RESEARCH PROTOCOL

Bioequivalence and Clinical Effects of Generic and Brand Bupropion

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Version 1.02: November 19, 2015 (Includes Amendment 2)

1. SYNOPSIS

Study Title	Bioequivalence and clinical effects of generic and brand bupropion
Objective	Determine 1) steady-state bioequivalence between branded and three generic 300mg XL bupropion products in patients with major depressive disorder, 2) patients' perception of differences in release patterns, clinical effectiveness, and adverse events between drug products, 3) patients' clinical response using validated objective measures of depression
Study Period	Planned enrollment duration: Approximately 2 1/2 years Planned study duration: Approximately 28 weeks per subject
Number of Patients	60 evaluable patients diagnosed with major depressive disorder (up to 75 enrolled)
Study Medication Administration	Subjects will be studied for 28 weeks: a 4 week lead-in phase during which participants remain on their existing bupropion product, and then four randomized cross-over phases of 6 weeks on each of the four bupropion study drugs (brand Wellbutrin 300mg XL and 3 generics)
Study Design	Prospective, randomized, double-blinded, single-center crossover study in patients with major depressive disorder currently taking bupropion 300 XL
Inclusion and Exclusion Criteria	Inclusion Criteria 1. Adult outpatients age 18-75 years 2. Currently on once daily bupropion HCl 300mg XL (brand or any generic) for a minimum of 4 months 3. Diagnosis of major depressive disorder in partial or full remission for ≥4 months, confirmed by Structured Clinical Interview for DSM Axis I Disorders (SCID) 4. Ability to understand and willingness to comply with study procedures, and to provide written informed consent Exclusion Criteria 1. Remission from depression not clearly attributed to bupropion treatment 2. Current severe side effects attributable to bupropion 3. Poor adherence to bupropion treatment per patient self-report and history of refill persistence 4. History of active seizure disorder, or seizure treatment within past year 5. History of significant hepatic or renal disease, based on physician assessment 6. Currently taking drugs or natural products known to influence cytochrome P450B6 (CYP2B6) activity 7. Currently taking drugs for hepatitis C or multiple sclerosis, due to their ability to cause depression 8. Dementia or other significant cognitive impairment, per diagnosis or investigative team's assessment 9. Lifetime diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, delusional disorder, or current psychotic symptoms diagnosed by SCID 10. Abuse of or dependence on alcohol or other substances within the past 6 months as determined by SCID, and confirmed by study physician interview 11. Current suicidal ideation
Measurements	Plasma and urine samples obtained over 24 hr during each study drug treatment (4 times). Bupropion and metabolite (hydroxybupropion, erthrohydrobupropion, threohydrobupropion) concentrations determined by stereoselective LC-MS-MS. Depression outcomes measured using the Montgomery-Asberg Depression Rating Scale (MADRS). Drug side-effects assessed with the self-report Antidepressant Side-Effect Checklist. Subjects' daily reports of side effects and symptoms using smart phone-based Ecological Momentary Assessments (EMA).
Statistical Methodology	Primary: Plasma and urine Cmax and AUC ratios for racemic bupropion, hydroxybupropion, erthrohydrobupropion, threohydrobupropion. Additional pharmacokinetic/bioequivalence endpoints:

	1. Plasma C_{max} and AUC_{0-24} for R- and S- bupropion 2. Plasma C_{min}, C_{av}, C_{trough}, CL/F, %PTF, and swing for RS-, R- and S-bupropion 3. Plasma AUC_{0-t} for RS-, R- and S-bupropion 4. Plasma C_{max}, AUC_{0-24}, C_{min}, C_{av}, C_{trough} %PTF, CL_f and swing for hydroxybupropion, erythrohydrobupropion, and threohydrobupropion; racemate and their individual isomers (enantiomers/diastereomers) 5. Plasma AUC_{0-24} hydroxybupropion/bupropion for racemate and individual enantiomers 6. Formation clearance of hydroxybupropion, erythrohydrobupropion, threohydrobupropion and glucuronides; racemate and individual isomers Secondary Endpoints: 1. Relapse of MDD 2. Change in symptoms of depression 3. Change in side effects of medication

Bioequivalence and Clinical Effects of Generic and Brand Bupropion

Amendment 2

November 19, 2015

Purpose

Administrative clarification

Changes

A. Additions:

2.7.1 Primary Assessments

From: Additional pharmacokinetic/bioequivalence endpoints: 6. Formation clearance of hydroxybupropion, erythrohydrobupropion, and threohydrobupropion, racemate and individual isomers

To: Additional pharmacokinetic/bioequivalence endpoints: 6. Formation clearance of hydroxybupropion, erythrohydrobupropion, threohydrobupropion, erythrohydrobupropion glucuronide, threohydrobupropion glucuronide: racemate and individual isomers

Rationale: Additional urine metabolites discovered during assay development (Change also made to Synopsis)

B. Deletions: None

C. Changes:

2.7.3.3 Objective evaluation of antidepressant effectiveness

From: The main clinical outcome is relapse of depression, defined using the MADRS and SCID depression module. Patients with a 2 point or greater increase from their average baseline open-label lead-in phase MADRS score, on two consecutive evaluations, will have the SCID depression module conducted. If the SCID reveals current MDD, they will be considered to have relapsed. Physician adjudication (by study Psychiatrist, who is blinded to randomization assignment) will be utilized as well.[2]

To: The main clinical outcome is relapse of depression, defined using the MADRS and SCID depression module. Patients with a 2 point or greater increase from their average baseline open-label lead-in phase MADRS score, ~~on two consecutive evaluations~~, and/or MADRS score of 15 or greater will have the SCID depression module conducted. If the SCID reveals current MDD, they will be considered to have relapsed. Physician adjudication (by study Psychiatrist, who is blinded to randomization assignment, who interviews participant at time of relapse) will be utilized as well.[2]

Rationale: This was a previously undetected word processing error. It would be infeasible to require two consecutive elevated MADRS scores because this measure is done only twice during each randomized phase, and, a subject may be withdrawn for relapse of depression after a single episode of elevated MADRS score and SCID. Also to also further clarify the exact relapse assessment process.

Bioequivalence and Clinical Effects of Generic and Brand Bupropion

Amendment 1

January 5, 2015

Purpose

Administrative clarification, per FDA.

Changes

A. Additions: None

B. Deletions: None

C. Changes

2.6.7 Study Drug and Doses

From: …application will be made to the RIHSC for approval to use after the expiration date

To: application will be made to FDA for approval to use after the expiration date

2. STUDY PROTOCOL

2.1 Background and Significance

Major depressive disorder (MDD) is one of the most common mental disorders and is currently the leading cause of disability in the world. One of the most important actions of antidepressant drugs is relapse prevention; that is, for patients with MDD who are stabilized (i.e., remitted or partially remitted) with an antidepressant, are far less likely to suffer a relapse or recurrence of depression if they are maintained on this medication. Relapse of depression is an adverse outcome with significant deleterious consequences, including not only the suffering, burden, and suicide risk during each episode, but also that each additional depressive episode is likely to become more chronic and treatment-resistant.[1]

Bupropion is an antidepressant efficacious in the treatment of major depressive disorder for both acute treatment and relapse prevention. Bupropion is commonly prescribed, because effectiveness and tolerability are equivalent to SSRIs, but with advantages of less somnolence, sexual dysfunction, and weight gain. Bupropion is commonly used both as monotherapy and in combination with other antidepressants, typically with SSRIs. Many individuals cannot tolerate, or do not respond to, SSRIs, and for them bupropion is a first-line switch agent. Bupropion XL is a once-daily formulation, leading to better medication adherence.

One principle of relapse prevention is "the dose that gets you well, keeps you well." That is, a patient stabilized on bupropion XL 300mg will be at elevated risk of depression relapse if the effective dose is diminished (either dose reduction or reduced bioavailability), and whether bupropion is used as monotherapy or in combination therapy.[2,3] Bioequivalence of generic bupropion is particularly critical, because a switch between non-bioequivalent forms could cause relapse (if bioavailability decreases) or toxicity (if bioavailability increases).

2.1.1 Generic Drugs

The public health importance and economic impact of generic drugs, to patients individually and to the US healthcare system in aggregate, are manifest.[4-6] Total US drug expenditure was $320B in 2011. Generic drugs accounted for 80% of prescriptions dispensed, and were dispensed 94% of the time that they were available. The economic value of generics is staggering: While over 80% of prescriptions are for generic drugs, they account for just 27% of total drug spending. Generic drug use has saved the US health care system an estimated $1.07 *trillion* over the past decade (2002-2011), with $193B saved in 2011 alone. Generic market share has risen substantially, from 47% of prescriptions in 1999, to 67% in 2007, 74% in 2009, and 80% in 2011. Cost savings have also risen, from $60B in 2002, to $101B in 2007, and $193B in 2011, and this trend is only expected to escalate.

Aside from obvious cost advantages attendant to branded-generic switching, generic-generic switching also occurs due to availability, stocking from a specific manufacturer, pharmacy-negotiated costs, and requirements by third-party payers.[7] Switching decisions may be made by prescribers, pharmacists, or patients. Interchangeability of generic drugs influences drug prescribability (whether a patient is treated for the first time with a branded vs a generic drug) and drug switchability (when a branded drug is switched to a generic, or there is a change from one generic to another).[8]

The *key underlying premise* on which rests patient safety, medical therapeutics, healthcare economics, and the public trust, is that generic drugs are therapeutically equivalent to the branded innovator, and to each other. Therapeutic non-equivalence can have profound health, ethical, cost, and broad economic implications.

