CLINICAL PHARMACOLOGY PROTOCOL

A PHASE 1, SINGLE CENTER RANDOMIZED, THREE-WAY CROSSOVER, DOUBLE-BLINDED, PLACEBO- AND MOXIFLOXACIN-CONTROLLED THOROUGH QT (TQT) STUDY TO DETERMINE THE EFFECTS OF SERTRALINE (ZOLOFT®) ON THE CARDIAC REPOLARIZATION IN HEALTHY SUBJECTS

Compound:	[redacted]
Compound Name:	Sertraline Hydrochloride
United States (US) Investigational New Drug (IND) Number:	[redacted]
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Phase:	1

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Document History

Document	Version Date	Summary of Changes
Original protocol	26 October 2015	Not applicable (N/A)

[redacted]

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	Screening	Periods 1, 2 and 3 (Treatments A, B and C)																	
		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17/Early Termination
Informed Consent	X																		
CRU confinement		X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X[b]																	
Medical History[d]	X	X[c]																	
Physical Exam[e]	X	X																	X[f]
Height and weight	X																		
Safety laboratory	X	X							X[g]							X[g]			X[f]
12-Lead ECG (single)	X																		
12-Lead ECG (triplicates)[h]			X	X												X	X	X	X[f]
Demography	X																		
Vital Signs (BP/PR, temperature)	X		X	X															X[f]
Pregnancy Test[i]	X	X																	X
FSH[j]	X																		
Confirm Proper Contraception is being used	X	X																	X
Urine Drug Screen	X	X																	
Study treatment Administration[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PK Blood sampling[l]			X	X												X	X	X	X
Baseline Symptoms/ Adverse Event Monitoring		X----------																	----X
Prior/Concomitant Treatment	X	X[m]----------																	----X
Suicidality assessment[n]	X	X														X			X[o]
Discharge from Unit																			X

a. Subjects to be admitted on Day 0 and may be discharged after collection of the 72 hour (following Day 14 dosing) PK sample and ECG reading on Day 17.

b. Period 1 only.

c. Medical history includes complete history of all prescription and non-prescription drugs and dietary and herbal supplements taken 28 days prior to the planned first dose, as well as illegal drug, alcohol and tobacco use.

d. Medical history updated on Day 0 (Period 1 only).

e. Full physical examination either at screening or Day 0 Period 1; otherwise brief exam if findings during previous exam or new/open AEs if appropriate at Investigator discretion.

f. To be conducted on Day 17, Period 3 and for Periods 1 and 2 at PI's discretion or upon early withdrawal.

g. Pre-dose.

h. Detailed ECG collection time points are provided in PK and ECG assessment Flow Chart below.

i. Female of childbearing potential. Also at discharge of each period.

j. Serum FSH (follicle-stimulating hormone) will be done for any female who has been amenorrheic for at least 12 consecutive months.

k. Treatment A will be active drug given on Day 1 to 14 based on escalation schema specified in Section 3.1. Treatment C will be matching placebo administered on Days 1 to 14 using the same escalation schema as active drug. Treatment B will be matching placebo on Days 1 to 13 using the same escalation schema as active drug, and a single dose, open-label administration of moxifloxacin on Day 14. The washout period between treatments will be 14-days.

l. Detailed PK sample collection time points are provided in PK sampling and ECG assessment Flow Chart below.

m. To be repeated if subjects discharged to home after 72 hour assessment.

n. Columbia - Suicide Severity Rating Scale (C-SSRS) – Lifetime/Baseline Assessment at Screening; all other assessments are Since Last Visit Assessment.

o. To be performed upon early termination.

PHARMACOKINETIC SAMPLING AND ECG ASSESSMENT FLOW CHART

Protocol Assessment	**Periods 1, 2 and 3 (Treatments A, B and C)**																							
Study Day	**Day 1**											**Day 2**	**Day 14**									**Day 15**	**Day 16**	**Day 17**
Hours Post Dose	-1	-0.5	0[a]	1	2	3	4	5	6	8	12	24	0[a]	1	2	3	4	5	6	8	12	24	48	72
PK blood sampling[b]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (triplicates)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The pre-dose PK sampling (0 hour) occurs immediately prior to the morning dose.

b. All study treatments will have identical sample collection time points. Placebo samples will only be analyzed if deemed necessary. For moxifloxacin treatment, Day 14 plasma samples will be analyzed for the 1, 2, 3, 4, and 5 hour time points if a positive signal (QTc prolongation) is not observed; moxifloxacin samples will be held until notification by the clinical team before analysis.

c. ECG assessment will be triplicate recorded approximately 2 min apart, the pre-dose assessments (-1, -0.5 and 0 hours) should occur immediately prior to the morning dose on Day 1.

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PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Sertraline is a selective serotonin reuptake inhibitor (SSRI). ZOLOFT® (Sertraline hydrochloride) is indicated for the treatment of major depressive disorder; obsessions and compulsions in patients with obsessive-compulsive disorder (OCD); panic disorder, with or without agoraphobia, as defined in Diagnostic and Statistical Manual of Mental Disorders-I (DSM-I); posttraumatic stress disorder; premenstrual dysphoric disorder (PMDD); and social anxiety disorder, also known as social phobia, in adults (ZOLOFT® United States Package Insert [USPI] Revised August 2014).

This study is being conducted to fulfill a United States (US) Food and Drug Administration (FDA) Post Marketing Requirement (PMR) and the study design is in accordance with the International Conference on Harmonisation (ICH) E14 Guidance for a thorough QTc (TQT) study. This study is designed to assess effect of sertraline on the QTc interval at supratherapeutic concentrations.

The approved therapeutic dosage regimen for sertraline is an initial dose of 25 or 50 mg administered once daily and the dose may be increased up to a maximum of 150 mg/day or 200 mg/day, depending on the indication. The proposed starting dose for this study is 50 mg on Day 1. Thereafter, the dose will be increased in increments of 50 mg/day or 100 mg/day to a maximum dose of 400 mg/day, achieved on Day 7. The 400 mg/day dose will then be continued from Day 8 to Day 14. This dose escalation schema is anticipated to be well tolerated in healthy volunteers and is designed to achieve supratherapeutic concentrations by Day 14. It is anticipated that by Day 14, the supra-therapeutic concentration of sertraline following the 400 mg/day dose will be about 3-fold higher than the concentration achieved after the maximum therapeutic dose of 200 mg/day. Pharmacokinetics and QTc will be evaluated on Day 1 and on Day 14 for an assessment of concentration-QTc relationship.

OBJECTIVES AND ENDPOINTS

Objectives

Primary:

- To determine the effect of sertraline on QTc intervals relative to time-matched placebo in healthy subjects.

Secondary:

- To evaluate study sensitivity by evaluating the effect of moxifloxacin on QTc intervals relative to time-matched placebo at moxifloxacin historical T_{max} (3 hours post-dose).

- To evaluate the safety and tolerability of sertraline in healthy subjects.

- To evaluate the relationship of the QTc interval with plasma concentrations of sertraline, and its metabolite, N-desmethylsertraline.

Tertiary:

- To evaluate the pharmacokinetics of sertraline and its metabolite, N-desmethylsertraline.

Endpoints

Primary:

- Post-dose QTcF (Fridericia's correction) intervals on Day 14 for placebo, sertraline, and moxifloxacin.

Secondary:

- Safety and tolerability assessed by reporting of adverse events, vital signs, physical examinations and laboratory safety assessments.

- Exposure-response relationship between QT/QTc and plasma concentration of sertraline and metabolite, N-desmethylsertraline.

Tertiary:

- Pharmacokinetic parameters of sertraline and N-desmethylsertraline [Day 1: C_{max}, C_{max} (dn), T_{max}, AUC_{24}, AUC_{24}(dn), and metabolite ratio (MR); Day 14: C_{max}, C_{max} (dn), C_{min}, T_{max}, AUC_{24}, AUC_{24}(dn), AUC_{last}, $t_{½}$, Rac (obs), Rac (C_{max}) and MR].

