Equivalence Among Antiepileptic Drug Generic and Brand Products in People with Epilepsy: Single-Dose 6-Period Replicate Design
(EQUIGEN Single-Dose Study)

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Protocol Synopsis

Subject: Bioequivalence of antiepileptic drugs

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Estimated Duration of Study: Two years

Subjects of Study:

<table>
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<tr>
<th>Number of Subjects</th>
<th>Sex</th>
<th>Age Range</th>
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<tr>
<td>54</td>
<td>M/F</td>
<td>&gt; 18 years</td>
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Project uses ionizing radiation: X

Project involves use of Durable Power of Attorney: X

Multi-Institutional Project: X
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1.0 **Background and Significance**

Generic drug substitution saved the American public more than $734 Billion from 1999-2008 with savings of approximately $121 Billion in 2008 alone.\(^1\) The data available to the United States Food and Drug Administration (FDA) supports bioequivalence of approved brand and generic drugs and suggest that generic anti-epileptic drugs (AEDs) can be safely interchanged with the brand product or other generic products. In the case of epilepsy, however, professional and patient support organizations around the world have expressed concerns about safety and efficacy with indiscriminate generic product substitution. These concerns are based on case reports and claims database analyses. These organizations have issued position statements stating that generic AED variability can be problematic for some people with epilepsy.\(^2\) Published reviews suggest that extra caution may be needed for patients at highest risk of seizure complications, such as pregnant patients, patients with recurrent status epilepticus, or patients who have been seizure-free for long periods of time and are driving. These authors argue that the total risks and benefits of generic substitution may not be fully understood.\(^3\) There is clearly a level of concern and debate in the epilepsy medical community to motivate resolution of this controversy.

The FDA uses two pharmacokinetic measures, the area-under-the-drug concentration-time curve (AUC) and the maximum drug concentration (C\(_{\text{max}}\)), to determine *in vivo* bioequivalence in the Abbreviated New Drug Application (ANDA) process. Using a two-period, order-randomized, pharmacokinetic study, equivalence is established when the 90% confidence interval of the log-transformed ratio of the test (typically generic) to reference (typically brand) products for the AUC (both the measured AUC to time of last blood sample and the calculated AUC to time infinity) and C\(_{\text{max}}\) fall within an 80% to 125% range. The average bioequivalence (ABE) pharmacokinetic testing is typically performed using a single dose in 24 to 36 healthy adults.

The FDA has published three studies quantifying the differences between generic and brand products. In 1987 they reported that the average difference between the reference and generic mean AUCs was 3.5% in 224 approved drugs.\(^4\) In 1997 they reported that the average differences between the reference and the generic means were 3.47% for the AUC (standard deviation of 2.8) and 4.3% for the C\(_{\text{max}}\) (standard deviation of 3.7) in 127 drugs. In 2009 they reported that the average difference in mean C\(_{\text{max}}\) was 4.35%
and mean AUC was 3.56% in 2070 ABE studies submitted to the FDA from 1996-2007. In the 1986 study, there were 13 drugs (6%) that had a mean AUC difference of 10% or greater and in the 2009 study, 2.4% of the drugs had a mean AUC difference of more than 10% from the reference mean AUC.

Therapeutic equivalence and bioequivalence are closely related, but differ in important respects. That difference may prove to be part of the controversy regarding the efficacy and adverse effects of generic AEDs. Bioequivalence implies that the reference and generic drug produce comparable plasma concentrations over time and is assessed by determining if selected pharmacokinetic parameters are similar. Therapeutic equivalence implies that the reference and generic drugs provide equal therapeutic effect and requires evidence of equivalent efficacy and tolerability. For example, in the case of epilepsy treatment, therapeutic equivalence means a generic and corresponding brand AED product will be identical in controlling seizures and avoiding adverse effects at the same dose. Therapeutic equivalence is not directly measured in the ANDA process, but is presumed by the FDA if the products meet FDA standards for bioequivalence. The study outlined below is designed to test bioequivalence. Prospective tests of therapeutic equivalence will await future study.