2.1.2 FDA Bioequivalence, Pharmaceutical, Therapeutic, Clinical Equivalence

FDA evaluation of generic drugs uses bioequivalence as a surrogate for therapeutic equivalence, obviating the need for generic drugs to undergo clinical testing.[9-11] A generic drug is considered bioequivalent to the reference (or branded drug) if the active compound or moiety exhibits the same rate and extent of absorption (more generally, systemic exposure). Systemic exposure is determined from plasma C_{max} and AUC (area under the curve), and the entire 90% confidence interval for the geometric mean of the log-transformed generic-to-reference C_{max} and AUC ratios must be within the bioequivalence limit of 80 to 125%. Generic drugs must also show pharmaceutical equivalence (same active ingredients, route of administration, dosage, form, and strength as the branded drug). Drugs are considered "therapeutic equivalents", without the need for clinical data, if they are both pharmaceutical equivalents and show bioequivalence. While this is reasonable and usually accurate, non-therapeutic equivalence can occur despite bioequivalence, for both

conventional and narrow therapeutic index drugs.[12,13] More importantly, it is now clear that single-dose studies in healthy volunteers may not predict steady- state bioequivalence in patients, particularly for modified release forms.[13,14]

2.1.3 Branded and Generic Bupropion

GlaxoSmithKline (GSK) was the innovator of bupropion (Wellbutrin®), first in immediate release (IR) form (TID dosing), then Wellbutrin SR® (sustained release, BID dosing), then Wellbutrin XL® (extended release, once daily dosing). Introduction of generic bupropion IR was followed by generic bupropion SR, then generic bupropion XL.

Approval of the first bupropion XL 300mg generic (Budeprion XL, 2006) was based on a prior bioequivalence study of 150mg Budeprion XL and Wellbutrin XL in healthy subjects, which were then extrapolated to the 300mg product.[15,16] The pharmacokinetic profile was not expected to differ between 300mg and 150mg bupropion XL; FDA decided not to test bioequivalence of the 300mg products.

Shortly thereafter, FDA received numerous reports of clinical issues when switching from Wellbutrin XL to Budeprion XL. In 2010, FDA sponsored a single-dose crossover bioequivalence study in healthy subjects comparing 300mg Budeprion XL to Wellbutrin XL, completed in August, 2012.[15,17] Budeprion XL failed bioequivalence testing. Based on these results, Budeprion XL 300mg was withdrawn from the market in October, 2012. In fact, none of the currently available 300mg XL generics has undergone bioequivalence or clinical equivalence testing.

2.1.4 Bupropion Disposition and Clinical Effect

Bupropion pharmacokinetics have been well-described for branded Wellbutrin IR, SL and XL.[18] Steady-state for all three formulations was reached in 8d. Bupropion is extensively metabolized. The three major metabolites are hydroxybupropion (via cytochrome P4502B6, CYP2B6), and erythrohydrobupropion and threohydrobupropion (by carbonyl reductase). Metabolite exposure is considerably higher than that of parent drug. At steady-state, hydroxybupropion, threohydrobupropion and erythrohydrobupropion C_{max} are 6-fold greater, 5-fold greater, and comparable to that of bupropion. Bupropion is racemic, and bupropion and metabolite disposition are stereoselective.[19-24]

Bupropion metabolism is important for therapeutic effectiveness. In mice, the activity of hydroxybupropion is approximately 50% of the parent drug.[25-29] While R- and S-bupropion have similar antidepressant activity,[30] only (S,S)-hydroxybupropion, but not (R,R)-hydroxybupropion, is pharmacologically active. Accordingly, (S,S)-hydroxybupropion is now considered the most active metabolite of bupropion, and the mediator of pharmacologic effect. Thus, bupropion hydroxylation is a bioactivation pathway.

Bupropion reduction to erythrohydrobupropion and threohydrobupropion is an inactivation pathway. The specific human carbonyl reductase(s) which catalyze bupropion reduction are unknown. There are hundreds of known carbonyl reductase(s).[31,32] Recent evidence suggests the relevant reductase(s) are microsomal, and that one of them, 11ß-hydroxysteroid dehydrogenase 1, can convert bupropion to threohydrobupropion but not erythrohydrobupropion.[33] Other reductases have not been identified.

2.1.5 CYP2B6, Genetics and Bupropion Metabolism and Disposition

There is extensive interindividual variability in CYP2B6 activity, due to variability in protein expression, susceptibility to inhibitors (clopidogrel, ticlopidine, thiotepa) and inducers (rifampin, phenobarbital, phenytoin),[34-36] and *CYP2B6* genetic polymorphisms.[36,37] Moreover, CYP2B6 is highly polymorphic, with 37 haplotypes (star alleles) identified to date, several of which have major clinical importance.[36,37] Bupropion hydroxylation is diminished, both in expressed CYP2B6.6 compared with wild-type CYP2B6.1,[38,39] and in human liver microsomes from CYP2B6*6 carriers.[39,40] After 7 days of sustained-release bupropion dosing, CYP2B6*6 and *18 carriers had significantly reduced plasma hydroxybupropion concentrations, with no effects on bupropion.[41,42]

2.2 Preliminary Studies

We conducted the first ever investigations showing the stereoselective disposition of bupropion and hydroxybupropion.[20,22-24] Although the influence of *CYP2B6* polymorphisms on the disposition of bupropion was recently reported, the studies evaluated steady-state dosing and did not use a stereoselective assay.[41,42] We

therefore determined the influence of *CYP2B6*6* genetic polymorphisms on the disposition of bupropion and hydroxybupropion using a single 150mg immediate-release dose, to evaluate metabolism and clearance, and that of bupropion and hydroxybupropion isomers. To date, 46 subjects have been enrolled, of genotypes *CYP2B6*1/*1* (n=17), *CYP2B6*1/*6* (n=20), *CYP2B6*6/*6* (n=6). *CYP2B6* genotype had no effect on R-, S-, or total bupropion plasma concentrations. In contrast, *CYP2B6*6* significantly influenced hydroxybupropion concentrations (R,R- more than S,S-), and there was a gene-dose effect. These results demonstrate the interaction between *CYP2B6* genetics and stereoselective bioactivation of bupropion to hydroxybupropion.

2.3 Objective

1) Determine bioequivalence between branded and generic bupropion extended release (XL) products (and between generic products) at steady state in patients with major depressive disorder.
2) Compare patients' self-reported clinical differences (release patterns, antidepressant effectiveness, and adverse events) between four bupropion 300mg XL products (brand vs. generics, and between generics).
3) Compare objective evaluations of patients' clinical response between each bupropion 300mg XL product evaluated, using standard, well-validated measures of depression response and side effects.

2.4 Study Drug Selection

Bioequivalence of branded Wellbutrin SR® and generic bupropion SR in all dosages has been established. Bioequivalence of 150mg Wellbutrin XL® and all 150mg bupropion XL generics has also been established. In contrast, no 300mg bupropion XL generic has undergone bioequivalence testing. This is the bupropion XL dose used for depression, hence the public health importance of testing clinical equivalency of 300mg bupropion XL is significant. Thus, the unmet need is to evaluate branded and generic 300mg bupropion XL products. Therefore bioequivalence of (1) branded Wellbutrin XL® 300mg (Valeant Pharmaceuticals, initially developed by GSK), (2) generic bupropion XL 300mg (Mylan Pharmaceuticals) (3) generic bupropion XL 300mg (Anchen/Par Pharmaceuticals), and (4) generic bupropion XL 300mg (Watson Labs) will be compared.

To ensure full double-blinding, all four drug products in the randomized portion will be over-encapsulated with the same opaque capsule (DBcaps® overencapsulation capsules, Capsugel Inc, or equivalent) to conceal product identity from investigators and patients, and to conceal the occurrence of a product switch from patients. Over-encapsulation will begin at the start of the lead-in phase, to avoid symptom reporting due to expectancy effects from change in appearance of the medication after randomization. An IND is not required for the conduct of this study.

2.5 Patient Selection

An estimated 75 subjects with MDD in partial or full remission who are currently taking bupropion 300mg XL (branded or generic) will be enrolled. The target enrollment is 60 evaluable subjects. A 25% drop-out rate is conservatively assumed. Subjects must be on stable therapy (minimum of 4 months on bupropion 300mg XL). Subjects will be recruited from the Washington University patient population, by referrals from community physicians, and by public advertisements. Potential subjects will also be contacted by the pharmacy benefit manager Express Scripts, given a brief description of the study, and invited to contact the investigators for further information and potential recruitment/enrollment. The study will be posted on clinicaltrials.gov, once reviewed and approved by the Research Involving Human Subjects Committee (RIHSC), the FDA's Institutional Review Boards (IRB). Subjects will be screened with the Structured Clinical Interview for DSM Axis I Disorders (SCID) to determine eligibility.[43] SCID assesses current and lifetime depression, as well as other psychiatric disorders, and is used to clarify psychiatric inclusion and exclusion criteria. Participants must have MDD which is in partial or full remission. All risks and benefits will be explained, and subjects will sign an informed consent form. After enrollment a blood sample will be obtained, coded for deidentification (see **3.3.4** below) and stored at -80°C in the PIs lab for later DNA analysis. DNA is stored until all reports and manuscripts are completed and accepted.