STUDY DESIGN

This will be a Phase 1, single-center, randomized, double-blind, placebo- and moxifloxacin-controlled, 3-period, 6-sequence, 3-treatment (sertraline and placebo blinded; moxifloxacin open label) 3-way crossover thorough QT (TQT) study of the effects of sertraline on cardiac repolarization in 54 healthy subjects.

A sample size of approximately 42 subjects (7 per sequence) was estimated to be required for the study to attain statistical power to demonstrate lack of effect of sertraline on QTc and also show assay sensitivity. To allow for dropouts, 54 (9 per sequence) subjects will be randomized to have 42 evaluable subjects. Subjects will not be replaced. However, if the total number of subjects falls below 36, additional subjects will be randomized. Additional subjects will be randomized in multiples of six (block size).

Study Treatments

The subjects, investigator and site personnel involved in the study (except for the pharmacy staff) will be blinded to study treatments (except open label moxifloxacin), while the sponsor (Pfizer) will be un-blinded.

Sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C) will be administered in a randomized sequence in Periods 1, 2 or 3.

The following treatments will be administered:

- **Treatment A (Sertraline hydrochloride - double blinded):** dose titrated from a starting single dose (QD) of 50 mg sertraline in the morning on Day 1 followed by BID (given at approximately 12 hours apart) escalating doses administered on Days 2 through 6, followed by 400 mg/day (BID) on Days 7 through 13, and on Day 14 only the morning dose of 200 mg will be administered, and no evening dose will be administered, according to the dose titration scheme in Figure 1.

- **Treatment B (Moxifloxacin - positive control, open label):** double blinded placebo (matching for sertraline) will be given from Day 1 to Day 13, according to dose titration scheme in Figure 1. On Day 14, a single dose of 400 mg moxifloxacin (Avelox®) will be administered open label.

- **Treatment C (Placebo - double blinded):** placebo control – placebo administered on Days 1 through 14, according to the dose titration scheme in Figure 1.

Sertraline 50 mg tablets and matching placebo tablets will be used in the study.

Summary of Assessments

Pharmacokinetic (PK) Assessment:

A blood sample (4 mL) will be collected immediately prior to dosing and after dose administration at the time points as described below:

PK sampling for all treatments: sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C):

- Day 1: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Day 2).

- Day 14: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 48 (Day 16), and 72 hours (Day 17).

Placebo samples will only be analyzed if deemed necessary. For moxifloxacin treatment, Day 14 plasma samples will be analyzed for the 1, 2, 3, 4, and 5 hour time points if a positive signal (QTc prolongation) is not observed (Moxifloxacin PK samples will be held until notification from the clinical team before analysis).

Electrocardiogram (ECG) Assessment:

ECG assessment for sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C) (triplicate recorded approximately 2 min apart):

- Day 1: pre-dose (-1, -0.5, 0), 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Day 2).
- Day 14: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 48 (Day 16) and 72 hours (Day 17).

During the treatment with active drug or placebo, if any subject who has a confirmed change in QTcF value from baseline of greater than 45 msec or a QT value greater than 500 msec, the principal investigator should assess the subject for potential discontinuation for safety reason.

Other Assessments:

Tolerability and safety will be assessed for all treatments by monitoring adverse events.

Assessment of Suicidal Ideation and Behavior (SIB) - Columbia Suicide Severity Rating Scale

The assessment of suicidal ideation and behavior will be performed during the Screening visit, on Day 0 and after the last study treatment administration on Day 14 for all treatments using the Columbia Suicide Severity Rating Scale (C-SSRS).

DATA ANALYSIS/STATISTICAL METHODS

Sample Size Determination

A sample size of 42 subjects (7 per sequence) will provide at least 99% power to exclude that the upper bound of a two-sided 90% confidence interval (CI) (one-sided 95% CI) of time-matched difference between sertraline and placebo is more than 10 msec at each time point. The overall study power for 9 post-dose time points on Day 14 will be at least 90%. These calculations are based upon the assumption that the expected mean difference between sertraline and placebo is no greater than 5 msec at each time point and the intra-subject variability is 5.36 msec.

Given a one-sided significance of 0.05, 42 subjects will provide 99% power to detect at least a 5 msec difference between moxifloxacin and placebo at 3 hours post-dose (historical moxifloxacin median T_{max}) to demonstrate assay sensitivity.

To allow for dropouts, 54 subjects (9 per sequence) will be randomized to have 42 evaluable subjects.

Pharmacokinetic Analysis

The pharmacokinetic (PK) concentration population is defined as all subjects enrolled and treated who have at least 1 concentration determined.

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the pharmacokinetic parameters of primary interest determined.

Statistical Analyses

Averages of triplicate ECG measurements will be used in all statistical analyses.

If subjects vomited on Day 14 within 2 hours of dosing, data from these subjects on those days will be excluded from PK and ECG statistical analyses.

Primary Analysis: Primary analysis will be conducted in the Primary ECG Analysis Population. The raw post-dose QTcF intervals will be analyzed (Day 14 data for sertraline, placebo, and moxifloxacin) with baseline as a covariate. Analysis of covariance using a mixed effect model with sequence, period, treatment, time, treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate will be conducted.

If there is a significant period effect, a mixed effect model with sequence, period, treatment, period-by-treatment interaction, carry-over, time, treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate will be conducted.

The 90% confidence intervals (equivalent to a one-sided 95% confidence interval) for time-matched change from placebo in QTcF at each time point on Day 14 will be computed for sertraline. Similarly, the 90% confidence interval for time-matched change from placebo in QTcF at 3 hours post-dose on Day 14 will be computed for moxifloxacin.

- **Lack of Effect of Sertraline on QTc Intervals Assessment:**

A lack of an effect of sertraline on QTc intervals will be concluded if the upper bounds of the two-sided 90% (equivalent to one-sided 95%) confidence intervals for all the time-matched mean differences between sertraline and placebo are less than 10 msec.

- **Assay Sensitivity Assessment:**

This study will be deemed adequately sensitive to detect QT/QTc prolongation if the lower bound of the two-sided 90% confidence interval for the mean difference between moxifloxacin and placebo is greater than 5 msec at the historic T_{max} of moxifloxacin (3 hours post-dose).

Sensitivity Analysis:

At the completion of the trial, if more than 10% of subjects dropped out or have missing data for one or more treatment periods, primary analysis outlined above will be conducted in the Completer ECG Analysis Population also.

Additional Analyses:

Additional analysis will be conducted in the Primary ECG Analysis Population.

Relationship between QTc prolongation and sertraline/metabolite plasma concentration will be examined graphically. Exposure response analysis will be performed to establish relationship between change in QTc from baseline and drug concentration.

Categorical analysis of QTcF of both absolute post-dose maximum and maximum increase from baseline will be provided.

QT, QTcF, PR (pulse rate), HR (heart rate), and QRS will be summarized by treatment group, study day, and time point – both observed and change from baseline.

Analyses conducted on QTcF may be repeated on QTcB (Bazett's formula), QTcI (individually corrected QT interval) and QTcN (population-based approach) if deemed necessary.

Safety Analysis

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

Adverse events, ECGs, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern as defined Appendix 2 will be described. Suicidality will be assessed using Columbia - Suicide Severity Rating Scale (C-SSRS). Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Sertraline is a selective serotonin reuptake inhibitor (SSRI).

ZOLOFT® (Sertraline hydrochloride) is indicated for the treatment of major depressive disorder; obsessions and compulsions in patients with obsessive-compulsive disorder (OCD); panic disorder, with or without agoraphobia, as defined in DSM-I; posttraumatic stress disorder; premenstrual dysphoric disorder (PMDD); and social anxiety disorder, also known as social phobia, in adults (ZOLOFT® USPI Revised August 2014).[1]

1.2. Background

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of central nervous system (CNS) neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, gamma-amino butyric acid (GABA), dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to down regulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.[1]

Pharmacokinetics

Pharmacokinetics of sertraline has been extensively evaluated following approved therapeutic doses of 50 to 200 mg.