It is important to consider that a switch from one generic product to another could produce even more variation in \( C_{\text{max}} \) and AUC compared to a brand to generic product switch. In clinical practice, the switch from one generic product to another is common because pharmacies often dispense different generic products to patients at the time of prescription refills. In most cases, 5 or more different companies manufacture generic versions of the currently available AEDs.

Many health care providers, patient support organizations, and professional organizations believe that people with epilepsy have an unacceptable incidence of seizures or adverse effects when switching to generic products. Approximately half of responding neurologists in both a United States and a German-Austrian-Swiss group reported patient problems when switching from a brand name to a generic product. Case reports document problems related to generic AED substitution in individual patients. The FDA has received many reports of suspected generic inequivalence of AED products via their MedWatch voluntary reporting system, but note that the reports
are not sufficiently detailed to exclude other possible causes of seizures or adverse effects. Two Canadian studies in 2007 and 2008 demonstrated that switchback rates from generic to brand are 5-10 times higher for AEDs than other classes of medications.\textsuperscript{9, 10} In one of these studies, investigators analyzed health care utilization data and found significantly higher numbers of outpatient visits and mean length of hospital stays in people on generic AEDs compared to those on brand.\textsuperscript{10} In a 2007 United States case-controlled database analysis of healthcare for 12-64 year olds with epilepsy and AED product changes, there was an 81% greater probability of an AED product switch compared to controls in those that had ambulance or emergency room care.\textsuperscript{11} Similarly, in two other recent claims database studies, the odds of an epilepsy-related event was 1.57 (adjusted)\textsuperscript{20} and 1.84\textsuperscript{21} higher for those that switched AED products. All three of these database studies met significance at their respective 95% confidence intervals. In contrast, another recent database trial reported an adjusted odds ratio of 1.08 (95% CI: 0.91-1.29) indicating that the absence of an effect of switching AED products on epilepsy-related events could not be ruled out.\textsuperscript{22}

In a direct test of bioequivalence, Olling et al.\textsuperscript{15} found statistically significant differences in one or more pharmacokinetic parameters in 2 of 3 carbamazepine generic products compared to the brand product. Ficker, et al.,\textsuperscript{12} found clinically important differences in adverse effects, quality of life, and seizure control in an open label trial comparing immediate release to sustained release formulations of carbamazepine, indicating that modest differences in pharmacokinetic parameters (expected in that study) could produce clinically relevant differences in efficacy and tolerability. The differences in the Ficker, et al., study favored the extended release formulation suggesting that $C_{\text{max}}$ differences of a magnitude predicted to be seen with generic product changes may be clinically important. In contrast, Oles, et al.\textsuperscript{13} compared brand Tegretol and a single generic product of carbamazepine (Epitol) and found no statistically significant difference in AUC or $C_{\text{max}}$, although mean time to $C_{\text{max}}$ occurred earlier with Epitol. In a study of 9 subjects that reported problems with switching to generic lamotrigine, Nielsen, et al., determined that 5 of the subjects had differences in pharmacokinetic parameters of more than 10% in the direction consistent with the reported adverse effect.\textsuperscript{24} These discrepant findings in small studies highlight the need for a larger study. Carefully studying a population of people with epilepsy is more likely to reveal if switching among products has or does not have a clinical effect.
If there truly is bioequivalence and therapeutic equivalence among brand and approved generic products, why would health care providers and patients report so many problems? A nocebo effect (i.e., negative symptoms from an inert treatment) involving generic substitutions might be involved. If patients are warned by caregivers or other medical information sources that generic products may be less effective than the brand name product, patients may complain of adverse effects more often. They may be more attentive to adverse effects, more diligent about counting or reporting seizures, or may be more apt to attribute an unrelated or coincidental symptom to the generic substitution. In epilepsy clinical trials, placebo groups often experience changes in seizure frequency or adverse effects compared to baseline. Lack of sleep and self-reported stress and anxiety levels were associated with seizure occurrence in a study by Haut et al.\textsuperscript{14} It is conceivable that a person with epilepsy who believes that he or she is receiving a less effective generic product could experience anxiety and stress leading to a seizure or adverse effect. In this situation, the seizure or adverse effect could be due to the generic switch but unrelated to a shift in bioequivalence or therapeutic equivalence.