2.5.1 Inclusion Criteria

Each subject must meet all of the following criteria:

1. Adult outpatients age 18-75 years
2. Currently on once daily bupropion HCl 300mg XL (brand or any generic), for a minimum of 4 months

3. Major depressive disorder (MDD), in partial or full remission for at least 4 months, as confirmed by the SCID. Spontaneous relapse of depression unrelated to medication changes is less likely – about 5% chance per year – after remission has been maintained for at least 4 months.[2]
4. Ability to understand and willingness to comply with study procedures, and to provide written informed consent

2.5.2 Exclusion Criteria

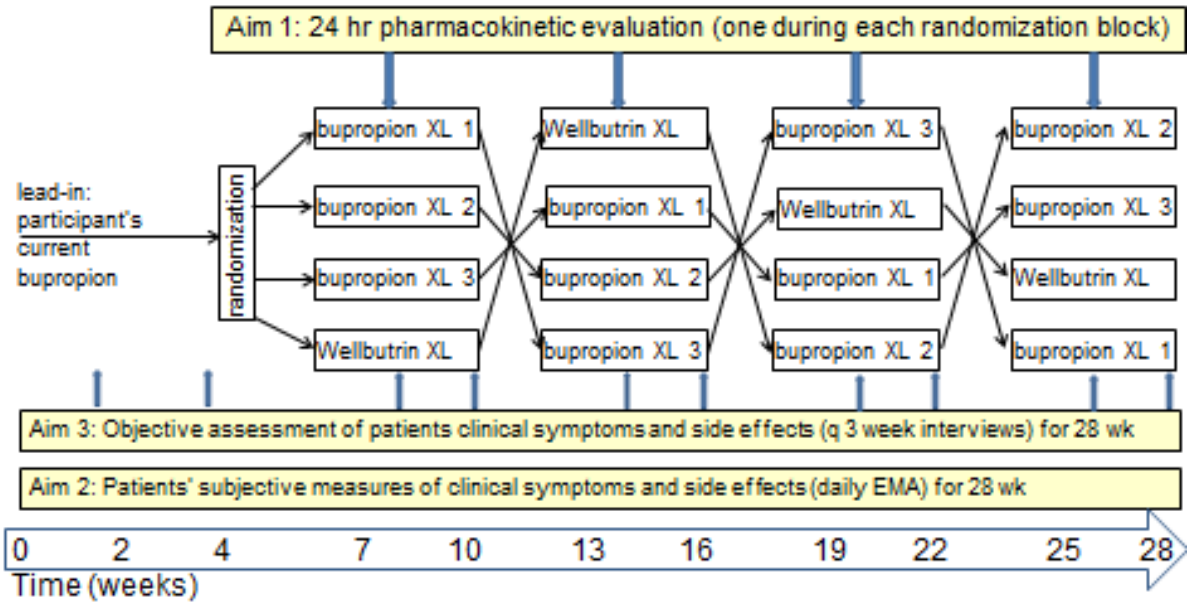
Subjects will not be enrolled if any of the following criteria exist:

1. Remission from depression not clearly attributed to bupropion treatment
2. Current severe side effects attributable to bupropion
3. Poor adherence to bupropion treatment per patient self- report and history of refill persistence
4. History of active seizure disorder, or seizure treatment within past year
5. History of significant hepatic or renal disease, based on physician assessment
6. Currently taking drugs or natural products known to influence cytochrome P450B6 (CYP2B6) activity
7. Currently taking drugs for hepatitis C or multiple sclerosis, due to their ability to cause depression
8. Dementia or other significant cognitive impairment, per diagnosis or investigative team's assessment
9. Lifetime diagnosis of schizophrenia, schizoaffective or schizophreniform dis-order, delusional disorder, or current psychotic symptoms diagnosed by SCID
10. Abuse of or dependence on alcohol or other substances within the past 6 months as determined by SCID, and confirmed by study physician interview
11. Current suicidal ideation

2.6 Design and Procedures

2.6.1 Study Design

The protocol is a prospective, randomized, double-blinded, crossover study in 75 subjects (target, 60 evaluable) with Major Depressive Disorder (MDD) receiving bupropion HCl 300mg XL (branded or generic). Subjects will be studied for a total of approximately 28 weeks: an approximately 4 week lead-in phase during which participants remain on their existing bupropion product, and then four randomized cross-over phases of approximately 6 weeks on each of the four bupropion study drugs (brand and 3 generics). For each of the four bupropion products, subjects will have (a) formal pharmacokinetic evaluation (24 hr plasma and urine) at steady-state, (b) every 3-week in-person standard structured clinical evaluations of depressive symptoms and side effects, and (c) once daily smart phone-based assessments to capture information on symptoms and side effects. See Figure 1 for a pictorial description.



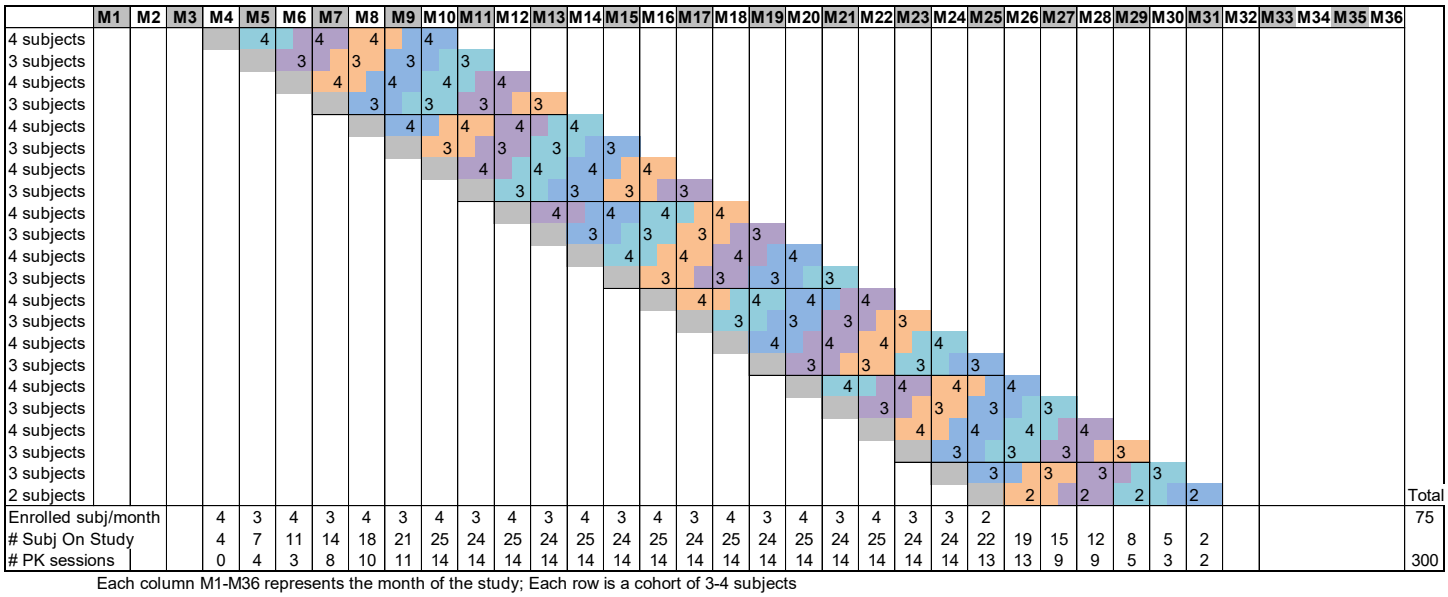
2.6.2 Randomization

The order of the four study drugs will be randomized and balanced across the study. The randomization table will be generated by the Barnes-Jewish Hospital Investigational Pharmacy. Each subject will be assigned the next available number. Subjects, investigators, and all study team members will be blinded to drug treatment. In the case of dropouts (either subject- or investigator-initiated), subjects will be replaced, to provide the required number of subjects. Randomization of replacements will be as follows:

1. Subjects withdrawn prior to randomization (before or during the lead-in) will simply be replaced in that former subject's randomization, and receive that subject's order of drug products
2. Subjects withdrawn after randomization, while receiving the study drugs, will be replaced using the next scheduled randomization sequence.

2.6.3 Enrollment Timeline

Figure 2 conceptually illustrates the anticipated enrollment timeline for the randomized 4-way crossover. For illustration purposes, subjects are shown to be randomized in blocks, however study drug order will be individually randomized and balanced across the study.



Each column M1-M36 represents the month of the study; Each row is a cohort of 3-4 subjects
Grey box represents the drug product at the time of enrollment and entry into the study
Each color box is a different bupropion XL drug product
Each drug product is administered for 6 weeks
Pharmacokinetic sessions are performed during the day 10-20 window on each drug product
The number in each box shows the time of the PK session (2nd-3rd week) and the number of subjects

Figure 2: Protocol schematic for the clinical trial of 4 bupropion products

2.6.4 Initial Lead-in Period

Subjects will enter the study after reviewing and signing the informed consent document. They will remain on their current bupropion product for the initial 4 weeks. Their specific supply will be turned over to the investigators and replaced by the identical product, now over-encapsulated during the run-in to minimize expectancy (**3.4.2**). During this period, subjects will undergo daily smart phone-based self-report assessments. At the end of the 4 week period, subjects will visit the study clinic at Washington University Medical Center for objective assessments of depression and side effects. These procedures will familiarize subjects with assessment approaches, and also provide baseline data against which to compare similar data when subjects take the same bupropion product during the blinded portion of the study. Non-adherent subjects will be excluded from further participation. At the end of the prestudy period, subjects will be randomized and then receive their first study drug in the sequence, without washout.

