohibited from smoking during their in-house stay.

- **Medications**

  All subjects will be asked about their medication history. They will be instructed not to take any medication until the study is completed; particularly during the last 14 days preceding the first dosing for any prescribed medication, the last 7 days before for OTC medicinal or herbal products used for therapeutic purposes, and the last 30 days before for any enzyme inhibiting / inducing drugs preceding the first dosing.

Subjects will be specifically reminded that the restriction mentioned above includes analgesics, cold & anti-allergic preparations, vitamins and natural products used for therapeutic benefits and antacid preparations.

Vitamins used as nutritional supplements in non-therapeutic doses (as judged by the principal investigator or designee) may be accepted, but their consumption must be stopped from at least 7 days prior to the dosing and until the study is completed.

If a drug therapy other than that specified in the protocol is required prior to, during the study or in the washout period, the Principal Investigator shall decide whether to continue or discontinue the subject's participation based on the following:

- The pharmacology and pharmacokinetics of the non-study medication.
- The likelihood of a drug–drug interaction, which may affect the pharmacokinetic comparison of the study drugs.
- The time and duration of administration of the non-study medication.

- **Diet**

All subjects will be instructed to avoid the consumption of any xanthine-containing food or beverages (tea, coffee, theobromine, theophylline, chocolates, cola drinks, etc.) at least 72.00 hours prior to the dosing and until the last blood sample collection in each study period.

Subjects will be instructed to avoid the consumption of alcohol (or related products) as well as smoked or carbon cooked food from at least 72.00 hours prior to the dosing, until the last blood sample collection in each study period.

Subjects will be instructed to avoid the consumption of pomelos or grapefruit juice or products containing grapefruit extract (e.g. soda) from at least 72.00 hours prior to the dosing, and till the last blood sample collection in each study period.

The consumption of above-mentioned products will also be prohibited during their in-house stay.

Fluid (water) restriction

The subjects will not be allowed to drink water 1 hour before and until 2 hours post-dose except for the 250 mL of water provided for the dosing, unless it is clinically indicated; at all other times water will be provided *ad libitum*.

Postural (activity) Restriction

The dose will be administered to all subjects at the scheduled time and subjects will be instructed to remain in comfortable sitting position for the first 02.00 hours following the drug administration except when clinically indicated or protocol specified activity (blood sample collection) or due to natural exigencies.

After 02.00 hours post-dose, subjects will be allowed to wander and will be advised to avoid any severe physical exertion.

In case of an adverse event (AE), subjects will be maintained in the proper position as per physician's assessment in each study period.

- **Recommendations during washout period and visits to the center (ambulatory samples)**

In case a subject has symptoms of COVID-19, the following recommendations will be provided (the same as dictated by the WHO):

- Isolation for 14 days at home: Staying at home except to get medical care immediately if having an emergency warning sign (i.e., trouble breathing).
- Monitoring temperature: average human body temperature is 36-37°C.
- Any related-COVID-19 symptom, worsening or recovery, must be reported to their primary care provider and to Avant Santé Principal Investigator.

9.4 Housing

Subjects will be in the clinical facility from at least 10.50 hours prior to the dosing until the last in-house blood sample collection i.e. 24 hours in each study period.

Subjects will visit clinical facility at 36.00, 48.00 and 72.00 hours for the collection of the ambulatory samples in each study period.

Subjects will be instructed to self-quarantine during the outpatient period of the study i.e. until 72 h blood sample collection in period-2 or until withdrawal, whichever is earlier, and to monitor at home their daily body temperature.

9.5 Sampling Schedule

In each study period, a total of 24 blood samples (4 mL each) will be collected from each subject as per the following schedule:

- The first blood sample will be collected within 1.50 hours prior to the dosing (00.00 hours / pre-dose).
- The remaining samples will be collected after the dosing of the test or reference drug at 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 09.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours.
- The samples corresponding to 36.00, 48.00 and 72.00 hours post dose will be collected on separate visits as ambulatory sample in each period of the study.

The total blood volume collected from each subject will not exceed 223 mL, which includes about 10 mL for the selection process (selection and enrollment), 21 mL for the discarded heparinized blood and 192 mL for the pharmacokinetic evaluation.

If circumstances arise, where more than 223 + 10 mL (may be collected for safety evaluation purpose) of blood from each subject needs to be withdrawn the subject will be asked for additional consent and the REC / RC will be informed.

Table 6 Blood volume of samples to be collected during the study

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Screening	10 mL	1	-------	-------	10
PK Blood Samples	4 mL	-------	48 samples (Period 1,2)	-------	192
Heparinized blood	0.5 mL	-------	42 samples (Period 1,2)	-------	21

TOTAL	**223**

At the time of each blood sample collection, 4 mL will be collected through an indwelling cannula placed temporarily (for at least 24.00 hours post-dose) in a forearm vein or as per subject's convenience for practical reasons and the remaining sample(s) will be collected through direct venipuncture.

Blood samples will be obtained in K_2-EDTA vacuum tubes (pre-labeled with project number, period number, subject number and sample number).

If the times of sample collection vital signs or medical examination and food consumption overlap during the housing period, the order will be as follows.

Sample collection → vital signs or medical examination → food consumption.

Blood samples shall be collected not earlier or later than (±) 2 minutes of the specified sampling time for all the in-house samples and not earlier or later than (±) 60 minutes of the specified sampling time for ambulatory samples. Blood sampling will be registered in the respective source documents.

If blood samples are collected earlier or later than this period from the scheduled time, this shall be reported as a deviation from this protocol.

Heparin-lock technique (with 0.5 mL) will be used to prevent coagulation of the blood in the cannula. Prior to the blood collection through the cannula, 0.5 mL of heparinized blood will be withdrawn and discarded in order to prevent the heparin interfering with the sample analysis. If for any reason the indwelling cannula is blocked or removed, direct venipuncture will be performed to collect the samples.

All this process is described in detail in the procedure CP021 (Phlebotomy Performance).

If any subject misses any blood sampling point, it will be considered as missing sample.

The same will be denoted as (M), it will be considered as protocol deviation and mentioned in the clinical study report.

9.6 Sample Processing and Storage

Once collected, the blood samples will be placed in an ice-filled container or another cooling device until the centrifugation process is started.

Centrifugation process will be started within 45 minutes from the time of blood sample collection and will be performed at 3000 rpm for 10 minutes at 4 ± 2 ºC.

The plasma obtained from blood samples will be transferred as soon as possible into two different cryo-tubes (aliquot 1 and aliquot 2), pre-labeled with project number, period number, subject number, sample number and aliquot number.

The plasma volume obtained from blood sample will be allocated as follows:

Aliquot 1: 1.0 mL of plasma (approximately).

Aliquot 2: rest of the plasma.

All plasma samples (aliquot 1 for sample analysis and aliquot 2 as back-up) will be stored in the Clinical facility at a temperature of -50 °C or below until transferred in dry ice to the Bioanalytical facility, where they will be stored at a temperature of -50 C or below until their analysis.