Other factors that may contribute to variations in AED effects include lot-to-lot differences attributable to manufacturing processes and natural biological variations. Biological variations are presumed to have similar effects regardless of the product the person is taking (brand or any of the generics) and lot-to-lot differences are covered by the same standards, governed by the USP, for both brand and generics. However, the magnitude of variation in daily use of AEDs, brand or generic, is not well described. Thus, a replicate design is planned to enable us to determine variations over time in the pharmacokinetics for the brand product within each subject (intra-subject variances and subject-by-formulation interaction). Establishing the amount of variation from these factors for the brand product is important for understanding how much variation among generic products is acceptable. That is, if there is a wide variation in the in vivo pharmacokinetic measures from a replicate study of the brand product, then similar wide variations among generic products should be acceptable. In contrast, if the differences in a replicate study of the brand product are small, especially if two different lots are tested, then wider variations among generics may be unacceptable.
The study proposed in this protocol will determine if bioequivalence testing performed for the FDA translates into similar bioequivalence in a population of people with epilepsy when switching among different generics of the AED. Based on a variety of pharmacokinetic data and clinical reports of concern, the example AED used for this study will be lamotrigine (LTG).

In this single dose study, people with epilepsy taking AEDs, but not currently taking the test medication, lamotrigine, will be studied. We will use an order-randomized three-sequence six-period replicate design with the two most disparate generics studied in two replicate periods each and the brand (reference) product studied in two additional periods. A standard single dose of the test drug (lamotrigine 25mg) will be administered under controlled conditions (fasting with subsequent standardized meals) with a 12-hour in-facility blood sample collection followed by a collection every 24 hours for a total of a 96 hour sample collection that will be used to establish the pharmacokinetic measures of Cmax, AUC\textsubscript{96} and AUC\textsubscript{∞}. Each period will be separated by at least a 12 day washout interval.

The replicate studies will be used to determine the intra-individual variability of the pharmacokinetic responses of the brand and the two generic products, as well as subject-by-formulation interaction variances. The data will also be used to calculate simultaneously all parameters that are needed to compare the 3 products in average and individual bioequivalence and outlier analyses. The differences between the disparate generics will be used to establish if the current standards translate to equivalence within the limits of the brand intra-subject variation.

The factors we will use to determine the most disparate generics include the results from the \textit{in vivo} data from the ABE studies submitted to the FDA in the ANDA and \textit{in vitro} chemical assay (potency) and dissolution data performed on several currently available lots. The intent is to study the specific lot of the generic product predicted to result in the lowest levels and compare it to the specific lot from another generic product predicted to result in the highest levels. Similarly, if multiple lots of the brand products are available, we will perform \textit{in vitro} testing to establish the most desirable lot to study.
Factors that alter metabolism, including concomitant AEDs that may have hepatic enzyme induction effects will be tracked but not excluded, as long as the dose remains constant, as the goal is to reproduce the ‘real life’ situation as closely as possible within the practical limits of funding and study size. Subjects receiving valproate as concomitant medication will be excluded because the prolongation of half life would not allow LTG to reliably be completely cleared by 13 days. The criteria that establish an enriched population will also be tracked and used in a secondary analysis, but will not be used as an inclusion requirement. The enriched population is defined as people who experienced an otherwise unexplained increase in seizures or adverse effects, or a substantial change in AED level after a switch in AED products.