2.6.5 Randomized Study Period

Subjects will take each 300mg bupropion XL product for 6 weeks, and then be switched to another product without washout, according to their randomization schedule. During the 2nd-3rd week on each product, subjects will visit the study clinic for a bupropion pharmacokinetic session, an objective assessment of depression and side effects, and to receive another 3 week supply of study drug. During the 6th week on each product, subjects will again visit the study clinic for objective assessments of depression and side effects. Subjects will then be switched to their next scheduled drug product, and the sequence repeated for the four study drugs. Each subject will therefore be studied for four 6-week study drug epochs. *Subjects will not be informed when they are being switched, in order to minimize bias.* A Medication Event Monitoring System, (MEMS 6 TrackCap, or equivalent) will be used to assess compliance and compile drug dosing histories for the quantitative analysis of adherence during each subject's 28 week study period.

The rationale for the timing of the pharmacokinetic assessments is as follows: Subjects must be at steady-state on their new bupropion product. Steady-state bupropion concentrations have been reported to occur by 8d for all formulations.[18] Nevertheless, to ensure that metabolites disposition is also at steady-state, and metabolite elimination is known to be somewhat slower than parent, at least 10d will be allowed before assessing pharmacokinetics. Assessment should not wait too long, however, in case a patient reports loss of effectiveness or side effects after starting a new bupropion product, causing a product switch or other intervention, and this risk increases with time. Therefore the 10-20 day window will be targeted for the bupropion pharmacokinetic session for each product.

The rationale for not informing subjects of the timing and frequency of product switching is to minimize expectancy. Patients are more likely to report an increase in depressive symptoms or side effects if they identify a change in medication. In previous relapse prevention studies, patient complaints about lack of efficacy increased, regardless of treatment (continued medication or taper to placebo), when their medication changed from pills to over-encapsulated. In another, patients reported increased symptoms at the time of randomization, apparently from anticipation. Expectancy effects are particularly common in depression studies, and interfere with detection of product switch-related clinical effects. Therefore: (1) participants will not be told when or how many times they are being crossed over; (2) all bupropion products will be over-encapsulated to look identical throughout the study, including during the lead-in phase.

Particular attention will be paid to maximizing medication adherence. To maximize adherence:

- Patients will be carefully screened, to screen out those with low likelihood of good medication adherence. Potential participants with known predictors of poor adherence (e.g. heavy drinking, dissatisfaction with their bupropion therapy, adverse side effects, perceived lack of benefit from bupropion) will not be enrolled.
- Adherence and timing of medication will be evaluated during the lead-in phase; subjects showing non-adherence during the lead-in phase will be removed.
- Subjects will receive daily reminders to take their pill, and reminders regarding the importance of exact adherence.
- Adherence and timing of medication will be confirmed with the MEMS system (cap with a microprocessor, providing real-time data on container opening), in addition to self-reports and pill counts.
- Patients showing non-adherence in the 7 days before bioequivalence testing will be rescheduled. At other times, adherence will be corrected and reinforced using reminders, engaging participants and their support systems, and reassessing barriers and facilitators to adherence.

After the fourth 6-week drug session and at the last study clinic visit, subjects will be returned to their original bupropion product, resupplied with their own medication to take, and thanked and provided positive feedback for their participation.

2.6.5.1 Bupropion Pharmacokinetic Sessions

Subjects will be studied in the Clinical Research Unit at Washington University-Barnes Jewish Hospital, and remain in the Unit for approximately 24 hours. Subjects are instructed to 1) have nothing to eat or drink after midnight before the study session and 2) abstain from alcohol for 24 hours before each study period and until the last sample is collected. Because food increases plasma C_{max} and AUC of bupropion extended-release tablets by 11 and 17%, respectively (although changes were not statistically significant[18]), subjects will nonetheless be studied after an overnight fast to minimize potential variability. They will take their study drug with 240ml of water, receive a standard meal 4 hours after bupropion dosing, and have free access to food and water thereafter. An intravenous catheter will be placed by CRU

nursing staff in an arm vein for blood sampling (5cc, EDTA) immediately before and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hr after dosing (15 samples, 75 cc per session, 300 cc over the entire study), and samples centrifuged to obtain plasma. Urine will be collected for 24 hr, kept refrigerated, the volume measured, and aliquots frozen. Samples will be stored at -80°C in the PIs lab. At the end of the 24 study, the intravenous catheter is removed, and subjects leave the research unit. Plasma and urine concentrations of bupropion, hydroxybupropion, erythrohydrobupropion, and threohydrobupropion will be determined using a chiral LC/MS/MS assay.

2.6.5.2 Objective Depression and Side Effects Assessment Sessions

Subjects will visit the medical center twice during each 6-week drug crossover (every 3 weeks). The main outcome measurement for depression will be the Montgomery-Asberg Depression Rating Scale (MADRS).[44] This is a 10-item checklist, where each item is rated on a scale from 0-6 with anchors at 2-point intervals. It takes about 15 min to administer. A MADRS score of $\leq$15 at baseline will establish study eligibility. The MADRS was designed to assess treatment-sensitive changes in MDD, and can be used by both psychiatrists and non-psychiatrist raters. A structured interview will also be used, which provides high inter-rater reliability to maximize reliability.[45] Side effects will be assessed with the self-report Antidepressant Side-Effect Checklist (ASEC).[46] This well-validated scale has the advantage of being measurable via self-report (versus interview) and can be used in both in-person and EMA assessments.

MADRS and ASEC are the standard clinical methods for depression care (and also research instruments) and will be the clinical metrics to determine if patients have a change in clinical response to bupropion, and if patients should be withdrawn for therapeutic reasons.

2.6.5.3 Smart phone-based Assessments

Standard clinical measures of depressive symptoms are sufficient for detecting relapse, but may be insufficiently sensitive for more subtle changes caused by nonequivalent medication versions. Measuring patients' perspectives on complex, subjective, and often transient events such as symptoms or side effects is a methodological challenge, given both insight and memory biases that affect standard retrospective questionnaires.[47,48]

Therefore, to gather more frequent and potentially more precise information, daily symptoms and side effects will be assessed via a validated smart phone-based program. This approach (Ecological Momentary Assessments, EMA) is currently in use with other Washington University in St. Louis IRB-approved protocols. Specific procedures include:

- In-person demonstration of the smart phone application with a practice phone at the start of the study.
- Phones will be provided by the study team, and run only the EMA program (i.e., no other applications or calls).
- Participants receive a daily trigger for an assessment, with reminder cues until it is completed.
- The daily assessment (approximately 20 items) will measure: (a) depressive symptoms, using 8 items from the MADRS (excluding the suicide item and the depression observational item), (b) 6 most common self-reported side effects of bupropion, as assessed in the Antidepressant Side-Effect Checklist: dry mouth, insomnia, headache, nausea, agitation and sweating, and (c) a short list (no more than 6) symptoms reported by patients who have reported problems with switching between forms of bupropion.
- Data are automatically uploaded to the University server. They will be reviewed approximately weekly.

Smart phone-based assessments are for research only, and will not be used to determine if patients have a change in clinical response to bupropion, or if subjects should be withdrawn for therapeutic reasons. This will be made clear to subjects.

2.6.6 Post-Study Period

After the fourth 6-week drug session and at the last study clinic visit, subjects will be returned to their original bupropion product, resupplied with their own medication to take, and thanked and provided positive feedback for their participation.

2.6.7 Study Drug and Doses

Four study drugs will be evaluated during the randomization period (no IND is needed):
1) Wellbutrin XL® 300mg (Valeant Pharmaceuticals, NDC 64455-731, initially developed by GSK)
2) generic bupropion XL 300mg (Mylan Pharmaceuticals, NDC 00378-2009, ANDA 090942)
3) generic bupropion XL 300mg (Anchen/Par Pharmaceuticals, NDC 10370-102, ANDA 077284)
4) generic bupropion XL 300mg (Watson Labs, NDC 00591-3332, ANDA 077715)

A single lot number of each drug product will be used throughout the study, when available. Lot numbers and expiration dates will be recorded. Drugs will be stored at room temperature (59-77 °F, 15-25 °C) away from light and moisture, or as otherwise specified by the manufacturers. All medications will be secured and maintained by Barnes Jewish Hospital Investigational Pharmacy. Drug supply, dispensing, and accountability logs will be maintained.

Each lot number of each drug product will be characterized with respect to identity, content, and purity. Each lot number of each drug product will undergo appropriate dissolution testing. Bupropion tablets will be over-encapsulated with the same opaque capsule to ensure full double-blinding. Over-encapsulated bupropion tablets will also undergo dissolution testing.

If the drug lot number expires prior to the inclusion and completion of all subjects in the study, the drug remaining will be re-characterized with respect to identity, content, and purity, and undergo appropriate dissolution testing. If equivalence to the pre-study identity, content, purity, and dissolution is established (90-110%), in order to ensure that the product has the same quality, then application will be made to FDA for approval to use after the expiration date and extend the expiration date by 1 year.

2.6.8 Genotyping

Genotyping will be performed by PCR to determine relevant CYP2B6 SNPs. Additional genotyping may be performed to evaluate effects of genetic variability in relevant pathways of bupropion disposition. For example, if identities of the human enzymes responsible for bupropion reduction are published during this investigation, and clinically relevant mutants are identified, then additional SNPs may be evaluated.

2.7 Observations and Measurements

2.7.1 Primary Assessments

The primary outcome measure will be C_{max} and AUC_{0-24} for racemic bupropion, hydroxybupropion, erythrohydrobupropion and threohydrobupropion.