Following oral once-daily dosing over the range of 50 to 200 mg for 14 days in humans, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is approximately 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range.[1]

Pharmacokinetics of sertraline and its metabolite were also assessed in multiple dose study following oral administrations of either 100 mg BID (total dose of 200 mg per day), or 200 BID (total dose of 400 mg per day) or placebo for 13 days followed by a single dose on Day 14 in healthy subjects.[2] Following oral administrations of 200 mg or 400 mg per day, exposures (C_{max} and AUC) of sertraline and metabolites increased in a dose related manner, and the steady state of sertraline was reached by Day 7. The mean exposure (C_{max} and AUC) on Day 14 was approximately 3 folds higher than Day 1 for sertraline, and approximately 16 to 20 folds higher for the desmethylsertraline (Table 1). The mean exposures of 400 mg per day (the highest tolerated dose) sertraline at steady state (Day 14) were approximately 3 folds higher than that of 200 mg per day (the highest approved therapeutic dose) (Table 1). The mean elimination $t_{1/2}$ was 24-27 hours for sertraline, and 62-66 hours for desmethylsertraline.[2]

Table 1. Summary of Mean (n=8 per group) Sertraline and Desmethylsertraline Exposures following a Single & Multiple Doses of 100 mg BID (total dose of 200 mg per day) and 200 mg BID (total dose of 400 mg per day) in Healthy Subjects[2]

		C_{max} (ng/mL)			AUC_{1-12} (ng.h/mL)		
Dose	**Name**	**Day 1**	**Day 14**	**Ratio (D14/D1)**	**Day 1**	**Day 14**	**Ratio (D14/D1)**
200 mg (100 bid)	**Sertraline**	31.6	86.1	2.7	271	825	3.0
	Desmethylsertraline	5.1	85.5	16.8	40.0	816	20.4
400 mg (200 bid)	**Sertraline**	73.6	282	3.8	616	2780	4.5
	Desmethylsertraline	15.9	260	16.4	128	2455	19.2
Ratio (400/200 mg) on day 14	**Sertraline**		3.3			3.4	

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food.[1]

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. Approximately 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For

the same period, approximately 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.[1]

In vitro protein binding studies performed with radiolabeled H^3-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, ie., warfarin and propranolol.[1]

Liver Impairment

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.[1]

Renal Impairment

Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr = 30-60 mL/min), moderate to severe (CLcr = 10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment.[1]

Safety of Multiple Dose Sertraline

Safety and tolerability of sertraline were extensively evaluated in healthy subjects and patients.[1] Single and multiple doses up to 400 mg of sertraline were safe and well tolerated.[2,3]

A single dose titration study of safety, tolerability and PK following 10, 25, 50, 75, 100, 125, 175, 200, 250, 300, 350 to 400 mg in healthy subjects indicated that the main treatment related adverse events (AEs) were gastrointestinal (GI) including, diarrhea (42.5%), nausea (20%), and dyspepsia (15%), reported ≥125 mg.[3]

The safety evaluation of sertraline in a double-blind, placebo-controlled, parallel-group, multiple dose study following oral administrations of either 100 mg BID (total dose 200 mg per day), or 200 bid (total dose 400 mg per day) or placebo for 13 days followed by a single dose on Day 14 in healthy subjects reported no subjects withdrawn from the study due to intolerability. The incidence of side effects was greater with 200 mg bid dose group than either 100 mg bid dose group or the placebo. No clinical relevant effects on blood pressure, heart rate or ECG were observed. Adverse effect related temporary dose reduction occurred in 1 out of 8 subjects in the 100 mg bid dose group and 4 out of 8 patients in the 200 mg bid group. These subjects tolerated the full doses when it was gradually re-introduced. Insomnia, headache, tremor, and nausea were the most frequently reported side effects of sertraline, and they appeared to be dose related. Insomnia and headache were also reported in the placebo group. In general, the oral administrations of the 100 mg bid and 200 mg bid for 14 days was safe and tolerated in healthy subjects.[2]

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the SmPC for Brussels and the United States Package Insert for ZOLOFT® (Sertraline hydrochloride) (USPI Revised August 2014).[1]

1.3. Rationale

1.3.1. Study Rationale

This study is being conducted to fulfill a US FDA Post Marketing Requirement (PMR) and the study design is in accordance with the ICH E14 Guidance for thorough QTc (TQT) study.[4] This study is designed to assess effect of sertraline on QTc interval at supratherapeutic concentrations.

This study will consist of 3 periods and 3 treatments (supratherapeutic dose of the drug, placebo, and moxifloxacin). To achieve supratherapeutic concentrations of the drug and its active metabolite in healthy subjects, slow escalation of doses over a 2-week period is required for tolerability reasons. Similarly a washout period of approximately 2 weeks is necessary due to the long half-lives of the drug and its metabolite. Moxifloxacin is administered in this study in order to confirm assay sensitivity for detecting increases in QTc of 5 msec or greater.[4] A single dose of moxifloxacin is chosen as a positive control in the majority of TQT studies as it typically has a peak occurring between 1 and 3 hours post-dose in the range of 8 to 15 msec and a lower bound of the one-sided 95% CI above 5 ms.[5,6]

1.3.2. Dose Rationale

The approved therapeutic dosage regimen for sertraline is an initial dose of 25 or 50 mg administered once daily, and the dose may be increased up to a maximum of 150 mg/day or 200 mg/day, depending on the indication.[1] The proposed starting dose for this study is 50 mg on Day 1. Thereafter, the dose will be increased in increments of 50 mg/day or 100 mg/day to a maximum dose of 400 mg/day, achieved on Day 7. The 400 mg/day dose will then be continued from Day 8 to Day 14 (on Day 14 only the morning dose of 200 mg will be administered, and no evening dose will be administered). This dose escalation schema is anticipated to be well tolerated in healthy volunteers and is designed achieve supratherapeutic concentrations by Day 14. It is anticipated that by Day 14, the

supra-therapeutic concentration of sertraline following the 400 mg/day dose will be about 3-fold higher than the concentration achieved after the maximum therapeutic dose of 200 mg/day. Pharmacokinetics and QTc will be evaluated on Day 1 and on Day 14 for an assessment of concentration-QTc relationship.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary:

- To determine the effect of sertraline on QTc intervals relative to time-matched placebo in healthy subjects.

Secondary:

- To evaluate study sensitivity by evaluating the effect of moxifloxacin on QTc intervals relative to time-matched placebo at moxifloxacin historical T_{max} (3 hours post-dose).
- To evaluate the safety and tolerability of sertraline in healthy subjects.
- To evaluate the relationship of the QTc interval with plasma concentrations of sertraline and its metabolite, N-desmethylsertraline.

Tertiary:

- To evaluate the pharmacokinetics of sertraline and its metabolite, N-desmethylsertraline.

2.2. Endpoints

Primary:

- Post-dose QTcF (Fridericia's correction) intervals on Day 14 for placebo, sertraline, and moxifloxacin).

Secondary:

- Safety and tolerability assessed by reporting of adverse events, vital signs, physical examinations and laboratory safety assessments.
- Exposure-response relationship between QT/QTc and plasma concentration of sertraline and its metabolite, N-desmethylsertraline.

Tertiary:

- Pharmacokinetic parameters of sertraline and N-desmethylsertraline [Day 1: C_{max}, C_{max} (dn), T_{max}, AUC_{24}, AUC_{24}(dn),and metabolite ratio (MR); Day 14: C_{max}, C_{max} (dn), C_{min}, T_{max}, AUC_{24}, AUC_{24}(dn), AUC_{last}, $t_{½}$, Rac (obs), Rac (C_{max}), and MR].

3. STUDY DESIGN

3.1. Study Overview

This will be a Phase 1, single-center, randomized, double-blind, placebo- and moxifloxacin-controlled, 3-period, 6-sequence, 3-treatment (sertraline and placebo blinded; moxifloxacin open label), 3-way crossover thorough QT (TQT) study of the effects of sertraline on the cardiac repolarization in approximately 54 healthy subjects.

Number of Subjects

A sample size of approximately 42 subjects (7 per sequence) was estimated to be required for the study to attain statistical power to demonstrate lack of effect of sertraline on QTc and also show assay sensitivity. To allow for dropouts, 54 (9 per sequence) subjects will be randomized to have approximately 42 evaluable subjects. Subjects will not be replaced. However, if the total number of subjects goes below 36, additional subjects will be randomized. Additional subjects will be randomized in multiples of six (block size).