9.7 Sample transfer

At the end of each period or clinical phase, samples will be separated and sorted by subject, period and aliquot as per the procedure CP031 (Biological Samples Processing, Storage, Shipment and Spillage Handling). Once the samples of each subject are sorted, they will be placed in propylene storage containers or in an auto-sealed bag, previously labeled with the project number, period number, subject number, aliquot number and number of samples.

Process of separation, sorting and sample verification will be done with sufficient dry ice. Temperature will be monitored during the separation sorting and verification process with a calibrated data-logger and under supervision of quality assurance department personnel.

At the end of the clinical phase of the study or each study period, aliquot 1 (used for the quantification and re-analysis) samples will be shipped for analysis to the Bioanalytical

facility in a container with dry ice while transfer and temperature will be monitored. The aliquot 2 (for back-up) samples will be shipped using the same procedure and only after confirming the reception or loss of the aliquot 1 samples. If required, Aliquot 2 will be used. Aliquots will be stored in different deep freezers under the same condition in bioanalytical area.

The process of reception, handling, storage and disposal of biological samples in the Bioanalytical unit, will be carried out according to procedure BL021 (Reception, Management, Storage, Transfer and Disposition of Biological Samples).

CP personnel shall send the information "subjects samples to be analyzed" (including the reason or justification for not analyzing other samples of subjects) to the Bioanalytical department with the approval of the Principal Investigator and authorized by QA.

10.0 ASSESSMENT OF EFFICACY

As this is a bioequivalence study, no efficacy assessment will be performed. The pharmacokinetic parameters of the test and reference formulations will be assessed.

11.0 ASSESSMENT OF SAFETY (CLINICAL SAFETY MEASURES)

11.1 Recording of Vital Signs and Medical Examination

Medical examination, which consists on subject's anamnesis, inquiry for possible AEs, evaluation of vital sings and overall health status to determine if further physical examination is required will be performed before check-in, prior to the dosing and before the check-out in each study period.

Nevertheless, it may also be performed at any time during the study conduction if judged necessary by the physician.

Physical examination, which consists on subject's anamnesis, examination of the head, neck, thorax, abdomen, and extremities (but not limited), inquiry for possible AEs and evaluation

of vital sings will be performed before check-in of each study period and may also be performed at any time during the study conduction if judged necessary by the physician.

Vital signs (sitting blood pressure, pulse rate, respiratory rate and axillary body temperature) will be measured and registered before check-in, prior to dosing, at 03.00, 05.00 and 12.00 hours (within ±45 minutes) hours after the dosing, before the check-out and at the time of each ambulatory sample collection in each study period.

The subjects' well-being (assessed by verbal questionnaire to gather information about AEs) will be asked at the time of the medical examination, during the vital signs recording and at the time of each ambulatory sample collection in each study period; this will be registered in the respective source document.

Seven (7) to 9 days after the collection of 72-h blood sample in second period or after the withdrawal, a telephone call will be made to each subject by the personnel designated by the PI to monitor any serious adverse event, specifically, subjects will be questioned about any symptoms related to COVID-19.

11.2 Identification, Handling and Reporting of AE and SAE

- **Definitions**

Adverse Event (AE): Any untoward medical occurrence that may occur in a research subject during the clinical research phase of a drug or vaccines but which does not necessarily has a causal relationship with this.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug (research product), whether or not considered related to the research product.

Abnormal laboratory results will be reported as adverse events under the following circumstances:

- When the abnormal lab report is accompanied with associated symptoms.

- When a medical or surgical intervention is required.
- When an additional diagnostic test is required.
- When it precedes and is associated with any of the outcomes included in the definition of serious adverse event.
- When it is so considered by the PI.
- Abnormal laboratory value as well as a significant shift from baseline within normal range which the qualified investigator or medically qualified delegate considers to be clinically significant (CS). If the Principal Investigator or the qualified medical delegate considers the abnormalities to be not Clinically Significant (NCS), the abnormalities do not need to be reported as AE.

Therefore, a clinically significant laboratory value is one that indicates a new disease process, exacerbation or worsening of an existing condition or that requires additional measures.

Adverse Drug Reaction (ADR): Any undesirable effect, associated with the use of a drug that may occur as part of the drug's pharmacological action or may be unpredictable in its occurrence.

Suspected Adverse Drug Reaction (SADR): Any unwanted clinical manifestation that gives an indication or appearance of having a causal relationship with one or more drugs.

Unexpected Adverse Drug Reaction (UADR): an adverse reaction which nature or severity is not described in scientific literature, neither in the label nor in the applicable product information, nor in the documentation presented for its registration, additionally, that it is not possible to infer it from its pharmacological activity and that it may be more serious that indicated on the label.

Serious Adverse Event (SAE): any medical occurrence that at any dose:

- Put patient’s life in risk or results in death.

- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other important medical events: events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition.

- **Identification of Adverse Events**

  The subjects will be monitored throughout the study for any adverse event manifestation. They will be encouraged to report any sign, symptom, and any health change to the clinical staff. The severity of each AE and its relationship to the study treatments will be determined by the PI based on observation and questioning of the subjects and in accordance to the following classification: non-assessable or unclassifiable, conditional or unclassifiable, unlikely, possible, probable or certain.

  The following measures will be employed to ensure that the adverse event is detected at the earliest:

  - The physical examination and vital signs recording will be performed at regular intervals after the study drug administration.
  - The subjects' well-being will be enquired at regular intervals (see section 11.1).
  - All subjects who have received at least a single dose of the study drug will undergo a complete medical evaluation after the completion of the last sample collection for safety reasons.

- **Management of Adverse Events**

  A medically qualified designee will be available round-the-clock during the period of housing at the clinical facility. If any subject develops an AE the following measures will be adopted:

  - Subject will be evaluated by the physician or designated personnel, treated and/or followed-up until the symptoms disappear or laboratory values return to normal levels, as judged by the PI.
  - In case of a SAE, subject will be treated by a physician in the ICU, fully equipped with all the emergency handling material like defibrillator, ventilation mask, ECG machine, suction apparatus, etc., or may be referred to the contract hospital.

- **Recording of Adverse Events**

  Any symptom, sign or significant abnormal laboratory finding (after repeat test confirms the abnormality) whether observed or reported during the course of the study (i.e., within 7 to 9 days after the last sample collection or after the withdrawal) will be recorded as an adverse event whether it has a causal relationship with the drug or not.

  The following information has to be individually recorded for each AE in an Adverse Event reporting form:

  - Description of the AE.
  - Subject number, period, date and time of last dosing.
  - Type of adverse event.
  - Seriousness of adverse event.
  - Date and time of onset/reporting.
  - Date and time of resolution.
  - Intensity (mild, moderate or severe).

- Relatedness to the study medication (non-assessable or unclassifiable, conditional or unclassifiable, unlikely, possible, probable or certain).
- Action taken or treatment given.
- Outcome of adverse event (resolved or unresolved).
- Follow-up.
- Further details of the AE (if any).