The discovery of any subject-by-formulation interaction outliers (i.e. subjects with differential pharmacokinetic reactions to a pair of formulations) will raise considerable concerns about equivalence. Recently established methods in the statistical analysis of outliers in crossover studies will be used to determine if any outliers are present.26

A chronic dose study protocol accompanies this protocol. Depending on the results of these studies, future studies may include: 1) similar protocols evaluating other AEDs; 2) prospective designs directly testing therapeutic equivalence; 3) a blinded design with small AED dose increments in subjects on a clinically maximized dose of the AED to determine tolerable range variations; and 4) specific testing of a highly enriched population with subjects carefully chosen to be most likely to show product inequivalence.
2.0 Objectives
This investigator initiated study will evaluate the bioequivalence of brand and disparate generic AED products in a population of people with epilepsy. We will determine if disparate generic lamotrigine products as defined by single dose average bioequivalence studies, *in vitro* analyses, and tablet composition, are bioequivalent when dosed in people with epilepsy. The study will compare pharmacokinetic parameters measured after a single dose using a sequence-randomized 3-sequence 6-period design with subjects and site personnel blind to which is the predicted high and which is the predicted low generic product.

2.1. Primary Objectives

a. To determine if $C_{\text{max}}$ or AUC are significantly different in the high generic product compared to the low generic product taking one as the reference and the other as the test product. Bioequivalence will be established per the current FDA ABE criteria if the 90% confidence interval of the geometric mean of $C_{\text{max}}$ and AUC for the high generic product compared to the low generic product are entirely within the 80%-125% range using the two one-sided standard analyses (Figure 1B). If the confidence interval contains the 125% upper or 80% lower limit for either the $C_{\text{max}}$ or AUC, the result indicates that the two products should not be considered bioequivalent (Figure 1D). If the lower limit of the confidence interval exceeds the 125% upper limit or the upper limit is below the 80% lower range for either the $C_{\text{max}}$ or AUC (Figure 1C), the products will be considered to be bio-inequivalent.

b. To measure the intra-subject variances of the investigated reference (brand) and generic products, as well as subject-by-interaction variances, by using two replicate periods for the brand and two replicate periods for each generic product. These estimated variances will be used to investigate individual bioequivalence and detect subject-by-formulation interaction outliers.26
c. To examine individual bioequivalence by comparing the brand to each of the two generic products. Individual bioequivalence (IBE) will be determined using the FDA 2001 guidance criteria.

Figure 1: Comparison of brand and generic products

**BASELINE VS. SWITCHED PRODUCT COMPARISON (90% CI)**

<table>
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<th>A. FDA RANGE FOR ABE</th>
<th>B. EQUIVALENT</th>
<th>C. INEQUIVALENT</th>
<th>D. INDETERMINATE</th>
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The figure illustrates the 90% confidence interval (CI) range (80-125%) of the log-transformed data around the reference (brand) product used by the FDA to assess bioequivalence in ABE studies (row A). A generic product with 90% CI falling completely within the permitted range is considered equivalent (row B). A generic product with 90% CI completely outside the range, either higher or lower, is considered inequivalent (row C). A generic product with 90% CI that partially overlaps, or completely overlaps the range is considered to be indeterminate as to equivalence (row D). A generic manufacturer must submit bioequivalence data to the FDA that falls completely within the range (as in row B) to receive approval for marketing. Both C and D suggest lack of evidence for a bioequivalence claim.
2.2. Secondary Objectives

2. To determine the number of subjects who are outliers and to identify these subjects for potential further study. Any subject that meets the following outlier criteria will raise the concern of product inequivalence between two of the investigated products: the absolute value of the studentized residual corresponding to the linear contrast reflecting subject-by-formulation interaction is greater than or equal to 3. A subject satisfying this criterion will be considered to have a reaction to one formulation that is significantly different to his/her reaction to the other formulation. Studentized residuals will be computed separately for $C_{\text{max}}$ and AUC.