Study Treatments

The subjects, investigator and site personnel involved in the study (except for the pharmacy staff) will be blinded to study treatments (except open label moxifloxacin), while the sponsor (Pfizer) will be un-blinded.

Sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C) will be administered in a randomized sequence in Periods 1, 2 or 3.

The following treatments will be administered:

- **Treatment A (Sertraline hydrochloride - double blinded):** dose titrated from a starting single dose (QD) of 50 mg sertraline in the morning on Day 1 followed by BID (given at approximately 12 hours apart) escalating doses administered on Days 2 through 6, followed by 400 mg/day (BID) on Days 7 through 13, and on Day 14 only the morning dose of 200 mg will be administered, and no evening dose will be administered, according to the dose titration scheme in Figure 1.

- **Treatment B (Moxifloxacin - positive control, open label):** double blinded placebo (matching for sertraline) will be given from Day 1 to Day 13, according to dose titration scheme in Figure 1. On Day 14, a single dose of 400 mg moxifloxacin (Avelox®) will be administered open label.

- **Treatment C (Placebo - double blinded):** placebo control – placebo administered on Days 1 through 14, according to the dose titration scheme in Figure 1.

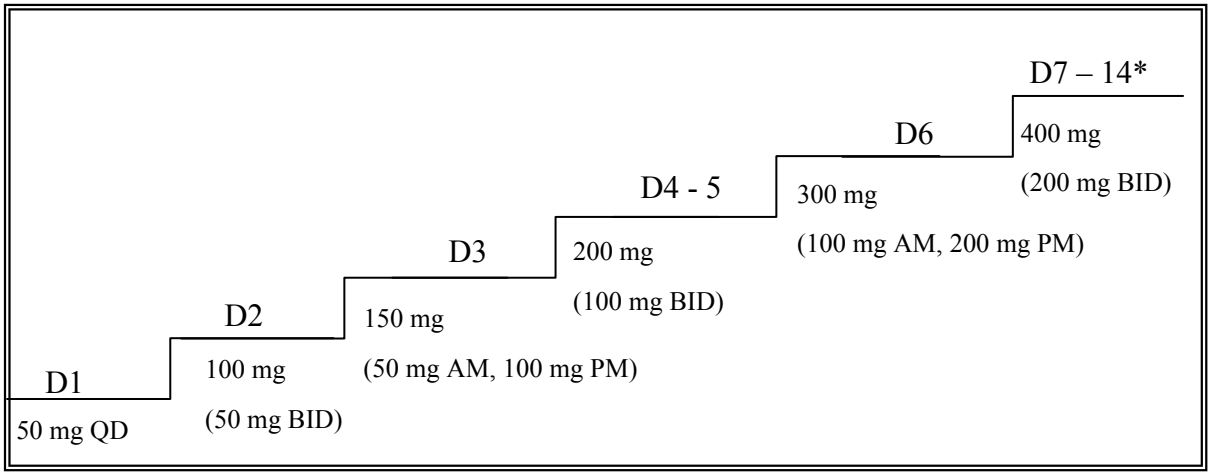
Sertraline 50 mg tablets and matching placebo tablets will be used in the study.

Table 2. Treatment Sequences

	Treatment		
	Period 1	**Period 2**	**Period 3**
Sequence 1 (n=9)	Treatment A	Treatment B	Treatment C
Sequence 2 (n=9)	Treatment C	Treatment B	Treatment A
Sequence 3 (n=9)	Treatment B	Treatment C	Treatment A
Sequence 4 (n=9)	Treatment C	Treatment A	Treatment B
Sequence 5 (n=9)	Treatment A	Treatment C	Treatment B
Sequence 6 (n=9)	Treatment B	Treatment A	Treatment C

n = number of subjects

Figure 1. Dose Titration Scheme for Treatment A – Sertraline Administration



* On Day 14, only the morning dose of 200 mg will be administered, and no evening dose will be administered.

Each subject will participate in the study for approximately 4 months, including screening, study periods, and washout. It is estimated that the clinical portion of the study will be completed in approximately 3 months (ie, 93 days). Participation will include a screening evaluation conducted within 28 days before dosing in Period 1, admission to the unit on study Day 0 and a subsequent 17-nights inpatient stay, respectively, for treatments A, B and C. There will be a washout period of at least 14 days after completion of treatment A, B and C.

Subjects will undergo screening evaluation within 28 days of dosing. Day 0 is defined as the day prior to first day of dosing (Day 1) for each period. Eligible subjects will be admitted to the Clinical Research Unit (CRU) on Day 0 and will remain at the CRU until the last pharmacokinetic sample is collected at the end of the treatment period.

Double blind test article or placebo administration will occur on Days 1 through 14 for Treatment A and C (sertraline and placebo treatment, respectively). Double blind placebo

administration will also occur for Treatment B (moxifloxacin) on Days 1 to 13 following by single dose of open label moxifloxacin 400 mg on Day 14. An overnight fast of at least 10 hours will be observed before the morning dose administrations on Days 1 and 14 (when PK and ECG assessments are planned), and the evening dose on Day 1 can be given with food, and a fasted morning dose on Day 15 when obtaining trough measurement for all treatments. Breakfast may be completed by 30 minutes prior to drug administration on other study days (Days 3 through 13) of study Treatments A, B and C.

Each subject will participate in 3 study periods and receive all three treatments. The study is planned for a single investigational site.

A standard breakfast, lunch and dinner will be provided at appropriate times. Subjects must abstain from drinks, including water, for 0.5 hours prior to any ECG measurement. Subjects will be restricted to consuming ambient temperature beverages in each study period.

During the treatment periods, subjects who experience repeated episodes of vomiting will be assessed by the principal investigator for potential discontinuation from the study.

Summary of Assessments

PK Assessment:

A blood sample (4 mL) will be collected immediately prior to dosing and after dose administration at the time points as described below:

PK sampling for all treatments: sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C):

- Day 1: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Day 2).
- Day 14: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 48 (Day 16), and 72 hours (Day 17).

Placebo samples will only be analyzed if deemed necessary. For moxifloxacin treatment (Treatment B), Day 14 plasma samples will be analyzed for the 1, 2, 3, 4, and 5 hour time points if a positive signal (QTc prolongation) is not observed (Moxifloxacin sample will be held until notification from the clinical team before analysis).

ECG Assessment:

ECG assessment for sertraline (Treatment A), moxifloxacin (Treatment B), and placebo (Treatment C) (triplicate recorded approximately 2 min apart):

- Day 1: pre-dose (-1, -0.5, 0), 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Day 2).
- Day 14: pre-dose (0), 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 48 (Day 16) and 72 hours (Day 17).

During the treatment with active drug or placebo, if any subject who has confirmed change in QTcF value from baseline of greater than 45 msec or QT values of greater than 500 msec, the principal investigator should assess the subject for potential discontinuation for safety reason.

Other Assessments:

Tolerability and safety will be assessed for all treatments by monitoring adverse events.

Assessment of Suicidal Ideation and Behavior (SIB) - Columbia Suicide Severity Rating Scale

The assessment of suicidal ideation and behavior will be performed during the Screening visit, on Day 0 and after the last study treatment administration on Day 14 for all treatments using the Columbia Suicide Severity Rating Scale (C-SSRS).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy female subjects and/or male subjects who at the time of screening are between the ages of 18 and 55 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests.

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

2. Body Mass Index (BMI) of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lbs).

3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

4. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy).

3. A positive urine drug screen.

4. History of regular alcohol consumption exceeding 14 drinks/week for females or 21 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.

5. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study medication (whichever is longer).

6. Screening supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

7. Screening supine 12-lead ECG demonstrating QTcF >450 or a QRS interval >120 msec. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTcF values should be used to determine the subject's eligibility.

8. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

- Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transminase (SGOT) **or** alanine aminotransferase (ALT)/serum glutamic pyruvic transminase (SGPT) ≥1.5 x upper limit of normal (ULN);

- Total bilirubin ≥1.5 x ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤1 x ULN.

9. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use at least 1 highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product or longer based upon the compound's half-life characteristics.

10. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication;

    Herbal supplements and hormone replacement therapy must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Contraceptive methods are allowed as described in Section 4.4.4.