Additional pharmacokinetic/bioequivalence endpoints:

1. Plasma C_{max} and AUC_{0-24} for R- and S- bupropion
2. Plasma C_{min}, C_{av}, C_{trough}, CL/F, %PTF, and swing for RS-, R- and S-bupropion
3. Plasma AUC_{0-t} for RS-, R- and S-bupropion
4. Plasma C_{max}, AUC_{0-24}, C_{min}, C_{av}, C_{trough} %PTF, CL_f and swing for hydroxybupropion, erythrohydrobupropion, and threohydrobupropion; racemate and their individual isomers (enantiomers/diastereomers)
5. Plasma AUC_{0-24} hydroxybupropion/bupropion for racemate and individual enantiomers
6. Formation clearance of hydroxybupropion, erythrohydrobupropion, threohydrobupropion, erythrohydrobupropion glucuronide, threohydrobupropion glucuronide: racemate and individual isomers

Secondary Endpoints:

7. Relapse of MDD
8. Change in symptoms of depression
9. Change in side effects of medication

2.7.2 Pharmacokinetic Calculations

Pharmacokinetic parameters will be determined essentially per FDA Guidance.[10] The primary metrics will be 1) Peak drug exposure, assessed from maximum plasma drug concentration (C_{max}) obtained directly from the data without interpolation; and 2) Total exposure, assessed as the area under the plasma concentration-time curve from time zero to time tau over the dosing interval at steady state (AUC_{0-tau}), analyzed using non-compartmental methods, where tau is the dosing interval (24 hr, hence AUC_{0-24}). In addition:

- Trough plasma concentration (C_{trough}) will be measured at the end of the dosing interval (24 hr)
- Minimum plasma concentration (C_{min}) is the lowest concentration during the dosing interval
- Average plasma concentration (C_{av}) is AUC_{0-tau}/tau (i.e. AUC_{0-24}/24)
- As a measure of plasma concentration flux, %Peak-trough fluctuation (%PTF)=100%•(C_{max}−C_{trough})/C_{av} and Swing =100%•(C_{max}−C_{trough})/C_{trough} will be used

- Time to peak plasma concentration (T_{max}) will be recorded, for both parent and metabolites, although it is expected to be highly variable (variability in T_{max} for extended release drugs at steady-state is recognized.[13]
- As an exploratory metric, and an index of early exposure (potential "dose-dumping"), various partial AUCs from 0-t, and t-24 will be evaluated, with various cutoff times for t (including the population T_{max}, while also recognizing T_{max} as a potential source of error), as recently described by FDA,[13,49] and for sustained-release bupropion.[50]
- Plasma hydroxybupropion AUC_{0-24}/bupropion AUC_{0-24} will be used as an index of CYP2B6-mediated bupropion hydroxylation
- Apparent oral bupropion clearance(CL/F) will be determined as dose/AUC
- Metabolite formation clearance (CL_f) will be calculated as the product of the molar fraction of the dose recovered in urine and CL/F.

All results are determined for each subject and each drug product, and reported as arithmetic mean, SD, CV, and geometric mean (and Tmax as the median and range).

Per FDA Guidance,[10] all parameters will be determined for the parent drug released from the dosage form (RS-bupropion). Due to the unusual nature of bupropion (racemate, enantioselective bioactivation, and different pharmacologic effects of the metabolites and their stereoisomers) parameters will also be determined for the major metabolites (hydroxybupropion, erythrohydrobupropion, threohydrobupropion), and for both the individual stereoisomers and the racemate for each analyte.

Additional exploratory analysis may be performed using a population pharmacokinetic approach. In brief, multi-compartmental models will be defined and optimized for bupropion, and then for bupropion and hydroxybupropion simultaneously (and if identifiable, other metabolites). The influence of covariates on the model parameters will be analyzed, where covariates will include age, sex, weight, race/ethnicity, bupropion XL drug product, and *CYP2B6* genotype. Optimal models will be selected based on goodness-of-fit plots, precision of estimates, likelihood ratio test, and evaluation of population predicted estimates, conditional weighted residuals, and relative standard errors of population estimates.

2.7.3 Statistical Methods

2.7.3.1 Bioequivalence

Bioequivalence will be determined essentially per FDA Guidance,[9,10] using an average bioequivalence approach. A repeated measures model will be fit for each parameter separately. Interpatient variability for each compound will be examined separately prior to assuming that they are all the same. It is anticipated that most parameters will be log-transformed prior to statistical testing, but the distributional assumptions will be examined for each parameter and the most appropriate data transformation used. Following the standard FDA guidance the two one-sided test procedure will be used to determine whether each generic product is significantly less bioavailable than Wellbutrin XL, and whether Wellbutrin XL is significantly less bioavailable than each generic product. This is expressed as a limit of test average/reference average of 80% for the first statistical test and a limit of reference average/test average of 80% for the second statistical test. In practice, the 90% confidence interval around the geometric means of the test/reference ratio for each parameter must be entirely between 0.80 and 1.25 for bioequivalence.

Bioequivalence will be determined using the standard pharmacokinetic parameters (AUC and C_{max}) and equivalence definition (90% CI of the generic/brand geometric mean is within 80-125%) for bupropion (primary), the active metabolite hydroxybupropion (secondary), and for the other metabolites (tertiary). The test for each generic compound will not be adjusted for the other comparisons, e.g. to control the study-wide error rate. Similarly, analysis will not control for multiple comparisons involved in testing each of the parameters. As an aid to interpretation of the results, however, the False Discovery Rate will be computed for the observed results. The generics will also be evaluated using the criteria for bioequivalence for narrow therapeutic index drugs (90% CI of ratio within 0.95-1.05).

The influence of *CYP2B6* genetics on the disposition of bupropion, hydroxybupropion, and bioequivalence between brand and generic bupropion XL products will be determined through exploratory analyses to fit individual bioequivalency models by adding random effects for each agent and covariances between the responses. Order effects (omitted in the model described above) will also be determined. Predictors of overall response of each individual for each parameter,

especially CYP2B6 genetics, will be evaluated, specifically the most common variant allele *CYP2B6*6,* comparing *CYP2B6*1/*6* and *CYP2B6*6/*6* genotypes with non-carriers of *CYP2B6*6*, and with true *CYP2B6*1/*1* genotypes.

The influence of stereochemistry on (i) bupropion disposition, (ii) bupropion bioactivation to hydroxybupropion, and (iii) bioequivalence between bupropion XL products will be examined by fitting an expanded model where both the enantiomers and diastereomers will be included by introducing an additional factor, examining the significance of this factor, and its interaction with the specific compound.

2.7.3.2 Patient perception of antidepressant effectiveness and side effects

Patients' self-reported clinical differences (release patterns, antidepressant effectiveness, and adverse events) will be compared between all bupropion 300mg XL products (brand vs. generics, and between generics).

Reports will be determined by the daily patient smart phone assessments. Daily depressive symptom scores, side effect scores, and focus group-nominated symptoms (e.g., sensations regarding drug release) during each randomized bupropion phase will be compared with each other, and with those from the open-label lead-in period. Repeated measures ANOVA analogues of the models described above for the pharmacokinetic parameters will be used for assessing patents' perceptions. Since there are no well-accepted criteria for the equivalence of scores using this method, any systematic effects of differences between patient's responses to Wellbutrin XL and each generic product will be tested.

Analysis will explore whether differences in smart phone-collected depression symptoms, side effects, and patient reports regarding release patterns are related to pharmacokinetics by augmenting the models above with pharmacokinetic parameters as covariates. Analysis will determine if there are differences in bupropion products by correlating, on an individual basis, the ratio of the two pharmacokinetic parameters to the difference in symptoms or side effects.

2.7.3.3 Objective evaluation of antidepressant effectiveness

The main clinical outcome is relapse of depression, defined using the MADRS and SCID depression module. Patients with a 2 point or greater increase from their average baseline open-label lead-in phase MADRS score, and/or MADRS score of 15 or greater, will have the SCID depression module conducted. If the SCID reveals current MDD, they will be considered to have relapsed. Physician adjudication (by study Psychiatrist, who is blinded to randomization assignment) will be utilized as well.[2] An appropriate generalized linear model with a binomial link function will be used. Relapse of depression will also be considered an end-point in the study.

Subjects suffering a relapse will be removed from the study and will return to their pre-study bupropion product. Subjects will be advised to contact their treating physician for follow-up. Data and specimens collected for these subjects will be included in the analysis.

The secondary clinical outcomes are symptomatic change in depression (MADRS scores) and side effects (Antidepressant Side Effect Checklist scores) determined at the every 3-week interviews. Repeated measures ANOVA analogues of the models described above will be used for each of these analyses. Analysis will test for any systematic effects of differences between patient's symptom/side effect levels with Wellbutrin XL and each generic preparation.

2.7.4 Sample Size Justification

Calculations for sample size and power of the proposed studies are based on information from the confidence intervals for the ratio of the pharmacokinetic parameters for the generic (Budeprion XL) to the innovator (Wellbutrin XL) which was recently reported by the FDA in their evaluation of Budeprion XL.[51]

SAS 9.3's Proc Power was used to conduct the correct power analysis for the two one-sided tests (TOST) approach per the FDA guidance on bioequivalence. Using a 90% confidence interval and ratios needing to be between 0.80 and 1.25, the power for sample sizes ranging from a conservative estimate of 60 to the recruitment goal of 75 was computed. If the comparators are indeed bioequivalent (ratio=1.0) then the study power would be >0.999 for a pharmacokinetic parameter such as AUC and 0.98 for a more variable parameter such as $C_{max.}$ If the generic is 10% under (or over), e.g. ratio=0.90,

then for AUC the power would be 0.78=0.83 to declare a significant difference between the compounds at an alpha of .05 even if the CI for the ration was still contained within the 0.80-1.25 bounds.