Severity (Intensity) of the adverse event, adverse reaction suspicion and adverse reactions, will be classified according to the clinical manifestation as:

Mild**:** Signs and symptoms easily tolerable, which do not need treatment, do not prolong hospitalization and do not require medicine product suspension.

Moderate**:** Interferes with usual activities (may cause work or school casualties), without directly threatening the patient's life. It requires pharmacological treatment and may or may not require the suspension of the causative drug.

Severe**:** Interferes with usual activities (may cause work or school dropouts). It requires pharmacological treatment and the suspension of the causative drug.

Adverse reactions are classified according to the assessment of causality as (see table 7):

Table 7 Adverse Reaction Classification

Causality Term	Assessment Criteria
Certain	• Clinical event, including alterations in laboratory tests, which manifests itself with a plausible temporal sequence in relation to the administration of the drug. • It cannot be explained by the concurrent disease, or by other drugs or substances. • The response to drug suppression (withdrawal) must be clinically plausible.

Causality Term	Assessment Criteria
	• Event shall be definitive pharmacologically or phenomenological, using, if necessary, a conclusive re-exposure procedure.
Probable	• Clinical event, including alterations in laboratory tests, which manifests itself with a reasonable temporal sequence in relation to the administration of the drug. • Unlikely to be attributed to the concurrent disease or by other drugs or substances, and that when the drug is withdrawn, a clinically reasonable response is presented. • It is not required to have information on re-exposure to assign this definition.
Possible	• Clinical event, including alterations in laboratory tests, which manifests itself with a reasonable temporal sequence in relation to the administration of the drug. • Could also be explained by the concurrent disease or by other drugs or substances. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Clinical event, including alterations in laboratory tests, manifested with an unlikely temporal sequence in relation to the administration of the drug. • It could be explained more plausibly by the concurrent disease, or by other drugs or substances.
Conditional / Unclassifiable	• Clinical event, including alterations in laboratory tests, reported as an adverse reaction, from which it is essential to obtain more data in order to make an appropriate evaluation, or additional data are under examination.

Causality Term	Assessment Criteria
Unassessable / Unclassifiable	• Notification that suggests an adverse reaction, but that cannot be judged because the information is insufficient or contradictory and cannot be verified or completed with provided data.

- **Reporting of non-serious Adverse Events / non-serious Adverse Drug Reactions**

  All non-serious, ADRs (expected or unexpected) and AEs occurred during the study conduction shall be notified to the REC/RC and the sponsor by the PI in the final study report according to SOP CP025 (Adverse Events and Serious Adverse Events Recording, Monitoring and Reporting).

- **Reporting of Serious Adverse Events / Serious Adverse Drug Reactions**

  All SAEs and SADRs shall be reported immediately (within the first 24 hours after their occurrence) to the REC/RC, Sanitary Responsible and Sponsor's responsible person either by telephone or written form.

  The information to the sponsor shall be sent in attention to:

  PPD

  GlaxoSmithKline México, S.A. de C.V.

  Calzada México Xochimilco No. 4900

  Col.San Lorenzo Huipulco 14370 Ciudad de México

  Phone number: PPD

  Email: PPD

  The event must also be documented on the "Adverse Event" section in the CRF and in the clinical report. All SAEs must be transcribed in the CRF, whether or not there is a causal relationship with the drug or medicinal product being evaluated.

The regulatory authorities (CNFV) shall be notified according to what is established in the "Pharmacovigilance guide for the notification of AE, SADR, ADR, and ESAVI or any safety problem related to the use of drugs" and according to the NOM-220-SSA1-2016, through the platform assigned by the CNFV for this purpose and in the Final Safety Report.

The notification through the platform assigned by the CNFV for this purpose shall be performed according to the timelines stablished in the valid NOM-220-SSA1-2016.

Notification to the CNFV of serious adverse events will be made by Avant Santé, using the current MedDRA terminology. [7-10]

Actions to be taken if Pregnancy Occurs

If a female subject becomes pregnant during their participation in the clinical study, she will be immediately withdrawn from the study and will be monitored throughout the pregnancy to assess drug AEs and ADRs in the mother / fetus or infant. The investigator must inform the Sponsor's safety division within 24 hours after being aware of a confirmed report of pregnancy fulfilling any of the following criteria:

- Reports of congenital anomaly(ies) in fetus, child,
- Reports of spontaneous abortion,
- Reports of late fetal death,
- Reports of ADRs in new born / neonate that is fatal, life threatening, resulting in persistent or significant disability / incapacity or resulting in or prolonging hospitalization,
- When the medicinal products are known (or suspected) to induce teratogenic or foeto-toxic effects and are therefore contraindicated (or not recommended) in pregnant women, the circumstances relating to the pregnancy must be documented (e.g. patient "not aware" of the risk, contraception failure). Cases with all such drugs whether or not associated with any congenital anomaly and / or serious adverse drug reaction must always be considered serious and reported on expedited basis to regulatory authorities. Teratogenic potential of the drug must be determined from the safety section of the literature.

All pregnancy reports not fulfilling the above criteria must be reported by the Principal Investigator at the earliest and no later than 3 working days of receipt of confirmed report of pregnancy.

The Principal Investigator/ Designated personnel will follow up and collect pregnancy information as per the following schedule to determine outcome including spontaneous or voluntary terminations, details of birth, presence or absence of congenital anomalies, and maternal or newborn complications etc.

Table 8 shows the follow-up schedule in case of pregnancies during the study.

Table 8 Pregnancy follow up

No.	Follow up
1	Initial Contact
2	First Trimester (3 months Gestation)
3	Second Trimester (6 months Gestation)
4	Third Trimester (9 months Gestation)
5	At birth
6	30 days after birth
7	6 months after birth (In-case of congenital anomalies)

The principal investigator / designee must obtain the minimum required information, with documentary evidence, if any, from the subject's Obstetrician / Gynecologist / Pediatrician.

- **Follow-Up of Adverse Events**

Classification of AE will be done by the PI, as well as causality relation. In case of SAE, causality will be confirmed by the sponsor (for test product).

Subjects will be instructed to report at the clinical facility for any AE during the washout period. All the adverse events will be treated by the PI or CI at the clinical facility or in the contract hospital. All AEs will be followed up wherever possible until their resolution or until the CI or PI believes that there will be no further changes. This may involve additional visits.

Follow-up and closure of adverse events will be done according to the procedure CP025 (Adverse Events and Serious Adverse Events Recording, Monitoring and Reporting).

12.0 BIOANALYSIS

12.1 Sample analysis

The concentrations of Paroxetine in plasma samples will be quantified using a validated bioanalytical UPLC/MS-MS method (LOQ - 0.106 ng/mL) according to COFEPRIS guidelines, GLP and in-house SOPs.

Method validation and subject sample analysis will be performed using same the anticoagulant (K_2-EDTA) that will be used for blood sample collection in clinical phase.