3. To compare the brand/generic and generic1/generic2 ratios for $C_{\text{max}}$ and AUC by the following subgroups:
   a. Subjects on a concomitant enzyme inducing AED compared to subjects not on a concomitant enzyme inducing AED.
   b. Male subjects compared to female subjects.
   c. Enriched population – segregated by predicted high and low groups.
   d. Age.

4. To determine if the brand/generic and generic1/generic2 ratios for $C_{\text{max}}$ and AUC meet the European bioequivalence standard and the recently proposed scaled bioequivalence standard.
3.0 Study Design

The EQUIGEN-Single Dose Study is a prospective, multi-center, masked, cross-over, sequence-randomized, 3-sequence 6-period single-dose pharmacokinetic trial in people with epilepsy on concomitant AEDs (Figure 2). Each subject will be administered each of the 3 products of a single AED (the brand and its two most disparate generics) twice giving a total of 6 different study periods. Each subject will be randomized to one of the three sequences where G1 and G2 represent the two generics and B the brand:

1. G1-G2-B-G1-B-G2
2. G2-B-G1-G2-G1-B
3. B-G1-G2-B-G2-G1

With 45 subjects completing the 6 periods, the power for rejecting the null hypothesis of non-bioequivalence between two products is 90% (SAS program available upon request). We plan to recruit 20% more subjects, 54, to allow for dropouts. If one-half of the 54 subjects withdraw from the study after the 3rd period (and the rest complete all 6 periods), the power will be 87%. The number of subjects recruited at each site will be a multiple of 3 to achieve sequence balance across recruiting sites. We plan to replace subjects who withdraw from the study without providing valid data from the initial three periods.

The statistical analysis follows from the 2001 FDA Guidance for Industry on Statistical Approaches to Establishing Bioequivalence. The sequence orders were selected based on the guidance criteria (Appendix B of the guidance) and modified based on the discussion of the EQUIGEN-2 Committee with the FDA at a meeting on 10/11/2011. Advantages of the sequence order include:

1. Each period has all 3 products represented, which will allow separation of period from formulation effects in statistical analyses.
2. No repeats in consecutive periods.
3. All three products are tested once in each sequence during the first 3 periods, providing for usable data if subjects withdraw from the study after the third
period. These data can be used in the ABE brand-generic and generic-to-generic analyses.

4 Replicate administrations of the 3 products will provide full information for performing all planned IBE and outlier analyses.

5 Statistical data analysis may be performed by fitting only one random-effects linear model that will provide simultaneously all means and variances needed to perform all planned ABE, IBE and outlier analyses (this guarantees a greater statistical efficiency than conducting separate 2-sequence 4-period crossover studies of comparable sample sizes).

6 The other possible 3-sequence alternatives that meet the above criteria are statistically equivalent to the above 3-sequence design.

3.1. Duration of Participation and Follow-up
Subjects completing the study will be followed after initiation of the study typically for 105 days (7+6x14+14) with a minimum of 86 days (2+6x12+12) and a maximum of 207 days (30+7x23+16) by trained site physicians and research coordinators.

3.2. Study Overview
Qualified subjects will be screened and upon fulfilling inclusion/exclusion criteria and signing the informed consent will be enrolled in the study and enter the randomization phase (2-30 days). Subjects will be randomized according to a sealed allocation list that will be balanced for sequence and provided to each site prior to the first subject enrollment. Subjects that withdraw prior to completing the third period will be replaced in a randomized manner. The randomization list will be generated by the study statistical group. There are six test periods in three sequences for a sequence-randomized study. During two test periods subjects will receive a single dose of the brand AED and during the other four test periods subjects will receive a single dose from one of the two investigated generics (each twice). The single doses will be administered in the fasting state during an in-facility 12-hour pharmacokinetic session to collect samples to determine Cmax and AUCs. Four additional samples will be drawn at 24, 48, 72, and 96 hours after the dose as an outpatient (making each pharmacokinetic test last for 4 days). Each in-facility pharmacokinetic testing will be separated by a 12-23 day washout period; consistent washout periods of 14 days will be preferred. A final follow-up phone evaluation will be conducted 12-16 days (target 14 days) after the last dose. During the
study the subjects will continue their usual concomitant medications, including AEDs, without change.