The study is also powered in order to have a reasonable power of detecting clinical differences between compounds. If one of the generics is non-equivalent with respect to symptom and it is assumed that 25% suffer a relapse on this generic versus 5% for Wellbutrin or other (equivalent) forms, then using a McNemar's test for equality of proportions, a sample size of 60 and a 1-tailed alpha of 0.05, the power will be about 0.83. For continuous variables, there will be 0.80 power to detect a standardized difference of 0.37 (low-medium effect size).

3. MANAGEMENT OF INTERCURRENT EVENTS

There is a naturalistic recurrence (relapse) rate of depression of about 5% yearly for patients who maintain adherence with a stable dose of medication to which they initially responded. Thus, even if all forms of bupropion XL are clinically equivalent, about 3-4 participants may be expected to suffer a relapse during the trial. Relapse of depression is considered an end-point in the study: patients who have suffered a relapse will be removed from the study and will return to their pre-study medication formulation. Study staff will ensure that relapsed study subjects restart their medication and receive timely follow-up with their treating physician or other appropriate mental health professional. In the case that relapse of depression is associated with the emergence of suicidal ideation, this could include hospitalization. Patients who prematurely discontinue or are non-adherent to study medication will be removed from the study. The most likely outcome is for the patient to return to their pre-study medication formulation. Other risks are those that would follow a breach of confidentiality and the disclosure of clinical information. In addition, it is recognized that depressed individuals, especially those with chronic illness and disability, can easily feel overwhelmed or fatigued by what would be minimally demanding tasks for others, and, therefore, this discomfort is included in the potential risks. The instruments to be used in this study have been used by the investigators in other studies of older depressed adults (including older frail adults). There are very few older adults who are unable to tolerate the length of the questionnaires.

3.1 Adverse Events

Significant drug-related adverse events are expected to be uncommon, as participants in this study are being continued on bupropion at a dose that they are currently tolerating well (study inclusion criterion). Bupropion, tends to produce side effects early in treatment, so late-appearing side effects are unlikely, especially if bioequivalence is observed). Nevertheless, there is a rare risk for new, significant side effects, even with our procedures to select participants with low likelihood of these. The investigative team will closely monitor subjects for adverse events. Adverse events will be reported to the RIHSC and to the Washington University IRB according to applicable guidelines. Adverse events are followed until satisfactory resolution, as determined by the investigators. The description of the adverse experience will include the description, date and time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), any treatment required, and any follow-up and/or treatment required.

3.2 Premature Discontinuation

If a subject withdraws or drops out from the study, or is withdrawn by the investigators, they will be replaced, to provide the required number of subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study. Subjects' participation can be terminated by the investigator without regard to the subject's consent. Randomization of replacements will be as follows:

1. Subjects withdrawn or dropping out prior to randomization (before or during the lead-in) will simply be replaced in that former subject's randomization, and receive that subject's order of drug products
2. Subjects withdrawn or dropping out after randomization, while receiving the study drugs, will be replaced using the next scheduled randomization sequence.

3.3 Potential Risks

3.3.1 Potential risks from bupropion

Adverse effects from bupropion: Bupropion is a widely used and efficacious antidepressant also used for smoking cessation. All enrolled subjects will currently be taking this drug under the management of their treating physician at the time of enrollment. Bupropion is generally well-tolerated. In patients taking it chronically, it may cause agitation, anxiety or insomnia. A rare effect of bupropion is seizures, which are partially dose-related, and the risk is also increased in

patients with a history of seizure disorders or other predisposing factors. The incidence of seizure in patients receiving bupropion at doses <450mg daily is about 0.1-0.4%, similar to other antidepressants. The potential risks and side effects from versions of bupropion HCl manufactured by Valeant Intl (Wellbutrin), Anchen/Par Pharmaceuticals, Watson, and Mylan will be explored from this proposed research to determine if patients can perceive differences in release patterns, clinical effectiveness, and adverse events between drug preparations.

3.3.2 Potential Risks from Drug Cross-Over

The intent of the study is to determine whether the forms of bupropion 300mg XL are bio- and clinically-equivalent; therefore, there is some chance that some of the forms are not equivalent and patients will be switched to a form that is either ineffective or causes side effects. The risk of this is unknown. However, these risks are not unlike typical clinical care in which patients may be switched between generics for reasons of cost or availability at any refilling of medications.

3.3.3 Potential Risks from Discomfort Related to Interviews And Questionnaires

With respect to minimizing any discomfort that may result from the interview, raters have been or will be selected on the basis of personal attributes and interpersonal skills as well as substantive knowledge. They will be further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects. Furthermore, they are trained to recognize signs of significant stress or irritability and will be instructed that they should gently terminate the interview whenever distress is observed.

3.3.4 Potential Risks from Genotyping

1) The relevant genes are not associated with any known disorder(s), syndrome(s), or adverse condition. 2) Samples will be kept confidentially. They will be coded, with a key to the code linking code numbers to names kept at a separate location, under lock and key. 3) The link to identifiers will be destroyed at the end of the study. 4) A disease/syndrome is not being studied, hence there is no issue of effective treatments to be administered as a result of genotyping. There is no evidence that testing will provide evidence of previously undiagnosed or unrecognized illness, or susceptibility to illness. 5) Samples will not be used for any purpose other than to study genes related to the disposition and response to study drugs. 6) Blood samples will not be used to establish permanent cell lines. 7) Data will be stored under lock and key (office, file cabinet) and only the investigators will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 8) Genetic data will not be entered in subjects' medical records. 9) Studies are not likely to result in findings that meet the National Bioethics Advisory Commission criteria for disclosure. 10) Genetics counseling will not be available to subjects, as they will not be informed of results and there are no know implications with respect to disease. 11) DNA samples will be deidentified (i.e., stripped of identifiers and given a separate code numbers unrelated to the subjects' study identification numbers). The code key will be kept by the PI under lock and key. DNA samples are used for this study only, and are not used for any other purpose or study.

3.3.5 Other Potential Risks

Intravenous catheter placement can cause a bruise. The amount of blood drawn will not constitute a risk to subjects (300 cc over 7 months), since this is less than recommended limits. Subjects may experience a loss of confidentiality. Investigators will keep subjects' participation confidential to the extent permitted by law. However, it is possible that others may become aware of subjects' participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies subjects.

3.4 Procedures to Minimize Potential Risks

The PI and co-investigator (a board certified adult and geriatric psychiatrist), will have primary responsibility for monitoring of all actively enrolled study subjects. Inclusion/exclusion criteria, screening interviews and assessments will be reviewed by the investigators at baseline and monitored throughout the study. Subjects will have access to a 24-hour answering service with physician availability. Study investigators, coordinators, and research staff will meet weekly to review recruitment, data accrual, data confidentiality, adherence to protocol design, subject compliance, subject status (clinical symptoms, side effects, any possible adverse events, intercurrent medical conditions) and complaints. At these meetings, any possible changes to the risk-benefit level will be discussed.

3.4.1 General
Overnight study sessions will be conducted in the WU Clinical Research Unit (CRU) under the supervision of the PI, a board-certified anesthesiologist thoroughly trained and experienced in human subjects research, assessment of adverse effects, and treatment. Subjects will be monitored by trained research coordinators and (RN) nursing personnel. The CRU operates as an in-patient and out-patient clinical research unit for studies that require more "intense" nursing services or that require an inpatient stay, and has crash cart and ACLS staff available on the unit. Each room is equipped with wall suction, oxygen and standard hospital monitoring equipment. There is an emergency plan in place that assures direct access to emergency care if it would be required.

3.4.2 Medication Risks
Risks from study medications will be minimized by excluding individuals with elevated seizure risk from bupropion (e.g., any history of bupropion-related seizures, or eating disorder). Since only individuals already taking bupropion stably for at least 4 months and tolerating it well will be enrolled, bupropion risks are likely low. Additionally, the risk of clinical worsening will be mitigated by following participants closely for evidence of this and removing them from the study if they suffer a relapse or intolerable side effect, restarting them on their original form of bupropion XL.

3.4.3 Genotyping
With regard to the determination of CYP2B genotype: 1) CYP2B genes are not associated with any disorder(s), syndrome(s) or adverse condition. 2) Samples will be kept confidentially. They will be coded, with a key to the code linking code numbers to names kept at a separate location, under lock and key. 3) The link to identifiers will be destroyed at the end of the study. 4) A disease/syndrome is not being studied, hence there is no issue of effective treatments to be administered as a result of genotyping. There is no evidence that testing will provide evidence of previously undiagnosed or unrecognized illness, or susceptibility to illness. 5) Samples will not be used for any purpose other than to study genes related to the disposition and response to study drugs. 6) Blood samples will not be used to establish permanent cell lines. 7) Data will be stored under lock and key (office, file cabinet) and only the investigators will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 8) Genetic data will not be entered in subjects' medical records. 9) Studies are not likely to result in findings that meet the National Bioethics Advisory Commission criteria for disclosure. 10) Genetics counseling will not be available to subjects, as they will not be informed of results and there are no know implications with respect to disease. 11) DNA samples will be anonymized (i.e., stripped of identifiers and given a separate code numbers unrelated to the subjects' study identification numbers). The code key will be kept by the PI under lock and key.