The use of reference substances of Paroxetine and internal standard, calibration curve spiking and control points as well as subject sample analysis shall be performed according to the stability periods mentioned in the Method SOP and according to the procedure BL004 (Sample Analysis, Acceptance and Re-assay Analysis of Study Samples). Samples for reanalysis and its acceptance shall be performed according to the procedure BL004 and the cause of the same will be mentioned in the report.

Quality control samples will be distributed throughout each batch of the study samples analyzed. The analyst will not have access to the randomization schedule, which is used for dispensing.

12.2 Reporting of drug concentration data

After completion of the analysis, all the concentration data will be transferred to the Pharmacokinetic and Biostatistics Department. All concentration values below the lower limit of quantification (LLOQ) will be reported as BLOQ and any missing samples will be reported as "NE".

If the pre-dose concentration is above LLOQ, then pre-dose concentration will be reported as such for pharmacokinetic analysis.

All the concentration data should be reported in the bioanalytical report according to SOP: BL018 (Preparation of sample analysis report).

Overall (mean) accuracy and precision of the QC samples of all accepted runs should be calculated at each concentration level and reported in the bioanalytical report according to SOP BL018 (Preparation of sample analysis report).

13.0 PHARMACOKINETIC PARAMETERS

Non-compartmental pharmacokinetic analysis will be performed on the observed plasma concentration of Paroxetine using WinNonlin® software (6.4 version or higher).

- Any concentration below lower limit of quantification (BLOQ) including pre-dose concentrations will be converted to zero.
- If the pre-dose concentration is ≤ 5% C_{max} of the respective period and above LLOQ, then pre-dose concentration will not be converted to zero and the respective subject shall be considered for pharmacokinetic and statistical analysis.

Missing samples will be reported as "NE" and will not be included for pharmacokinetic and statistical analysis. The process will be performed according to the procedure PB003 (Procedure for Statistical Analysis using WinNonlin).

The following pharmacokinetic parameters will be computed.

Primary parameters

C_{max}	:	Maximum observed concentration following each treatment.
AUC_{0-t}	:	The area under the concentration versus time curve from time zero to the last measurable concentration using linear trapezoidal linear interpolation method.

Secondary parameters

T_{max}	:	Time of the maximum measured concentration.

$AUC_{0\text{-}inf}$	:	The area under the concentration versus time curve from time zero to infinity calculated; Where $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/ \lambda z$, Ct is the last measurable concentration and λz is the terminal elimination rate constant.
AUC_% Extrap	:	The residual area in percentage $[(AUC_{0\text{-}inf} - AUC_{0\text{-}t})/ AUC_{0\text{-}inf}] \times 100$
Lambda_z (K_{el})	:	First order rate constant associated with the terminal portion of the curve (log-lineal). This is estimated via linear regression of time vs. log concentration. This parameter will be calculated using at least three or more non-zero plasma concentration values.
HL_Lambda_z ($t_{½}$)	:	The elimination half-life will be calculated as $0.693/ \lambda z$

Note:

- For all the above computations, actual time points of the sample collection will be used in case of sample collection deviations i.e. beyond ± 2 minutes.
- No value of Lambda_z (K_{el}), $AUC_{0\text{-}inf}$, or HL_Lambda_z ($t_{½}$) will be reported for cases who do not exhibit a terminal Log-linear phase in the concentration versus time profile.
- Statistical methods used in the study will be mentioned in the Statistical Analysis Plan.

14.0 STATISTICAL ANALYSIS

Data from all treated subjects will be included in the statistical analysis.

If any of the subject's data is eliminated from the statistical analysis which meet the criteria of section 14.9 'Criteria for elimination of subject data from the statistical analysis', statistical analysis shall be performed and presented with and without the data of eliminated subject's data.

The statistical analysis will be carried out according to the PB005 procedure (Procedure for Statistical Analysis for a cross-over design).

Statistical analysis of PK parameters for establishing bioequivalence will be performed using the software SAS® (version 9.4 or higher). PROC GLM will be used for the estimation of the geometric least square mean differences (test - reference) of the test and reference formulations on the ln-transformed PK parameters C_{max} and AUC_{0-t} for Paroxetine and the corresponding standard errors of the differences will also be computed. Based on these parameters, 90% confidence intervals will be constructed for the geometric least square mean differences of ln-transformed C_{max} and AUC_{0-t} for Paroxetine.

The anti-ln (or exponential) of the limits obtained from the ln-transformed data will give the 90% confidence interval for the ratio of geometric least square means of test and reference formulations.

14.1 Descriptive Statistics

Geometric mean, arithmetic mean, median, minimum, maximum, standard deviation and coefficient of variation (arithmetic and geometric, respectively) will be calculated for each PK parameter (C_{max}, AUC_{0-t} and T_{max} for Paroxetine), logarithmically transformed and untransformed.

For PK parameters C_{max} and AUC_{0-t} for Paroxetine, the following shall be calculated:

- Difference of test and reference drugs.
- Quotient between test and reference drugs.
- The natural logarithm of the quotient between test and reference drugs.
- Histograms (ratios [A/B] and ln ratio [Ln (A/B)] will be performed.

14.2 Analysis of Variance

The ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} for Paroxetine) will be analyzed using Type III sum of squares, with the main effects of formulation, period, sequence as fixed effects and subjects nested within sequence as a random effect. A separate ANOVA model will be used to analyze each of the parameters. The sequence effect will be tested at the 5% level of significance using the subjects nested within sequence mean square as the error term. Formulation and period effects will be tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term. Each analysis of variance will include calculation of geometric least-squares means, the difference between the adjusted formulation means and the standard error associated with the difference.

14.3 Statistical Model

The statistical model used in this research is a general linear model, whose equation is:

$$Y_{ijkl} = \mu + F_i + Seq_j + P_k + S_l(Seq_j) + e_{ijkl}$$

Where:

Y_{ijkl} = Response of l^{th} subject of j^{th} Sequence when it received i^{th} Formulation in k^{th} Period

μ = general mean

F_i = fixed effect of i^{th} formulation

Seq_j = fixed effect of j^{th} sequence

P_k = fixed effect of k^{th} period

$S_l(Seq_j)$= random effect of l^{th} subject nested within the j^{th} sequence

e_{ijkl} = random error

14.4 Two One-Sided Test for Bioequivalence

A two one-sided test (Schuirmann) for the differences of least squares means between the formulations (test/reference) will be calculated for ln-transformed data of the C_{max} and AUC_{0-t} for Paroxetine.

The hypothesis approach for the Schuirmann two one-sided test is:

Null hypothesis H_0: $\mu_{test} / \mu_{ref} < (0.8)$ H_{0a}: $\mu_{test} / \mu_{ref} > (1.25)$ (not bioequivalent)

Alternative hypothesis H_1: $\mu_{test} / \mu_{ref} \geq (0.8)$ H_{1a}: $\mu_{test} / \mu_{ref} \leq (1.25)$ (bioequivalent)

Acceptance criteria: to support bioequivalence, the null hypothesis in both conditions shall be rejected with a significance level of 5% for each side. With regards to the classical generated 90% confidence interval, it shall fall within the bioequivalence range of 80.00% - 125.00%.