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

12. History of sensitivity to heparin or heparin-induced thrombocytopenia.

13. History of known QTc prolongation or ECG abnormalities.

14. Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the C-SSRS. In addition, subjects deemed by the investigator to be at significant risk of suicidal or violent behavior should be excluded.

15. Individuals with known hypersensitivity reactions to sertraline or SSRI (selective serotonin reuptake inhibitors).

16. Individuals with a known hypersensitivity to moxifloxacin or quinolones.

17. Subjects, who according to the product label for moxifloxacin, would be at increased risk if dosed with moxifloxacin (ie, including but not limited to subjects with history of myasthenia gravis, tendinitis/tendon rupture).

18. Unwilling or unable to comply with the Lifestyle Guidelines described in this protocol.

19. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

20. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

21. Self-reported history of risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesemia, congenital long QT syndrome, myocardial ischemia or infarction, congenital deafness, and family history of sudden death, or a family history of congenital QT syndrome.)

22. Self-reported history of sick sinus syndrome, first, second, or third degree atrioventricular (AV) block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval or conduction abnormalities, or any other clinically significant cardiovascular disease history.

23. Use of tobacco- or nicotine-containing products in excess of the equivalent of 5 cigarettes per day.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

4.4. Lifestyle Guidelines

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

- Days 1 and 14 (days when PK and ECG evaluations are planned) – morning dosing will occur on these days following an overnight fast of at least 10 hours before the morning dose administrations (PK and ECG assessments), and subjects will be required to continue fasting for 4 hours post-morning dose. Water is permitted until 1 hour prior to study medication administration. Water may be consumed without restriction beginning 1 hour after dosing.

- Subjects will have to be fasted on Day 15 when obtaining trough ECG and PK measurement for all treatments.

- Other days – Breakfast may be completed by 30 minutes prior to drug administration on other study days (Days 2 to 13) of Treatments A, B and C.

- The time of meals will be standardized between study days and study periods.

- Subjects will be restricted to consuming ambient temperature beverages in each study period until the 24-hour ECG has been collected.

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 8 hours prior to the start of pharmacokinetic sample collections.

- Subjects must abstain from drinks, including water, for 0.5 hours prior to any ECG measurement. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after morning dosing for each period.

- Dinner will be provided approximately 9 to 10 hours after morning dosing.

- An evening snack may be permitted.

- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study medication until collection of the final pharmacokinetic blood sample.

- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.4.2. Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until the final PK sample of each study period has been collected. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the Investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing until the final PK sample of each study period has been collected.

- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the research unit.

4.4.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.4.4. Contraception

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use at least 1 highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product.

If at least one form of highly effective contraception from the list is used, then contraception used by the partner is enough provided that the male subject knows it must be used consistently and correctly, tells the investigator it is being used consistently and correctly and the investigator documents the conversation. If the subject is unable to confirm that his partner is reliably and correctly taking her contraception, then the subject will need to use another form of highly effective contraception (and the use of a condom alone without spermicide would not be regarded as a highly effective form of contraception).

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected the most appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, transdermal, injected, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential as described below.

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.6. Rater Qualifications (If applicable)

Only qualified raters are allowed to evaluate and/or rate subjects in this study. C-SSRS raters will be qualified following completion of training on the use/administration of the C-SSRS.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

The investigator will assign subject numbers to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

5.2. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or subinvestigator should consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF)/data collection tool (DCT).

5.3. Subject Compliance

Study treatment will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to assure the study medication was taken.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

Sertraline hydrochloride 50 mg tablets and matching placebo will be supplied to the Pfizer Clinical Research Unit (PCRU) pharmacy in bulk by Pfizer.

Moxifloxacin (Avelox®) 400 mg film-coated tablets will be supplied locally by the PCRU.

The SRSD for Moxifloxacin (Avelox®) is the Summary of Product Characteristics (Avelox®, Bayer).[7]

Investigational product will be presented to the subjects in individual dosing containers.

5.4.2. Preparation and Dispensing

Sertraline hydrochloride and matching placebo tablets will be packaged at the PCRU in the individual dosing containers by 2 operators one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist).

Moxifloxacin 400 mg (Avelox®) tablets will be packaged at the Clinical Research Unit in the individual dosing containers by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist).

5.4.3. Administration

Following an overnight fast of least 10 hours (PK days 1, 14 and 15 only), subjects will receive study medication at approximately 08:00 hours (plus or minus 2 hours). Administration of study medication on the other days will occur under the conditions described in Section 4.4.1. Investigator site personnel will administer study medication during each period with ambient temperature water to an approximately volume of 240 mL. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing.

In order to standardize the conditions on pharmacokinetic sampling days, all subjects will be required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

Table 3. Total Number of Tablets or Matching Placebo Dispensed for Treatment A or C

Visit Day	# Sertraline 50 mg or matching placebo tablets dispensed	
	Morning (AM)	Evening (PM)
D1	1	0
D2	1	1
D3	1	2
D4-5	2	2
D6	2	4
D7-13	4	4
D14	4	0

Table 4. Total Number of Tablets Dispensed for Treatment B

Visit Day	# Placebo for sertraline 50 mg tablets dispensed		# Moxifloxacin 400 mg tablets dispensed
	Morning (AM)	Evening (PM)	
D1	1	0	0
D2	1	1	0
D3	1	2	0
D4-5	2	2	0
D6	2	4	0
D7-13	4	4	0
D14	0	0	1

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator agents and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label.

Storage conditions stated in the SRSD (eg, United States package insert [USPI]) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Subjects will abstain from all concomitant treatments, except for the treatment of adverse events. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Hormonal contraception treatments are allowed.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 28 days prior to administration of the study medication to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between Screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require re-screening if the Day 0 laboratory results meet the eligibility criteria.

The following procedures will be completed:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Collect demography.

- Obtain medical history, including history of illegal drug, alcohol and tobacco use (Period 1 only).
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Obtain supine blood pressure (BP) and pulse rate (PR) and oral temperature.
- Conduct a full physical examination including height and weight. The Screening physical examination may be performed on Day 0, Period 1.
- Collect a single 12-lead electrocardiogram (ECG).
- Administer the Baseline/Lifetime Columbia Suicide Severity Rating Scale (C-SSRS) (may be performed on Day 0 of Period 1).
- Following at least a 4-hour fast, collect blood and urine specimens for the following:
  - Safety laboratory tests;
  - Urine drug screening;
  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months;
  - Serum β-hCG for all females of childbearing potential;
  - Confirm proper contraception is being used.

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital signs and as close as possible to scheduled time, but prior to blood specimen collection;
- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection;
- Pharmacokinetic blood specimens: obtain at scheduled time;

- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.2.1. Day 0 (Periods 1, 2 & 3)

Subjects will be admitted to the Clinical Research Unit on the day prior to Day 1 dosing. The following procedures will be completed following admission to the CRU:

- Review Inclusion and Exclusion criteria (Period 1 only).

  Obtain blood and urine samples for safety laboratory tests. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.

- Collect urine for drug screening.

- Collect serum pregnancy test for females of childbearing potential.

- Confirm proper contraception is being used.

- Assess baseline symptoms/adverse events.

- Review changes in the subject's medical history including medication history (Period 1 only) since Screening.

- Conduct full physical examination, if deferred from the Screening visit (Period 1 only). Otherwise, conduct a brief physical exam if there is an open AE or clinically significant or relevant abnormal physical finding from the last exam or at the discretion of the investigator.

- Administer the Baseline/Lifetime Columbia-Suicide Severity Rating Scale (C-SSRS) if not performed at Screening (Period 1 only). If Baseline/Lifetime C-SSRS was collected at Screening, administer the Since Last Visit Assessment.

- Assess Concomitant Treatments.

Subjects will begin fasting of at least 10 hours prior to the morning dosing on Day 1.

6.2.2. Day 1 (Periods 1, 2 & 3)

Prior to morning dosing, the following procedures will be completed:

- Assess baseline symptoms/adverse events.

- Obtain supine blood pressure (BP) and pulse rate (PR) and oral temperature.

- Collect triplicate 12-lead ECG measurements at -1, -0.5 and 0 hours immediately prior to the morning dose on Day 1.