3.4.4. Suicide Risk Management
Suicide is a risk of depression and not of the study per se. Patients who are identified as having suicidal ideation will be excluded from the study. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all subjects eligible to participate in this study are statistically at a relatively higher risk for suicide than the general population. The subjects' absolute risk for completing suicide during this brief study remains very low and participation in the study does not create or increase the risk of completed suicide. Furthermore, all participants will be formally assessed every 3 weeks during the study. If the study personnel identify that a subject has become acutely suicidal, this subject will be referred to a mental health professional for further evaluation and treatment. This may lead to a clinical intervention that is lifesaving and may not have occurred had the subject not been participating in the study.

At each assessment point, trained research staff will probe for passive death wish, and suicidal ideation, intent or plan when they administer the MADRS. If a subject endorses suicidal ideation, intent, or plan, research staff is trained to follow an operationalized protocol developed to manage high-risk subjects in other studies of depressed subjects potentially at risk for suicide. This protocol has already been used successfully by the investigators to manage several acutely suicidal patients, and entails a specific determination of the suicidal risk and a prescribed set of actions. If a subject is determined to be at high and immediate risk, research staff is instructed to stay with the subject until a study psychiatrist has been contacted to discuss the situation. Coordinators will have cell phones and at least one study psychiatrist will be reachable at all times. In case of extreme emergency, coordinators are instructed to call their hospital security team or 911 for immediate help and to initiate commitment proceedings.

3.4.5 Discomfort
With respect to minimizing the discomfort that may result from interviews, coordinators will be selected on the basis of personal attributes, interpersonal skills, experience and substantive knowledge. They will be further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects. Furthermore, they are trained to recognize signs of significant stress or irritability and will be instructed that they should gently terminate the interview whenever distress is observed.

3.4.6 Data Integrity and Confidentiality
Subjects will be interviewed specifically to obtain research data. In addition to training and close supervision of research staff described above, a formal quality control mechanism will provide a systematic check on the quality of interview data. Of every 20 assessments, one will be selected for a random quality check. Selections will be made regardless of whether the interview was actually completed and will be random with the restriction that no more than two interviews will be checked for a given subject. Procedures designed to maintain confidentially include: (1) formal training sessions for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect subjects' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual subjects. Identities of participants will not be revealed in the publication or presentation of any results from this project. Research staff and subjects will provide data through paper forms and electronically. Smart-phone based data capture is transmitted immediately to a WU firewall-protected server at which point data are removed from the phone. All data capture by the device is encrypted and saved as numerics. In the event of difficulty with data transmission, encrypted data must be manually pushed to the server via a password protected user-interface. Only the research team would have access to the password for manual push of data, which then results in removal of stored data from the device. There are no patient identifiers saved to the devices.

3.5 Plans for Ensuring Necessary Medical Intervention
Subjects will remain under the care of the practitioner who is their treating physician. Subjects will be instructed to inform their treating physician of participation in the research study. Subjects will be told that in the event of a physical injury as the direct result of study procedures, they will be cared for by a member of the investigating team at no cost, within the limits of the Washington University compensation plan. Drug doses are chosen to be the same as currently used for medical management of depression. Side effects for each drug will be monitored daily by trained research personnel and the PIs.

3.6 Data and Safety Monitoring Plan
The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of different bupropion 300mg XL drug products, as there is no change in subjects' drug or drug dose, or medical management. Based on these considerations the monitoring plan involves a (board certified psychiatrist trained in treatment of depression) not involved in the study to serve in a monitoring capacity. Based on the small size and relatively low risks nature of the protocol, only a third person, rather than a full DSMB, is utilized. This individual will review the annual summary of adverse events. In addition, they will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event. This Plan is acceptable to our IRB, and has been used successfully by the PI for several years.

In general, the PI has a specific set of Standard Operating Procedures (SOPs) for clinical research. All individuals working under the PI are required to read and be totally familiar with and compliant with the SOPs, inclusive of the SOP for Adverse Event Reporting to the IRB (attached).

3.7 Notification of Subjects of New Findings
Significant findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

4. HUMAN SUBJECTS RESEARCH

4.1 Protection of Human Subjects

4.1.1 Human Subjects Involvement and Characteristics

The 28-week prospective, randomized, double-blinded, crossover study will involve enrollment of 75 subjects age 18-75 yrs who volunteer and meet all inclusion/exclusion criteria. All subjects will have been diagnosed with Major Depressive Disorder (MDD) and be taking bupropion HCl, 300mg XL (branded or generic versions). After all study related procedures, risks and benefits are explained and discussed, potential subjects will be asked to sign an informed consent form approved by the Washington University Institutional Review Board (IRB) and will be enrolled. The randomization table will be generated and kept by the Barnes-Jewish Hospital Investigational Pharmacy. Subjects will complete baseline research assessments conducted by trained research staff which include a) diagnostic and symptomatic measures of depression, b) review of medical conditions and medications, c) alcohol and drug use, and d) physical health. Subjects will remain on their own medication for the initial 4 weeks of the study. During this time they will undergo daily monitoring with smart phone-based Ecological Momentary Assessments (EMA). Upon completion of this 4 week period, subjects will visit the clinic for assessment of depression and side effects. Non-adherent subjects will be withdrawn from the study. Ongoing study participation will include 6 weeks on each of the four bupropion products (brand and 3 generics) without washout between drug crossover. Subjects will participate in overnight pharmacokinetic sessions at the Washington University Clinical Research Unit (CRU) approximately 2-3 weeks following each drug crossover. These sessions will occur 4 times and involve collection of blood and urine samples for up to 24 hours. Subjects will be provided with 3 weeks of study drug prior to discharge from the CRU. Periodic (approximately every 3 weeks) interviews will be conducted at WU Medical Center research offices and include monitoring of drug compliance (MEMS 6 TrackCap system), structured interview for assessment of depression symptoms, completion of Montgomery-Asberg Depression Rating Scale (MADRS) and assessment of drug effect(s). Subjects will receive an additional 3 week supply of study drug at each clinic visit. Subjects will complete smart phone-based EMA daily for real-time capture of patient-reported drug effects. Phones will also be used as a reminder to adhere to dosing instructions and provide instructions and trouble-shooting guidance. At the conclusion of the final session and last clinic visit, subjects will be returned to their original bupropion formulation and directed to resume their own medication. All studies are conducted under the supervision of the PI, a Board-Certified and GCP-certified and clinically active anesthesiologist with extensive experience in the conduct of human volunteer studies. We will examine bioequivalence, clinical equivalence, stereoselectivity, genomics, and patient perspectives regarding switches between commercially available forms of bupropion 300mg XL.

4.1.2 Criteria for Inclusion and Exclusion

Inclusion criteria:

1. Adult outpatients age 18-75 years
2. Currently on once daily bupropion HCl 300mg XL (brand or any generic) for a minimum of 4 months
3. Diagnosis of major depressive disorder in partial or full remission for ≥4 months, confirmed by Structured Clinical Interview for DSM Axis I Disorders (SCID)
4. Ability to understand and willingness to comply with study procedures, and to provide written informed consent

Exclusion criteria:

1. Remission from depression not clearly attributed to bupropion treatment
2. Current severe side effects attributable to bupropion
3. Poor adherence to bupropion treatment per patient self report and history of refill persistence
4. History of active seizure disorder, or seizure treatment within past year
5. History of significant hepatic or renal disease, based on physician assessment
6. Currently taking drugs or natural products known to influence cytochrome P450B6 (CYP2B6) activity
7. Currently taking drugs for hepatitis C or multiple sclerosis, due to their ability to cause depression
8. Dementia or other significant cognitive impairment, per diagnosis or investigative team's assessment
9. Lifetime diagnosis of schizophrenia, schizoaffective or schizophreniform dis-order, delusional disorder, or current psychotic symptoms diagnosed by SCID
10. Abuse of or dependence on alcohol or other substances within the past 6 months as determined by SCID, and confirmed by study physician interview
11. Current suicidal ideation

4.1.3 Involvement of Special Subject Classes
None

4.1.4 Procedures for Assignment to Study Group
Subjects will enter the study and remain on their current bupropion medication for the initial 4 weeks. The order of the four study drugs (all FDA-approved forms of bupropion XL 300mg) will be randomized and balanced across the study. The randomization table will be generated and kept by the Barnes-Jewish Hospital Investigational Pharmacy. Each enrolled subject will be assigned the next available number. Subjects, investigators, and all study team members will be blinded to drug treatment.

4.2 Sources of Materials
4.2.1 Research Material Obtained
Specimens include blood and urine obtained exclusively for determining study drug bioequivalence, stereoselectivity, and CYP2B6 genomics. Subjects will not be informed of their genotype. Subject completion of EMA data will be transmitted directly from research smart phones to a secure designated server at WU. The research team will administer the Montgomery-Asberg Depression Rating Scale (MADRS) and conduct structured interviews at all clinic visits. Side effects will be assessed with a self-reported Antidepressant Side-Effect Checklist. Drug compliance will be recorded with the MEMS system. Other data include past health and medical information obtained exclusively for research purposes.

4.2.2. Data Recorded
All research data will be recorded and saved to a secure password protected research designated server at WU. Data will be de-identified and stored under lock and key (secured building, locked office, locked cabinet) and only the research team will access.