14.5 Statistical Power

Statistical power is the probability of rejecting the null hypothesis when it is false. Power is 1-Type II (where Type II error is the false negative error). The statistical power will be reported but considered only as informative when the test product is bioequivalent to the reference product.

14.6 Ratio Analysis

Ratio of geometric least squares means of the test and reference drugs will be computed for un-transformed and ln-transformed primary pharmacokinetic parameters C_{max} and AUC_{0-t} for Paroxetine.

14.7 Intra-Subject Variability

Intra-subject variability will be computed for un-transformed data and for ln-transformed Pharmacokinetic parameters C_{max} and AUC_{0-t} for Paroxetine.

14.8 Analysis of Outliers

The outliers shall be identified (< -2.00 and > +2.00) using a ±2 studentized residuals using the software SAS® version 9.4 or higher and their exclusion in the statistical analysis shall be justified (if applicable).

The subject's data will not be excluded from the statistical analysis exclusively due to mathematical or statistical reasons.

If statistical analysis concluded after removing the outliers, the results shall be submitted with and without the inclusion of outliers with a justification. In this case, the persons responsible

for the study, along with quality assurance personnel will investigate the possible causes of the appearance of outliers, and scientific evidence will be provided in addition to the statistical evidence.

14.9 Criteria for elimination of subject data from the statistical analysis.

No data shall be eliminated from statistical analysis, except for the following.

a. Research (study) subjects with pre-dose concentrations in plasma:

   If the pre-dose concentration is 5% of C_{max} in that research subject, the data can be included without adjustments in all pharmacokinetic measurements and calculations. In cases where the pre-dose sample is >5% of the C_{max}, the research subject shall be eliminated from all bioequivalence assessments.

b. Data elimination due to vomiting or diarrhea.

   Since the study drug is an immediate release product; the data from research subjects who experience vomiting or diarrhea occur before 2 times the median t_{max} or 2 times the value of t_{max} obtained in the research subject in a given period shall be eliminated from all bioequivalence assessments.

c. A research subject who lacks measurable concentrations or with plasma concentrations well below that of the reference drug.

   A research subject is considered to have very low concentrations, if the AUC is less than 5% of the AUC geometric mean of the reference drug (shall be calculated without inclusion of the atypical values of the research subject data). The exclusion of data due to this reason will be accepted only with a scientific justification and with prior review by COFEPRIS.

d. Since the planned study is a crossover and balanced, subjects who did not complete in any of the study periods (subject that is discontinued or withdrawn) shall be eliminated from all bioequivalence assessments.

The AUC_{0-t} shall cover at least 80% of the AUC_{0-inf}. The research subjects shall not be excluded for the statistical analysis if the AUC_{0-t} covers less than 80% of the AUC_{0-inf}.

In case that a research subject elimination proceeds, according to the above-mentioned information, the excluded research subject samples shall be analyzed and the results shall be presented. Also, the statistical analysis shall be performed and shall be presented with and without the data of eliminated research subjects.

14.10 Bioequivalence Criteria

Based on the statistical results of classic 90% confidence interval for the ratio of the geometric least squares means for log-transformed PK parameters C_{max} and AUC_{0-t} for Paroxetine, a conclusion will be drawn for test product (A) vs. the reference product (B) under fasting conditions.

The bioequivalence of the test product (A) with that of the reference product (B) under fasting conditions will be concluded if the 90% confidence interval of the ratio of the test and reference product (test/reference) falls within the acceptance range of 80.00 – 125.00% for ln-transformed PK parameters C_{max} and AUC_{0-t} of Paroxetine.

15.0 AMENDMENTS AND PROTOCOL DEVIATIONS

A protocol deviation is an unintended excursion from the approved protocol.

A major protocol deviation is a protocol deviation that may, as evaluated by the principal investigator, or person designated by the investigator impact the safety of the subject or the integrity of the trial. Major deviations will lead to withdrawal of a subject from the study.. Deviations not classified as major are considered as minor protocol deviations.

All protocol deviations should be reported to the sponsor by the Avant Santé and monitor (if present on site) at the earliest possible time. The sponsor can propose to re-classify a protocol deviation (minor to major or vice versa) upon evaluation. In such case, the classification made by the sponsor prevails and will be communicated to Avant Santé together with a written justification.

Major protocol deviations will only be implemented after sponsor's approval and obtaining approval or a favorable opinion from the Research Ethics Committee (REC) and Research Committee (RC) and COFEPRIS.

The sponsor must be informed of minor protocol deviations, but before start of the following clinical study period or before start of the bioanalytical phase/ statistical phase.

Minor protocol deviations will be reported sponsor and Committees if applicable, and will be reported in study report:

- Logistic deviations (follow up visits that occurred outside the protocol required time frame because of the participant's schedule etc.)
- All post dose in-house blood samples collected beyond ± 2 minutes during housing period and ± 60 minutes for ambulatory samples from the scheduled collection time will be reported as protocol deviations.
- Deviations related to meal consumption.
- Administrative deviations (e.g. change of names).

Protocol deviation notification and reports are submitted to Health Authorities and/or relevant Research Ethics Committee (REC) and Research Committee (RC) according to applicable requirements/guidelines/law.

Procedure for documenting protocol deviations

The Principal Investigator, or person designated by PI, should document and explain any deviation from the approved protocol. The notification of protocol deviation to sponsor can be in exceptional cases communicated by verbal means (if immediate action/notification is needed) and must be followed-up with written documentation (e.g. by e-mail; period update). All major protocol deviations, as well as time point deviations or meal plan, must be described in the final study report.

16.0 TERMINATION OF A STUDY

If the Principal Investigator terminates or suspends a study due to safety concerns, investigator should inform the institution (Avant Santé) where applicable and the Principal Investigator/institution should promptly inform the sponsor, subjects and the REC & RC.

If the sponsor terminates or suspends a study due to safety concerns to assure volunteers well-being, the sponsor should promptly inform the institution/ Principal Investigator where applicable and the investigator/institution should promptly inform the REC / RC and subjects.

If the REC / RC terminates or suspends its approval / favorable opinion of a trial / study, the Principal Investigator should inform the institution where applicable and notify the sponsor.

The subjects would be informed on the reasons for the termination and compensated adequately.

Reasons for termination of study: Principal Investigator / Sponsor / REC / RC / Sanitary Responsible may discontinue / terminate the study at any time before study is complete. Some of the reasons for these early terminations are:

1. A significant number of subjects are withdrawn from the study due to adverse events.
2. A significant number of subjects intermediately dropped out from the study / subjects withdrew their consents to continue in the study, which may affect the overall power of the study.