- Collect a blood sample for pharmacokinetic analysis immediately prior to the morning dose on Day 1.

- After all pre-dose procedures have been completed, administer the study medication (see STUDY TREATMENTS and Administration Sections).

After morning dosing, the following procedures will be completed:

- Collect blood samples for pharmacokinetic analysis at 1, 2, 3, 4, 5, 6, 8 and 12 hours following dosing on Day 1.

- Collect triplicate 12-lead ECG measurements at 1, 2, 3, 4, 5, 6, 8 and 12 hours following dosing on Day 1.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assess Concomitant Treatments.

6.2.3. Day 2 (Periods 1, 2 & 3)

The following procedures will be completed:

- Obtain supine blood pressure (BP) and pulse rate (PR) and oral temperature at 24 hours after first dosing on Day 2.

- Collect blood samples for pharmacokinetic analysis at 24 hours after first dosing on Day 2.

- Collect triplicate 12-lead ECG measurements at 24 hours following first dosing on Day 2.

- Administer the study medication (see STUDY TREATMENTS and Administration Sections).

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assess Concomitant Treatments.

6.2.4. Days 3 through 13 (Periods 1, 2 & 3)

- Administer the study medication (see STUDY TREATMENTS and Administration Sections).

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- On Day 7, collect blood and urine samples for safety analysis.
- On Day 13, subjects will begin fasting of at least 10 hours prior to the morning dosing on Day 14.
- Assess Concomitant Treatments.

6.2.5. Day 14 (Periods 1, 2 & 3)

Prior to dosing, the following procedures will be completed:

- Collect triplicate 12-lead ECG measurements.
- Collect a blood sample for pharmacokinetic analysis immediately prior to dosing.
- Collect blood and urine samples for safety analysis.
- After all pre-dose procedures have been completed, administer the study medication (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- Collect blood samples for pharmacokinetic analysis at 1, 2, 3, 4, 5, 6, 8 and 12 hours following dosing on Day 14.
- Collect triplicate 12-lead ECG measurements at 1, 2, 3, 4, 5, 6, 8 and 12 hours following dosing on Day 14.
- Administer the "since last visit" Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- On Day 14, subjects will begin fasting of at least 10 hours prior to the morning dosing on Day 15.
- Assess Concomitant Treatments.

6.2.6. Days 15 through 16 (Periods 1, 2 & 3)

- Collect blood samples for pharmacokinetic analysis at 24, and 48 hours following dosing on Day 14.
- Collect triplicate 12-lead ECG measurements at 24, and 48 hours following dosing on Day 14.
- Obtain supine blood pressure (BP) and pulse rate (PR).

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assess Concomitant Treatments.

6.2.7. Day 17 (End of Treatment)

The following procedures will be completed prior to discharge on Day 17:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assess supine blood pressure, pulse rate and oral temperature at Period 3 and at Period 1 and 2 at PI's discretion.

- Obtain triplicate 12-lead ECG measurement at Period 3 and at Period 1 and 2 at PI's discretion.

- Collect blood and urine samples for safety laboratory tests at Period 3 and at Period 1 and 2 at PI's discretion.

- Collect a blood sample for PK analysis.

- Collect serum pregnancy test for females of childbearing potential.

- Conduct a limited physical examination if there is a new or open AE or clinically significant abnormal physical finding from the last visit at Period 3 and at Period 1 and 2 at PI's discretion.

- Reinforce contraception requirements.

- Assess Concomitant Treatments.

- Discharge from unit. Subjects may be discharged after collection of the 72 hour (following Day 14 dosing) PK sample and ECG reading on Day 17.

- There will be an interval of at least 14 days between 2 periods (ie, administration of subsequent doses of study medication will not occur until at least 14 days after the previous dose of study medication).

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every

effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Subject Withdrawal (Early Termination)

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. The early termination visit only applies to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Obtain information regarding the occurrence of adverse events.
- Assess supine blood pressure, pulse rate and oral temperature.
- Obtain triplicate 12-lead ECG measurement.
- Collect a blood sample for PK analysis.
- Collect blood and urine samples for safety laboratory tests.
- Collect serum pregnancy test for females of childbearing potential.
- Conduct a limited physical examination if there is a new or open AE or clinically significant abnormal physical finding from the last visit.
- Confirm proper contraception is being used.
- Administer the Since Last Visit Columbia Suicide Severity Rating Scale (C-SSRS).

- Assess Concomitant Treatments.
- Discharge from unit

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	FSH[b] Urine drug screening[c] β-hCG[d]
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b At Screening only, in females who are amenorrheic for at least 12 consecutive months.
c At Screening and Day 0 only.
d Serum β-hCG for females of childbearing potential.

- Minimum requirement for drug screening includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.

- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication.

7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at Screening, and Day 0 of all study periods and at discharge from each period. Results will be obtained prior to dosing during each period.

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.4. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in STUDY PROCEDURES section of this protocol. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after at least 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Blood pressure should not be taken from the arm with an intravenous infusion. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.5. Temperature

Temperature will be measured orally. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.6. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the STUDY PROCEDURES section of this protocol. Detailed ECG collection time points are provided in PK and ECG assessment Flow Chart.

Subjects must abstain from drinks, including water, for approximately 0.5 hours prior to any ECG measurement.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 minutes apart; the pre-dose assessments (-1, -0.5 and 0 hours) should occur immediately prior to the morning dose on Day 1; the average of the three triplicate ECG measurements collected pre-dose on Day 1 (ie, -1 hour, -0.5 hour, and 0 hour time points) of each period will serve as each subject's baseline QTc value. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure, pulse rate, and temperature. The actual times may change but the number of ECGs collected will remain the same.

During the treatment with active drug or placebo, if any subject demonstrates a change in QTc value from baseline of greater than 45 msec or QT values of greater than 500 msec the principal investigator should assess the subject for potential discontinuation from the study.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the average of QTc values from the triplicate measurements remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

The ECG source data for analyses on TQT studies conducted in healthy subjects will be the automated readings validated by trained human readers (semi-automated method).

7.2. Pharmacokinetics

Details regarding the collection, processing, and storage of the blood samples will be provided in the lab manual.

During all study periods, blood samples (4 mL) to provide approximately 1.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing sodium heparin at times specified in the STUDY PROCEDURES section of the protocol.

The actual times may change but the number of samples will remain the same. All study treatments will have identical sample collection timepoints. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

- Samples from Treatment A will be analyzed using a validated analytical method for sertraline and its metabolite in compliance with Pfizer standard operating procedures. Samples for Treatment C (placebo) will only be analyzed if deemed necessary. Samples from Treatment B (moxifloxacin) on Day 14 (1, 2, 3, 4 and 5 h only) will be analyzed if deemed necessary.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

- As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.2.1. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.3. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 394 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood

volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 6. Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs	10	1	12		130
PK*	4		66		264
TOTAL					394

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

* the additional blood sample (4 mL) for PK analysis to be collected from a withdrawal/early termination subject is not counted in the Number of Sampling Times.

7.4. Suicidality Assessment

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

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for Screening/Baseline and follow-up visits.

The C-SSRS should be collected at times specified in Section 6 of this protocol by an appropriately trained staff member. The C-SSRS can also be administered at any time in the study at the discretion of the investigator based on any reasonable concern.

At each suicidality assessment, subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/mental health professional (MHP) skilled in the evaluation of suicidal ideation and behavior in the subjects by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist) who will determine if it is safe for the subject to participate/continue in the trial. Specific criteria that indicate a need for such an assessment are:

Suicide ideation associated with actual intent and/or plan in the past year; "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent").

Previous history of suicide behaviors in the past 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years).

In the investigators judgment a risk assessment or exclusion is warranted.

Other possible suicidal ideation and behavior adverse events or other clinical observations may, based on the judgment of the investigator, also trigger a risk assessment and require a narrative.

Suicidality adverse events or other clinical observations may, based on the judgment of the investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS, and available information, prior to screening and baseline information, and the clinician/MHP assessment. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an adverse event has occurred.

At the Baseline (Screening or may be performed Day 0, Period 1) visit, a risk assessment will be done by qualified staff to determine whether it is safe for the subject to be enrolled or to continue to participate in the trial.