4.2.3. Linkages to Subjects and Access to Identifiers
Any information that is obtained in connection with research that can be identified with a subject will remain confidential. Medical information, case report forms, pharmacokinetic and genetic data will be given a code and only the research personnel will have access to this information. Statisticians involved in any of the projects will have access only to deidentified data for the purposes of analysis. The original informed consent forms will be kept by the PI and a copy will be given to all subjects. Genotyping samples will be coded, with the key to the code linking code numbers to names kept at a separate location, under lock and key, with access limited to research team members.

4.2.4. Method of Specimen Collection
On study days, one IV catheter will be inserted for blood sampling. After administration of study medication, blood and urine samples are obtained for up to 24 hrs.

4.3. Recruitment and Informed Consent
4.3.1 Recruitment Strategy and Feasibility
The projected enrollment is four participants per month, well within our recruitment abilities, based on previous experience in patients with MDD in clinical trials. Potential subjects will be identified through IRB-approved processes.

The main recruitment plan involves targeted screening of patients (potential subjects) taking bupropion: This strategy leverages collaboration with Express Scripts as a Pharmacy Benefits Manager (PBM) to identify and contact patients with stable use of bupropion XL 300mg (and no contraindicated medications). Express Scripts has 3 years of prescription claims data readily accessible. Many clients have provided consent to Express Scripts allowing the use of their prescription and medical claims data for research purposes. Prescription data provides the ability of Express Scripts to identify individuals taking 300mg XL bupropion products, their duration of use, and comorbid conditions which might preclude patients from inclusion in the study, based on the inclusion/exclusion criteria. To date, more than one thousand bupropion XL 300mg users in the St Louis metro area have given consent for these research purposes. Express Scripts will notify eligible subjects of the study, and subjects will contact the investigators if they are potentially interested. Investigators will not contact potential subjects without their prior permission. This method alone will likely be sufficient to meet recruitment needs; only a 7% consent and randomization rate would be needed to obtain 75 participants.

Should the above method be insufficient, three other robust strategies for recruitment are available:
1. Community Engagement Core of the Washington University CTSA: This service, provided at no cost for CTSA faculty, will engineer a study-specific plan to search the Core's volunteer patient database, and advertise directly to the selected participant population.
2. Primary care and specialty care clinic screening and advertisements. Screening staff will partner with several care networks, including Washington University clinics in primary and specialty medical care, psychiatry, geriatric psychiatry, and geriatric medicine, the Washington University Physician Network, and referrals from local psychiatric practitioners and the BJC Medical Group. Washington University psychiatry clinics alone have over 1000 patients.
3. Wide-based screening of self-nominated volunteers. This involves large, current research registries (e.g., the "Volunteers for Health" registry at Washington University) to potentially identify and contact patients with depression history. In addition, Washington University Public Affairs will engage local media for messaging the study, using newspaper or radio advertising. Our prior clinical trials of depression have been able to recruit in the hundreds by these wide-based screening methods.

4.3.2 Circumstances of Informed Consent
Study volunteers will be consented for participation and enrolled by trained research personnel at Washington University School of Medicine. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the investigative team will provide all study descriptions, informed consent, and answer all questions. No placebo is required for the purposes of this study. Subjects will be informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Subjects will be asked for permission to contact their psychiatrist or primary care physician (PCP) who is prescribing bupropion and to inform them that the patient is interested in participating in the study. If the psychiatrist or PCP believes that participation could endanger the patient, the patient will not be enrolled. Informed consent will be obtained before any study procedures are performed and before any private information is recorded. Proxy consent is not planned.

4.4. Potential Benefits of the Proposed Research to the Subjects and Others
Subjects will benefit by receiving medication at no cost during the duration of time on study treatment (28 weeks) and daily monitoring of signs and symptoms of depression and suicide (approximately 7 months).

In case participants do suffer a relapse or side effect from change in formulations, their bupropion pharmacokinetics will be examined to determine bioequivalence. If it can be determined that clinical worsening was attributable to a non-bioequivalent switch, this information will be provided to the patient and their treating physician. The patient and their treating physician will also be informed of the bupropion XL formulation associated with clinical worsening. Such participants would benefit from learning which bupropion products are less tolerated or ineffective for them.

Society will benefit from a better understanding of the quality, bioequivalence and therapeutic equivalence of bupropion 300mg XL products.

4.4.1 Why Risks to Subjects Are Reasonable in Relation to Anticipated Benefits to Subjects
In general, the risks to research subjects in this protocol are probably small and not different than the usual manner in which generic-generic switches occur. There will be no change to the subject's prescribed medication. There is a small potential for clinical ineffectiveness, or new or worsening side effects, due to non-bioequivalence, but in such cases participants will benefit from acquiring the knowledge of which bupropion forms are non-equivalent for them. The overall anticipated benefit to society is improved bupropion 300mg XL dosing guidelines in treatment of depression. These potential benefits are substantial in comparison to the potential risks, hence the risks to subjects are reasonable in relationship to the anticipated benefits.

4.5 Subject Compensation

Subjects are compensated for participation. A subject will receive $150 for completing the 4 week lead-in, and $250 for completing each of four 6-week drug evaluation periods (up to $1150). If they complete the entire protocol they will receive an additional $850. Maximum total compensation is therefore $2000. If a subject stops participating before the entire protocol is completed, they will receive the prorated amount for the number of sessions completed.

4.6 Importance of the Knowledge to be Gained

More than 3 billion generic drug prescriptions are filled annually in the US, and generic medicines save consumers and the U.S. healthcare system $190 billion annually. Generic drugs are usually only approved after demonstration of bioequivalence to the innovator (branded) drug. Bupropion is taken by more than 1 million Americans annually. One generic formulation of bupropion was recently found to be non-bioequivalent and withdrawn from the market. It is important that the bioequivalence of other bupropion 300mg XL products be assessed and verified.

4.7 Inclusion of Women

There is no exclusion of any sex/gender or racial/ethnic group for these studies. Studies and their advertisements actively encourage the participation of women in the research. The study goal is equivalent numbers of women and men. To ensure sufficient enrollment of both sexes, enrollment is typically closed once a sex quota is reached. Women of childbearing potential are not excluded. Bupropion is not contraindicated during pregnancy (http://www.womensmentalhealth.org/use-of-wellbutrin-bupropion-during-pregnancy/).[52,53] Subjects will be advised to follow the instructions of their bupropion-prescribing physician regarding pregnancy or pregnancy planning, and, per drug label, to inform the investigators and their treating physician if they become pregnant or intend to become pregnant during the course of the study.

4.8 Inclusion of Minorities

Studies and their advertisements actively encourage the participation of minorities in the research. Minority recruiting typically matches the demographic composition of the Washington University community from which subjects will be recruited (44% white, 51% Black, 2% Asian, 2% Hispanic).

4.9 Inclusion of Children

Subjects <18 yr will not be studied in these investigations.

4.10 Clincaltrials.gov requirements

The proposed research will be registered in ClinicalTrials.gov once the protocol has been reviewed and approved by the FDA RIHSC.

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Bioequivalence and clinical effects of generic and brand bupropion: Study Table

		Pre-randomlzation (4 weeks)	Randomization Study Period (24 weeks)									Entire Study	Post Study
			Study Drug 1 (6 wks)		Study Drug 2 (6 wks)		Study Drug 3 (6 wks)		Study Drug 4 (6 weeks)				
Procedure	**Phone Screen**	**Initial clinic Lead-in Visit 0**	**Randomization Visit 1**	**PK Session 1**	**Study clinic Visit 2**	**PK Session 2**	**Study clinic Visit 3**	**PK Session 3**	**Study clinic Visit 4**	**PK Session 4**	**Close-out Clinic Visit 5**		
Subject visit		1	2	3	4	5	6	7	8	9	10		
Subject contacts investigators. Telephone description of study purpose, procedures, benefits, risks. Screen potential eligibility. (E)mail informed consent doc to subject. Subject contacts investigators if interested	X												
Review study purpose, procedures, benefits, risks. Provide detailed orien-tation to study procedures (daily smart phone assessments, medications)		X											
Informed consent		X											
Structured Clinical Interview for DSM-IV Axis I Disorder (SCID) (as needed)		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
MADRS -Symptoms of depression questionnaire		X	X	X	X	X	X	X	X	X	X		
ASEC checklist (side effects)		X	X	X	X	X	X	X	X	X	X		
Training: Daily smart phone assessments and MEMS 6 TrackCap use		X											
Determine and confirm eligibility		X											
Replace subject's current bupropion product with same product, over-encapsulated (4 wk supply)		X											
Randomization			X										
Subject starts new crossover bupropion study drug			X		X		X		X				
Provide over-encapsulated study drug(3 wk supply)			X	X	X	X	X	X	X	X			
Download MEMS compliance data			X	X	X	X	X	X	X	X			
Review smart phone, download data (if required)			X	X	X	X	X	X	X	X	X		
DNA sample (blood)				X									
24 hour PK session, venous sampling (~15 samples, 75ml)				X		X		X		X			
24 hour urine collection				X		X		X		X			
Reinstruct subjects to all study related procedures			X	X	X	X	X	X	X	X	X		
Subject performs daily smart phone-based assessments												X	
Capture drug compliance and adherence (MEMS 6 TrackCap)												X	
Occasional phone calls if warranted												X	
24 access via pager to Research Team and Research MD												X	
Return subjects' original bupropion medication											X		
Remuneration for study participation (and completion)			X		X		X		X		X		
Collect all study equipment (phone, MEMS 6 TrackCap)											X		
30 day telephone follow-up													X