In case the sponsor finds that the investigational drug presents an unreasonable and significant risk to subjects. In this case, the sponsor will discontinue the investigation as soon as possible, and not later than 5 working days after making the decision. This will be communicated to Principal Investigator, REC / RC and COFEPRIS.

17.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Quality Assurance (QA) personnel, Research Ethics Committee, Research Committee of Avant Santé Research Center S.A. de C.V., sponsor/monitor and applicable regulatory

agencies (like Ministry of Health of México, COFEPRIS) will have access to the forms and other source documents during inspection and audits.

Source documents

- Monitoring details describing strategy including definition of study critical data items and processes, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Document Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing monitoring (remote or on-site) as per the Monitoring Plan 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.

18.0 QUALITY CONTROL AND QUALITY ASSURANCE

The raw data generated during the conduct of the study as well as the reports will undergo a thorough Quality Control check and retrospective Quality Assurance audits performed by QA personnel from Avant Santé Research Center, S.A. de C.V. to evaluate the conformity with this protocol and all the governing SOPs.

The final report will contain a certification of the Quality Assurance Audit, duly signed by the head of the Quality Assurance department.

19.0 INVESTIGATOR AND DELEGATION OF DUTIES

The Principal Investigator will ensure that the personnel involved in the study are adequately qualified, trained and informed about the protocol, any amendment(s) made, the study drugs, and their study-related duties and functions.

The investigator will maintain a list of the clinical investigator(s) and other appropriately qualified personnel to whom he delegates significant study-related duties. The actual delegation of the activities will be documented in the respective form and archived in the RMF or trial master file.

20.0 ETHICAL CONSIDERATIONS

20.1 Ethical Standards

This study will be conducted in compliance with the requirements of NOM-177-SSA1-2013, COFEPRIS guidelines, ICH-GCP and principles of Declaration of Helsinki (Fortaleza, Brazil, October 2013).

Protocol, Case Report Form (CRF) and the informed consent form (ICF) approval will be taken from the REC & RC, and COFEPRIS before initiation of the study.

20.2 Research Ethics Committee and Research Committee

This protocol, the informed consent form (ICF) and any other study-related material provided to the subject will be reviewed and approved by REC & RC and the corresponding regulatory agency.

The study will commence only after obtaining the written approval of the study protocol by the REC/RC and COFEPRIS. Any modifications made to this protocol after its approval will be presented to the REC/RC and COFEPRIS in accordance with the corresponding SOP and any other regulatory requirement. A list of the changes in reference to the previous version will be generated and included in the protocol as a "Change History" (Attachment-III).

20.3 Informed Consent Process

The informed consent documents used during the informed consent process must be approved by the REC / RC before providing to the subjects.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. Extensive discussion of nature and objectives of the study, risks and possible benefits of this study will be provided to each subject or subject's representative.

The designated study person will explain the details of the study to the subject or subject's representative in a language that the subject or subject legal representative comprehends and answer any questions that may arise. All volunteers shall sign the informed consent form before their participation in the study. Each subject will be informed that they may withdraw consent at any time throughout the course of the study.

A duplicate of the informed consent document will be given to the subjects. The subject has the right to withdraw consent and discontinue further participation in the study. If the subject decides to withdraw the study, subject will not face any penalties or loss of benefits to which they may otherwise be entitled.

20.4 Subject Participation Compensation

The subjects will be compensated based on NOM 177-SSA1-2013 (COFEPRIS), and previous approval of REC/RC) on account of their participation in the study. In case of dropout / withdrawal of a subject because of a cause or decision of Avant Santé Research Center, S.A. de C.V. before study is concluded, the subjects will receive the full compensation. In case the withdrawal is the result of any situation caused by the subject such as non-compliance, discipline etc. compensation will be according to the conditions established in the ICF, approved by the REC/RC.

20.5 Subject's Insurance

If a subject suffers any discomfort or injury, temporary or permanent, as a result of an event associated with the study drugs' administration, or that subject needs medical assistance, all the expenses will be met by the sponsor. through an insurance policy contracted by GlaxoSmithKline México, S.A. de C.V. Avant Santé Research Center S.A. de C.V. will ensure that if a subject needs emergency medical care, the same shall be provided at Tertiary care hospital, Swiss Hospital S.A.P.I. de C.V., contracted by Avant Santé Research Center S.A. de C.V. If required, ambulance of Emergencia Médica Profesional, S. C. [contracted by Avant Santé Research Center S.A. de C.V.] may be used for shifting the subject to Tertiary care hospital.

If a subject suffers any discomfort or injury to medical practice will be covered by a valid civil liability insurance policy of Avant Santé Research Center S.A. de C.V. to the extent of sum assured mentioned in the policy.

21.0 DATA HANDLING AND RECORD KEEPING

All clinical data generated during the conduct of the study will be entered directly in the source documents as per the SOPs of Avant Santé Research Center S.A. de C.V. Raw data information will be transcribed in to electronic Case Report Form (eCRFs) according with SOP CP064 Source Data Management. All study (raw data and transcribed data) documents

will be reviewed for completeness by the PI or delegated personnel followed by QA personnel verification. The computer-generated data such as ECGs, randomization schedule, diagnostic lab reports will also be treated as raw data. All data related to the study will be in the custody of the PI until archived. All bioanalytical raw data generated and compiled by the study personnel during the conduct of the same will be reviewed for completeness. All data generated in the Bioanalytical Unit will be exported and transferred electronically based on C-DISC standards as recommended by GSK, to the Pharmacokinetics and Biostatistics department for further evaluation.

21.1 Clinical Study Report

The Clinical study report will be prepared as per NOM-177-SSA1-2013 (COFEPRIS), Guía de Farmacovigilancia en Estudios clínicos, and sponsor requirements, having all the clinical, bioanalytical, pharmacokinetic and statistical data subjected to Quality Assurance audits.

21.2 Confidentiality of Data

The data related to the subject identity will be kept confidential according to what it is described in the informed consent form and will be accessible only to the study personnel and if necessary, to the QA auditors, sponsor/monitors, REC/RC and COFEPRIS.

21.3 Archiving

The raw data and reports (this protocol, all data generated in connection to the study, along with a copy of this protocol, the signed ICFs, bioanalytical method validation report, concentration data, chromatograms and the final report) will be kept in the Trial Master Files together with all the records and documents pertaining to this study and they will be archived in the archives of Avant Santé Research Center S.A. de C.V. for at least 30 years based on GSK SOP POL-GSK-506-GRS GSK Global Records Retention Schedule - Version 7.

Avant Santé Research Center S.A. de C.V. will not destroy/discard any document related to the study without written confirmation from the sponsor.

21.4 Publication Policy

All data and results, and all intellectual property rights in data and results of the study will be property of GlaxoSmithKline México, S.A. de C.V., who can use the same in different ways, such as to be submitted to regulatory authorities or for being sent to other investigators.

The investigator, as long as he/she is free of using data from the study for scientific purposes, shall discuss any publication with GlaxoSmithKline México, S.A. de C.V. prior to the same and obtain the written consent from the sponsor regarding the publication.