Any subject that responds yes to items 4 and 5 on the suicidal ideation subscale of the C-CSSRS or yes to any behavioral question – at the screening visit or baseline or post-baseline visit should simply be excluded from the study.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the Sponsor as a SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

- AEs (serious and nonserious) should be recorded on the case report form (CRF/DCT) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver Function Tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

Concurrent with:

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN or if the value reaches ≥3 X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRF/DCTs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF/DCT, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or

contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF/DCT, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnancy Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (See also Section on Subject Withdrawal (Early Termination))

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF/DCT page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAE, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF/DCT. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF/DCT. It should be noted that the form for collection of SAE information is not the same as the AE CRF/DCT. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRF/DCT as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document (SAP) may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

During treatment periods for active drug and placebo, subjects who experience vomiting on Day 14 within 2 hours of dose administration will continue to be studied and data reported, but, PK and ECG data for that day will be excluded from statistical analyses.

9.1. Sample Size Determination

A sample size of 42 subjects (7 per sequence) will provide at least 99% power to exclude that upper bound of a two-sided 90% confidence interval (CI) (one-sided 95% CI) of time-matched difference between sertraline and placebo is more than 10 msec at each time point. The overall study power for 9 post-dose time points on Day 14 will be at least 90%. These calculations are based upon the assumptions that expected mean difference between sertraline and placebo is no greater than 5 msec at each time point and intra-subject variability is 5.36 msec.

Given a one-sided significance of 0.05, 42 subjects will provide 99% power to detect at least 5 msec difference between moxifloxacin and placebo at 3 hours post-dose (historical moxifloxacin median T_{max}) to demonstrate assay sensitivity.

To allow for dropouts, 54 subjects (9 per sequence) will be randomized to have 42 evaluable subjects.

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

9.3.1. PK Analysis Populations

The pharmacokinetic (PK) concentration population is defined as all subjects enrolled and treated who have at least 1 concentration determined.

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the pharmacokinetic parameters of primary interest determined.

9.3.2. Determination of Pharmacokinetic Parameters

The following sertraline and metabolite PK parameters will be derived from the concentration-time profiles by noncompartmental methods as follows:

Parameter	Definition	Method of Determination
Single Dose:		
C_{max}	Maximum observed plasma concentration	Observed directly from data
C_{max} (dn)	Dose normalized C_{max}	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{24}	Area under the plasma concentration-time profile from time zero to the 24 hour time post dose	Linear/Log trapezoidal method
AUC_{24} (dn)	Dose normalized AUC_{24}	AUC_{24}/Dose
MR	Metabolite Ratio	(AUC_{24} metabolite/AUC_{24} parent) * (MW parent/MW metabolite)
Multiple Dose:		
C_{max}	Maximum plasma concentration	Observed directly from data
C_{max} (dn)	Dose normalized C_{max}	C_{max}/Dose
T_{max}	Time for Cmax	Observed directly from data as time of first occurrence
AUC_{24}	Area under the plasma concentration-time profile from time zero to the 24 hour time post dose	Linear/Log trapezoidal method
AUC_{24} (dn)	Dose normalized AUC_{24}	AUC_{24}/Dose
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
t½[a]	Terminal elimination half-life	Loge(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
C_{min}	Minimum plasma concentration over the dosing interval	Observed directly from data
R_{ac}(obs)	Observed accumulation ratio	[Day 14 AUC_{24}(dn)]/[Day 1 AUC_{24}(dn)]
R_{ac},C_{max}	Observed accumulation ratio for C_{max}	Day 14 C_{max} (dn)/Day 1 C_{max} (dn)
MR	Metabolite Ratio	(AUC_{24} metabolite/AUC_{24} parent) * (MW parent/MW metabolite)

[a] if data permit

dn = dose normalized to a 1 mg dose

MW = molecular weight

Actual PK sampling times will be used in the derivation of PK parameters.

9.3.3. Pharmacokinetic Analysis

Sertraline and metabolite pharmacokinetic parameters will be calculated using noncompartmental methods and subsequently summarized descriptively by treatment and Day.

Day	Parameter	Summary statistics
SD	C_{max} , C_{max} (dn),$AUC_{24,}$ AUC_{24}(dn), MR	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
	T_{max}	N, median, minimum, maximum
MD	C_{max}, C_{max} (dn),AUC_{24}, AUC_{24}(dn), $AUC_{last,}$ Rac [R_{ac} (obs) and R_{ac} (C_{max})] MR and C_{min}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
	T_{max}	N, median, minimum, maximum
	$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean

Supporting data from the estimation of $t_{½}$ will be listed by treatment: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); and the first, last, and number of time points used in the estimation of $k_{el.}$

9.4. Safety Analysis

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

Adverse events, ECGs, blood pressure, vital signs, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern as defined Appendix 2 will be described. Suicidality will be assessed using Columbia - Suicide Severity Rating Scale (C-SSRS). Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurologic examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

9.4.1. Assessment of Suicidal Ideation and Behavior (SIB) - Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior. Versions are available for Screening/Baseline (Lifetime assessment) and follow-up visits (Since Last Visit assessment).

The C-SSRS should be administered at times specified in the Schedule of Activities of the protocol by an appropriately trained staff member. The C-SSRS can also be administered at any time in the study at the discretion of the investigator based on any reasonable concern.

At each suicidality assessment as per Schedule of Activity (SOA), subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/mental health professional (MHP) skilled in the evaluation of suicidal ideation and behavior in the subjects by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist) who will determine if it is safe for the subject to participate/continue in the trial. Specific criteria that indicate a need for such an assessment are:

- Suicide ideation associated with actual intent and/or plan in the past year; "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent").
- Previous history of suicide behaviors in the past 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years).
- In the investigators judgment a risk assessment or exclusion is warranted.

Other possible suicidal ideation and behavior adverse events or other clinical observations may, based on the judgment of the investigator, also trigger a risk assessment and require a narrative.

Suicidality adverse events or other clinical observations may, based on the judgment of the investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS, and available information, prior to Screening and baseline information, and the clinician/MHP assessment. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an adverse event has occurred.

At the Baseline visit, a risk assessment will be done by qualified staff to determine whether it is safe for the subject to be enrolled or to continue to participate in the trial.

Any subject that responds yes to items 4 and 5 on the suicidal ideation subscale of the C-SSRS or yes to any behavioral question – at the screening visit or baseline or post-baseline visit should simply be excluded from the study.

Assessment of Suicidal Ideation and Behavior (SIB) based on Columbia Suicide Severity Rating Scale will be reported.

9.4.2. Electrocardiogram (ECG) (Pharmacodynamic) Analysis

If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical and statistical analyses unless the average from the triplicate measurements is also ≥500 msec. Changes from baseline will be

defined as the change between the average triplicate QTc post dose values and the mean of the three averages of the pre-dose ECGs (ie, the 3 pre-dose measurements, at -1 hour, -0.5 hour, 0 hour) on Day 1 of each period.

9.4.2.1. ECG Analysis Population

Primary ECG Analysis Population: The primary ECG analysis population is defined as all subjects randomized and treated who have at least 1 post-dose ECG measurement in at least 1 period. Analysis sets may contain different numbers of subjects for different ECG parameters based on availability of data.

Completer ECG Analysis Population: The completer ECG analysis population is defined as all subjects randomized and treated and have completed all three treatment periods, at least up to Day 15 (24 hour Day 14) ECG measurements.

9.4.2.2. ECG Derivation of ECG Parameters Prior to Analysis

The average of the triplicate ECGs collected at each time will be calculated. Baseline will be defined as the mean of the three average triplicate measurements taken at the following three time points (-1 hour, -0.5 hour, 0 hour) before dosing within each period. The QT intervals, QTcF, QTcB, PR intervals, RR, QRS intervals and heart rate will be recorded at each assessment time indicated by the Schedule of Activities. If QTcF is not supplied then it will be derived using Fridericia's heart rate correction formula:

- $QTcF(msec) = QT(msec)/(RR)^{1/3}$ where RR(sec) = 60/HR (if not provided)

If not supplied, QTcB intervals will be derived using Bazett's heart rate correction formula:

- $QTcB(msec) = QT(msec)/(RR)^{1/2}$ where RR(sec) = 60/HR (if not provided)

Changes from baseline for QTcF, QTcB, uncorrected QT, PR, QRS, and heart rate will be calculated for each subject and treatment at each time point.