We will compare the AED levels as measured by $C_{\text{max}}$ and AUC in each group using average bioequivalence (ABE) and individual bioequivalence (IBE) criteria. Average bioequivalence will be established if the 90% confidence intervals of the geometric mean of $C_{\text{max}}$ and AUCs for the most disparate generic products compared to each other are entirely within the 80%-125% range (the FDA criteria for bioequivalence) using the two one-sided standard analyses. Otherwise the products will be considered to not be bioequivalent. Similarly, the products will be considered to not be bioequivalent if the criteria for IBE for each generic product compared to the brand product are not met.

Study Population: Approximately 54 subjects (45 subjects to completion).

Number of centers: 5-6 sites

Duration of study: Approximately 2 years.
4.0 Selection and Withdrawal of Study Subjects

4.1. Inclusion Criteria

Eligible subjects must satisfy the criteria below at the time of enrollment:

1. 18 years or older.
2. BMI not less than 18.5 and weight not less than 110 pounds.
3. Not donated blood within the past 56 days before the first pharmacokinetic testing.
4. Agrees not to donate blood at any time during the trial and for 56 days after the final PK in-facility admission.
5. Has epilepsy for at least one year based on site PIs assessment.
6. Taking at least one AED, which is not the study medication (lamotrigine).
7. No changes in AED regimen for at least 28 days prior to first pharmacokinetic testing.
8. Have the ability to understand the informed consent form and be willing to provide informed consent.
9. Willing to remain on same AED regimen through entire study. Subjects will be responsible to supply all of their concomitant medications (except for the study medication, lamotrigine).
10. Willing to stay approximately 14 hours in the research facility on six separate occasions for pharmacokinetic testing.
11. Willing to fast overnight and the morning of each of the six pharmacokinetic testing sessions.
12. Willing to have at least 23 blood samples collected during the pharmacokinetic testing including the in-facility session and each of the following four mornings for 96 hours post the study medication dose to complete the sample collection for each of the 6 periods. The in-facility blood collections will mainly be performed using an inserted catheter. In the event of difficulty with the catheter, samples may be drawn by venipuncture. The outpatient collections will be drawn by venipuncture. The total amount of blood during each PK session will be equal to about 14 teaspoons (66.5 milliliters). The total amount of blood drawn throughout the entire study will be about 96 teaspoons (478.5 milliliters) or less. For reference, this amount is approximately equal to the quantity of blood drawn during a standard blood donation by the Red Cross.
13. Willing to completely abstain from alcohol consumption for at least 24 hours prior to each pharmacokinetic testing admission until after the last sample is drawn for each period (~96 hours after the initial dose at each pharmacokinetic admission). We encourage no or minimal alcohol use throughout the study, but alcohol is not restricted at other times.

14. Willing to remain on a consistent regimen of concomitant medications including over-the-counter drugs and herbal drugs, if they are being used and deemed to possibly affect the metabolism of the study medication.

15. Willing to not eat grapefruit or drink grapefruit juice through the duration of the study.

16. If a tobacco user, willing to continue with the same pattern of tobacco use, except that no tobacco use is permitted during the PK facility admissions of approximately 14 hours (includes all tobacco products).