This will be reviewed briefly and approval will not be delayed unnecessarily. In case of a difference in opinion between sponsor and investigator(s), the content of publication will be discussed with the objective of finding a solution that satisfies both parties

22.0 LIST OF ATTACHMENTS

Attachment-I: “Flowchart of Activities”

Attachment II: “Schedule of Events”.

Attachment-III: “Change History”.

23.0 REFERENCES

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11. NORMA Oficial Mexicana NOM-012-SSA3-2012, Que establece los criterios para la ejecución de proyectos de investigación para la salud en seres humanos, 04/01/2013.
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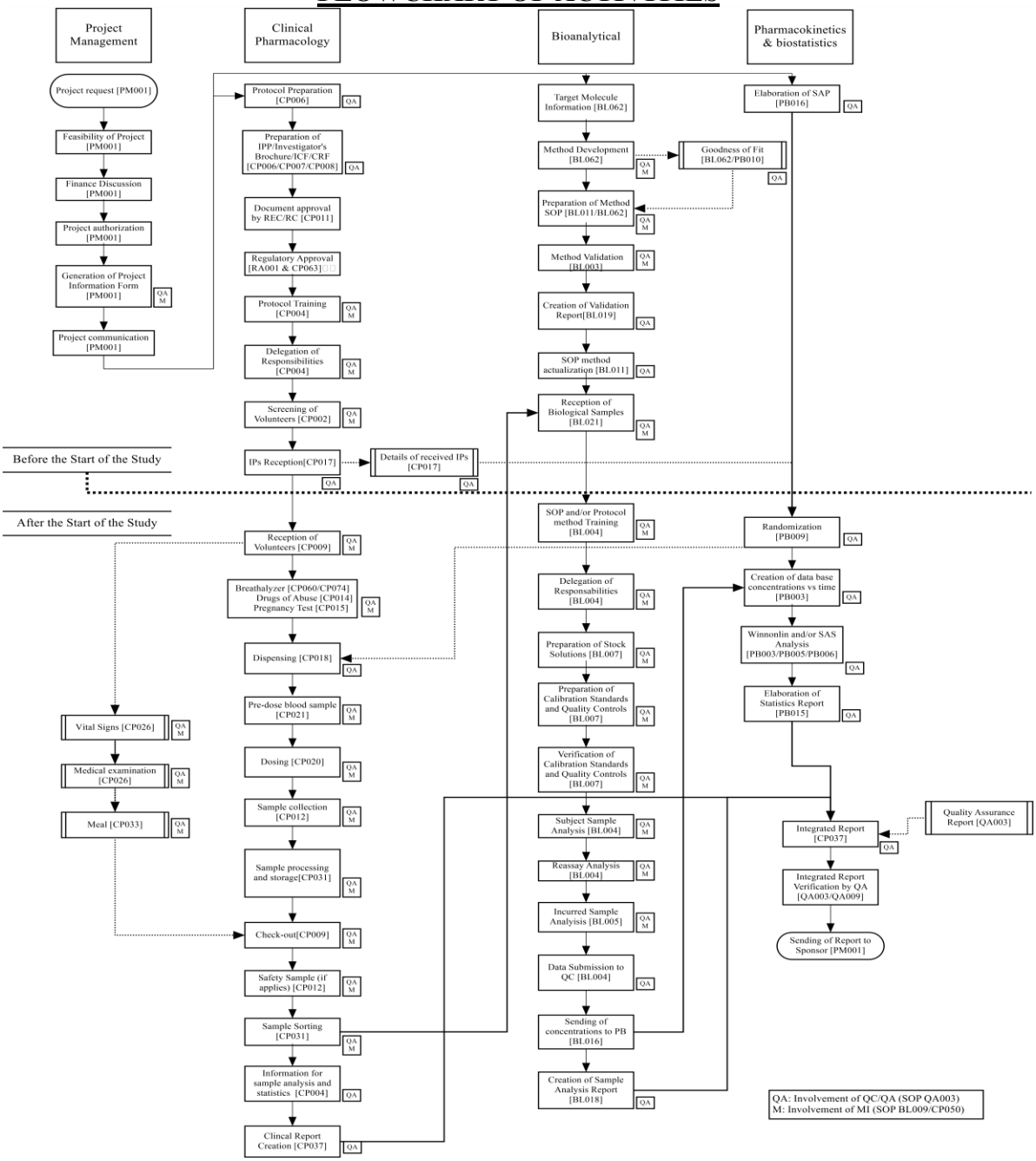
ATTACHMENT-I
FLOWCHART OF ACTIVITIES



ATTACHMENT-II

SCHEDULE OF EVENTS

SCREENING

Day	Hours	Scheduled Time	Activity
-90 days to day -1	N/A	N/A	Informed consent for screening and/or study.
			Recording of weight and height.
			Medical and Physical examination. Subject's well-being assessment.
			Laboratory: hematology, blood chemistry, urinalysis; serology; alcohol testing, urine test for drugs; pregnancy test in urine: ECG.
			Evaluation of inclusion and exclusion criteria.
-72 h	N/A	N/A	RT-PCR test for the detection and diagnosis of SARS-COV-2

PERIOD 1

Day	Hours	Scheduled Time*	Activity
-1	-20.00 – -10.50	12:00 – 21:30	Arrival in clinical facilities. Evaluation of inclusion and exclusion criteria based on screening tests (demography, medical history, physical examination findings, ECG, laboratory tests and RT-PCR). [a]
			Breath alcohol testing, urine drug screen, urine pregnancy test for females, medical & physical examination, vital signs recording, prior and concomitant medication and well-being assessment and admission into clinics (Check-in).
	-10.50 to -10.00	21:30– 22:00	Dinner.
1	-3.00	05:00	Wakeup time, bath following by pre-dose Medical examination, Vital signs recording and well-being assessment.
	-1.50 to 0.00	06:30 – 08:00	Cannulation and 1st blood sample (pre-dose 0.00 h) collection
	- 1.00 to 2.00	07:00 to 10:00	Water restriction period.
	0.00	08:00	Dosing (administration of test or reference product) with 250 mL of water.
	0.00 to 2.00	08:00 to 10:00	Posture restriction period.
	00.50	08:30	2nd blood sample collection.
	01.00	09:00	3rd blood sample collection.
	01.50	09:30	4th blood sample collection
	02.00	10:00	5th blood sample collection,
	02.50	10:30	6th blood sample collection.
	03.00	11:00	7th blood sample collection, Vital signs recording and well-being assessment.