The maximum absolute post-dose value and the maximum increase from baseline for QTcF, QTcB, uncorrected QT, PR, QRS, and heart rate will be determined for each subject and treatment.

Additionally, QTcI and QTcN may also be computed using individual and population correction methods. Change from baseline, maximum absolute post-dose value and the maximum increase from baseline for QTcI and QTcN may also be computed.

9.4.2.3. Statistical Analyses

Averages of triplicate ECG measurements will be used in all statistical analyses. For primary and sensitivity analysis, ECG measurements on Day 14 up to 24 hours will be used considering that 24 hour post-dose ECG will be sufficient to capture QT prolongation induced by active drug. However, for exposure response analysis all ECG data collected on Day 14, along with Day 1 data will be used.

If subjects vomited on Day 14 within 2 hours of dosing, data from these subjects on those days will be excluded from PK and ECG statistical analyses.

Primary Analysis:

Primary analysis will be conducted in the Primary ECG Analysis Population.

The post-dose QTcF intervals will be analyzed (Day 14 data for sertraline, placebo, and moxifloxacin) with baseline as a covariate. Analysis of covariance using a mixed effect model with sequence, period, treatment, time, treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate will be conducted.

If there is a significant period effect, a mixed effect model with sequence, period, treatment, period-by-treatment interaction, carry-over, time, treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate will be conducted.

The 90% confidence intervals (equivalent to a one-sided 95% confidence interval) for time-matched change from placebo in QTcF at each time point on Day 14 will be computed for Sertraline. Similarly, the 90% confidence interval for time-matched change from placebo in QTcF at 3 hours post-dose on Day 14 will be computed for moxifloxacin.

- **Lack of Effect of Sertraline on QTc Intervals Assessment:**

A lack of an effect of sertraline on QTc intervals will be concluded if the upper bounds of the two-sided 90% (equivalent to one-sided 95%) confidence intervals for all the time-matched mean differences between sertraline and placebo are less than 10 msec.

- **Assay Sensitivity Assessment:**

This study will be deemed adequately sensitive to detect QT/QTc prolongation if the lower bound of the two-sided 90% confidence interval for the mean difference between moxifloxacin and placebo is greater than 5 msec at the historic T_{max} of moxifloxacin (3 hours post-dose).

Sensitivity Analysis:

At the completion of the trial, if more than 10% of subjects dropped out or have missing data for one or more treatment periods, primary analysis outlined above will be conducted in the Completer ECG Analysis Population also.

Additional Analyses:

Additional analysis will be conducted in the Primary ECG Analysis Population.

Relationship between QTc prolongation and sertraline/metabolite plasma concentration will be examined graphically. Exposure response analysis will be performed to establish relationship between change in QTc from baseline and drug concentration.

Categorical analysis of QTcF of both absolute post-dose maximum and maximum increase from baseline will be provided.

QT, QTcF, PR, HR, and QRS will be summarized by treatment group, study day, and time point – both observed and change from baseline.

Analyses conducted on QTcF may be repeated on QTcB, QTcI and QTcN if deemed necessary.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer study sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs/DCTs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer study sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF/DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF/DCT is required and should be completed for each included subject. The completed original CRF/DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRF/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRF/DCTs is true. Any corrections to entries made in the CRF/DCTs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

In some cases, the CRF/DCT may also serve as the source document. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF/DCT, and for which the CRF/DCT will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRF/DCT and hospital records), all original signed informed consent documents, copies of all CRF/DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking each subject's numerical code to the his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application

in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of sertraline at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRF/DCTs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US basic results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted

for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by a principal investigator of the results of the study based on information collected or generated by a principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multi-center study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for [redacted][2] established by the [redacted]

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

[redacted]

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. [redacted]

Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
Abs	absolute
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BU	business unit
BUN	blood urea nitrogen
C_{av}	average concentration
CDS	core data sheet
C_{eff}	efficacious concentration
CI	confidence interval
CL/F	apparent oral clearance
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRU	Clinical Research Unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
CTC	Common Terminology Criteria
DAI	dosage and administration instructions
DCT	data collection tool
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSM-I	Diagnostic and Statistical Manual of Mental Disorders-I
EC	ethics committee

ECG	electrocardiogram
EDCMS	electronic data capture and management system
EDMC	external data monitoring committee
EDR	Extemporaneous Dispensing Record
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EIU	exposure in utero
ERB	external review board
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GABA	gamma-amino butyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
hCG	human chorionic gonadotropin
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IND	investigational new drug application
INR	international normalized ratio
OBU	Oncology Business Unit
IOBU-SDMC	Internal Oncology Business Unit -Safety Data Monitoring Committee
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IUS	Intrauterine system
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
N/A	not applicable
NOAEL	no observed adverse effect level

NOEL	no observed effect level
OEB5	occupational exposure banding 5
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamics
PG	pharmacogenomics
PI	principal investigator
PK	pharmacokinetics
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transminase
SGPT	serum glutamic pyruvic transminase
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
$T_{1/2}$	terminal half-life
T_{max}	time to reach maximum concentration
TQT	Thorough QT
THC	tetrahydrocannabinol
ULN	upper limit of normal
US	United States
USPI	United States package insert
V_z/F	apparent oral volume of distribution
WBC	white blood cell

Appendix 2. Criteria for Safety Values of Potential Clinical Concern

Hematology	
Hemoglobin	<0.8 times the lower limit of the reference range
Hematocrit	<0.8 times the lower limit of the reference range
RBC Count	<0.8 times the lower limit of the reference range
MCV	<0.9 or >1.1 times the limits of the reference range
MCH	<0.9 or >1.1 times the limits of the reference range
MCHC	<0.9 or >1.1 times the limits of the reference range
Platelets	<0.5 or >1.75 times the limits of the reference range
MPC	<0.9 or >1.1 times the limits of the reference range
Leukocytes	<0.6 or >1.5 times the limits of the reference range
Total Neutrophils (Abs)	<0.8 or >1.2 times the limits of the reference range
Eosinophils (Abs)	>1.2 times the upper limit of the reference range
Basophils (Abs)	>1.2 times the upper limit of the reference range
Lymphocytes (Abs)	<0.8 or >1.2 times the limits of the reference range
Monocytes (Abs)	>1.2 times the upper limit of the reference range
Chemistry	
Total bilirubin	>1.5 times the upper limit of the reference range
Direct bilirubin	>1.5 times the upper limit of the reference range
Indirect bilirubin	>1.5 times the upper limit of the reference range
AST	>3 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
Alk Phosphatase	>3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
BUN	>1.3 times upper limit of the reference range
Glucose, fasting	<0.6 or >1.5 times the limits of the reference range
Uric acid	>1.2 times upper limit of the reference range
Sodium	<0.95 or >1.05 times the limits of the reference range
Potassium	<0.9 or >1.1 times the limits of the reference range
Chloride	<0.9 or >1.1 times the limits of the reference range
Bicarbonate	<0.9 or >1.1 times the limits of the reference range
Calcium	<0.9 or >1.1 times the limits of the reference range
Albumin	<0.8 or >1.2 times the limits of the reference range
Total protein	<0.8 or >1.2 times the limits of the reference range
Creatine Kinase	>2.0 times upper limit of the reference range
Urinalysis	
Urine WBC	≥20/HPF
Urine RBC	≥20/HPF
Urobilinogen	≥1
Urine Bilirubin	≥1
Vital Signs	
Pulse Rate	Supine/Sitting: <40 or >120 bpm Standing: <40 or >140 bpm
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture Systolic <90 mm Hg Diastolic ≥20 mm Hg change from baseline in same posture Diastolic <50 mm Hg
Electrocardiogram	
PR interval	≥300 msec; ≥25% increase when baseline >200 msec Increase ≥50% when baseline ≤200 msec
QRS interval	≥140 msec; ≥50% increase from baseline
QTc interval	≥500 msec