17. Willing to complete the subject diary as outlined in the protocol.

18. Willing to adhere to all other protocol requirements as outlined in the informed consent document.

19. Females must be either of non-childbearing potential (defined as having undergone surgical sterilization or postmenopausal (greater than 50 years old and amenorrhea for greater than or equal to 12 months) or must be using at least one acceptable method of contraception as follows:
   a. Double-barrier method (e.g. condom plus spermicide, condom plus diaphragm with spermicide)
   b. Hormonal contraceptive treatment (progesterone only agents – use of any agents containing estrogen are an exclusion for the lamotrigine testing)
   c. Intrauterine Device (IUD)
   d. Monogamous relationship with a vasectomized partner
   e. Abstinent for 8 weeks prior to and throughout the study.

20. Subject must be at least 28 days from last participation in any other study.

4.2. Exclusion Criteria

1. Progressive CNS disorder that could influence adverse effects or seizure control.

2. Known medication non-adherence. Non-adherence is assessed by the investigator based on the procedures defined in the manual of procedures.
3. Taking the study medication (lamotrigine) within 28 days of enrollment.
4. Use of valproate (as divalproex sodium or valproic acid), any form of estrogens, rifampin, orlistat, felbamate or sertraline within 28 days of study entry.
5. Subject has a history of alcohol or substance abuse within 1 year prior to screening for study participation, or is currently using alcohol, drugs of abuse, or any prescribed or over-the-counter medication in a manner, which, in the opinion of the Investigator, indicates abuse.
6. History of psychogenic seizures within the past 2 years.
7. Any clinically significant psychiatric illness or psychological or behavioral problem which, in the opinion of the investigator, could interfere with the subject being able to participate in the study or comply with the study requirements.
8. Any clinically significant laboratory abnormality or illness which, in the opinion of the investigator, could interfere with the conducting or interpretation of the study or put the subject at risk.
9. History of allergic reaction with past use of the study medication (lamotrigine).
10. More than two allergic reactions (actual allergy, not medication intolerance) to an AED or one serious hypersensitivity reaction to an AED.
11. History of adverse effect associated with past use of the study medication (lamotrigine) which, in the opinion of the investigator, could pose substantial risk to the subject if it occurred during the trial.
12. Pregnant or lactating within 56 days of enrollment.
13. Unstable seizure control that makes AED changes likely during the course of the study.
14. Use of rescue AEDs (e.g. benzodiazepines) during more than two weeks of the 2 months prior to enrollment.
15. Subject is in the process of quitting smoking within 28 days of study entry or plans to quit smoking during the period of time the study will be conducted.

4.3. Subject Withdrawal

In accordance with the Declaration of Helsinki and the Code of Federal Regulations pertaining to clinical research practices, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. Subjects in this protocol are free to withdraw at any time
without penalty or prohibition from enrolling in other FDA protocols. Regardless of the subject’s ability to maintain adherence with the study medication regimen, follow-up will be continued per protocol for at least two weeks following randomization unless subject consent is withdrawn.

A subject will be withdrawn from the protocol if any of the following occur during the study:

- Any life-threatening adverse effect
- Any adverse effect associated with the study medication that, in the opinion of the investigator, represents a serious risk to the subject
- Pregnancy
- A modification of concomitant therapy (including over the counter and herbal medications) that could significantly alter the pharmacokinetic properties of the study medication
- Suspected non-adherence to the protocol including the medication regimen and completion of the subject diary.
- Subject decides to stop treatment for any reason

In addition, a subject will be withdrawn if seizure pattern changes in any of the following ways:

a) Status Epilepticus

b) One or more tonic clonic seizures when the subject has not experienced this seizure type before

c) An increase in the number of seizures per day or per month that in the opinion of the investigator indicates a substantial and problematic worsening of seizure frequency
5.0 Study Therapy