Day	Hours	Scheduled Time*	Activity
	03.50	11:30	8th blood sample collection.
	04.00	12:00	9th blood sample collection. Lunch.
	04.50	12:30	10th blood sample collection.
	05.00	13:00	11th blood sample collection, Vital signs recording and well-being assessment.
	05.50	13:30	12th blood sample collection.
	06.00	14:00	13th blood sample collection.
	06.50	14:30	14th blood sample collection
	07.00	15:00	15th blood sample collection.
	08.00	16:00	16th blood sample collection, Snacks.
	09.00	17:00	17th blood sample collection.
	10.00	18:00	18th blood sample collection.
	12.00	20:00	19th blood sample collection, Vital signs recording and well-being assessment, Dinner.
2	16.00	00:00	20th blood sample collection.
	24.00	08:00	21th blood sample collection. Medical examination with vital signs, well-being assessment and exit from clinics (Check-out).
	36.00	20:00	22nd blood sample collection, well-being assessment and vital signs recording.
3	48.00	08:00	23nd blood sample collection, well-being assessment and vital signs recording.
4	72.00	08:00	24nd blood sample collection, well-being assessment and vital signs recording.

*The schedule of events may change according to the dosing time [a:] Update of changes since screening visit

Washout Period	There will be a washout period of at least 7 days between successive dosing. Subjects will be instructed to self-quarantine during the outpatient period of the study and to monitor at home their daily body temperature

PERIOD 2

Day	Hours	Scheduled Time*	Activity
-1	-20.00 – -10.50	12:00 – 21:30	Arrival in clinical facilities.
			Breath alcohol testing, urine drug screen, urine pregnancy test for females, medical & physical examination, vital signs recording, prior and concomitant medication and well-being assessment and admission into clinics (Check-in).
	-10.50 to -10.00	21:30– 22:00	Dinner.

Day	Hours	Scheduled Time*	Activity
1	-3.00	05:00	Wakeup time, bath following by pre-dose Medical examination, Vital signs recording and well-being assessment.
	-1.50 to 0.00	06:30 – 08:00	Cannulation and 1st blood sample (pre-dose 0.00 h) collection
	- 1.00 to 2.00	07:00 to 10:00	Water restriction period.
	0.00	08:00	Dosing (administration of test or reference product) with 250 mL of water.
	0.00 to 2.00	08:00 to 10:00	Posture restriction period.
	00.50	08:30	2nd blood sample collection.
	01.00	09:00	3rd blood sample collection.
	01.50	09:30	4th blood sample collection
	02.00	10:00	5th blood sample collection,
	02.50	10:30	6th blood sample collection.
	03.00	11:00	7th blood sample collection, Vital signs recording and well-being assessment.
	03.50	11:30	8th blood sample collection.
	04.00	12:00	9th blood sample collection. Lunch.
	04.50	12:30	10th blood sample collection.
	05.00	13:00	11th blood sample collection, Vital signs recording and well-being assessment.
	05.50	13:30	12th blood sample collection.
	06.00	14:00	13th blood sample collection.
	06.50	14:30	14th blood sample collection
	07.00	15:00	15th blood sample collection.
	08.00	16:00	16th blood sample collection, Snacks.
	09.00	17:00	17th blood sample collection.
	10.00	18:00	18th blood sample collection.
	12.00	20:00	19th blood sample collection, Vital signs recording and well-being assessment, Dinner.
2	16.00	00:00	20th blood sample collection.
	24.00	08:00	21th blood sample collection. Medical examination with vital signs, well-being assessment and exit from clinics (Check-out).
	36.00	20:00	22nd blood sample collection, well-being assessment and vital signs recording.
3	48.00	08:00	23nd blood sample collection, well-being assessment and vital signs recording.
4	72.00	08:00	24nd blood sample collection, well-being assessment and vital signs recording. Final Compensation for subjects (applicable only for period 2).

Seven (7) to 9 days after the collection of 72-h blood sample in second period or after the withdrawal, a telephone call will be made to each subject by the personnel designated by the PI to monitor any serious adverse event, specifically, subjects will be questioned about any symptoms related to COVID-19.

*The schedule of events may change according to the dosing time

ATTACHMENT-III
CHANGE HISTORY

Current Version No.	Supersedes, Effective Date	Changes Made
01	N/A	N/A
02	01, 10/Jan/2020	1. Format number "CPF127-02E" of the protocol is modified to "CPF127-03E" 2. The Sanitary Responsible of Clinical Unit is modified on page 6. 3. COVID-19, SARS-CoV-2 and RT-PCR are added to abbreviations. 4. The address of the Clinical Diagnostic Laboratory is modified in section 2.3. 5. Real-time (RT-PCR) test for the detection and diagnosis of SARS-COV-2 is added in section 1.0 and 8.1 Screening (selection and enrollment). 6. "Have a negative test for active COVID-19, within 72 hours prior to the first period check-in. The testing should be done using a molecular (RT-PCR) approved by the country regulatory authorities" is added in section 8.3 (Inclusion criteria). 7. "Subjects with symptoms suggestive of active COVID-19 infection (i.e. fever, cough, respiratory difficulties) within 14 days of inpatient admission" and "Subjects with known COVID-19 positive contacts* within the past 14 days prior to the first period check-in. *Positive Contact; this means, if the subject has

		been living, providing, care, being within 1.5 m for at least 15 min or having exposure to respiratory secretions with/to a person who has COVID-19" is added in section 8.3 (Exclusion criteria). 8. In section 8.5, criteria b is added "In case a subject is positive for COVID-19 or has a related symptom (i.e. fever, cough, respiratory difficulties), they shall be isolated for 14 days and they shall be discontinued In case any other subject was exposed to a COVID-19 patient, they must report this to Avant Santé, GSK and/or their primary care provider". 9. In section 9.3 is added "Recommendations during washout period and visits to the center (ambulatory samples)". 10. "Subjects will be instructed to self-quarantine during the outpatient period of the study i.e. until 72 h blood sample collection in period-2 or until withdrawal, whichever is earlier, and to monitor at home their daily body temperature" is added in section 1.0 and 9.4 (Housing). 11. The assessment of vital signs at the time of ambulatory samples is added in section 1.0 and 11.1 (Assessment of safety). 12. " Seven (7) to 9 days after the collection of 72-h sample in second period or after withdrawal, a telephone call will be made to each subject by the personnel

		designated by the PI to monitor any adverse event, specifically, subjects will be questioned about any symptoms related to COVID-19" is added in section 1.0 and 11.1 (Assessment of safety). 13. The period of recording AEs "(i.e., within 7 or 9 days after the last sample collection or after withdrawal)" is added in section 11.2 (Recording of AEs). 14. The section 11.2 "The notification through the platform assigned by the CNFV for this purpose shall be performed as soon as possible but no more than 7 calendar days * from the time of awareness" is modified by "The notification through the platform assigned by the CNFV for this purpose shall be performed according to the timelines stablished in the valid NOM-220-SSA1-2016". 15. Typo errors are corrected in section 14.4. 16. Information regarding "source documents" was added in section 17.0. 17. In section 20.3 "a copy of the informed consent ..." is modified by "a duplicate of the informed consent ..." 18. Reference 9 is updated and reference 16 is added. 19. Attachment-I (Flowchart of activities) is updated. 20. Attachment-II (Schedule of events) is updated based on the new information provided above.