5.1. Determining the most disparate products:

Establishing the most disparate products is not trivial. We will use a three step process. In the first step, the ABE data submitted by the generic manufacturers in the ANDA will be used to identify manufacturers of disparate generics. This process was completed separately by the study steering committee (see below) and the FDA (Appendix 4). In the second step, all or most of the commercially available lots with adequate expiration dates and quantities from each of the selected products will be analyzed with in vitro testing including chemical assay (potency) and dissolution. In the third step, if there are two or more products that are close at either end from step 2, the excipients of these will be examined and used as a ‘tiebreaker’ such that the final choice of the most disparate products will be selected as those having different excipients, as appropriate. Thus, the products used for this study will be selected as those predicted to be most disparate based on the excipient content of those identified from the in vitro data selected from the group narrowed by the ANDA ABE data. All of these decisions will be made by consensus or, if necessary, majority vote of a committee consisting of the PharmDs on the Steering committee and a representative from the FDA.

Step 1 - Selecting low and high products based on ANDA ABE data.

Bioequivalence study data: The ANDA average bioequivalence data were obtained for approved generic AED products from the FDA Center for Drug Evaluation and Research (CDER), Office of Generic Drugs. Separate fasting and fed bioequivalence studies were performed for most generic products. Key data for test and reference products were the geometric mean ratios (GMRs) and their 90% confidence interval (CI) for the maximum concentration (Cmax) and for the area under the plasma concentration time curve (AUC).

The ANDA ABE data for AUC and Cmax in the fasting state (Appendixes 2 and 3) were scrutinized by the study steering committee on 5 May 2011 (Members MP, MJB, GK, JC, TW, and BG) and the following manufactures were selected as candidates for most disparate:
Products (with ANDA number) selected for Step 2:
Lamotrigine:

Predicted low: 1-Mylan 76630; 2-Apotec 78625
Predicted high: 1-Roxane 77392; 2-Zydus 77633; 3-Aurobindo 78956; 4-Taro 79204 & 78525

Separately, the FDA completed a similar process that included examination of the excipients (see Appendix 4). The study steering committee will meet to determine which products to use for Step 2.

**Step 2** – Use of *in vitro* chemical assay (potency) and dissolution data to determine the most disparate lots:

The lot from the low group with the lowest potency and slowest dissolution will be selected at the low end as determined by the study steering committee. The lot with the highest potency and most rapid dissolution will be selected for the high end as determined by the study steering committee. Where the potency and dissolution data conflict, the steering committee will examine the data to select the most disparate lots for the *in vivo* study.

**Step 3** – If there are two or more products that are close at either end from step 2, the excipients of these products will be examined and used as a ‘tiebreaker’ such that the final choice of the most disparate products will be selected as those having different excipients, as appropriate.

Selection of lots for the study:

Ultimately the intent is to study the specific lot of the generic product predicted to result in the lowest levels and compare it to the specific lot from another generic product predicted to result in the highest levels.
5.2. Study Medication Supply

Drug will be purchased from available lots of the products selected using the ABE ANDA data that meet the following criteria:

1. Purchased in commercial market without knowledge of the manufacturer
2. The entire study will be completed (including the \textit{in vivo} portion) before the purchase product reaches its expiration date, which will be required to be at least 1.0 year from purchase.
3. In the event the expiry date needs to be exceeded due to inadequate number of subjects completing the study prior to the shelf-life indicated expiry date, stability testing will be performed on the products. With the original purchase of product for the \textit{in vivo} portion, extra supplies will be purchased and stored under standard stability conditions for this possible stability testing. In the event that standard stability testing criteria are not met to permit ongoing use of the original purchased product, which is the preference in this circumstance, then product from corresponding lots will be purchased at the time of expiry and undergo \textit{in vitro} analysis to identify an equivalent product to the original selected study product for continuation of the study.
4. As many lots as possible will be purchased up to the number that resources are available to perform the \textit{in vitro} testing (planned 6 different manufacturers with 2 lots each for each of the low and high ABE predicted generics and estimated 5 lots of the brand Lamictal – giving ~17 total purchased bottles).
5. This initial purchase will be of an adequate amount of product (from each available lot) to complete the \textit{in vitro} study (anticipated one bottle of 100 tablets):
   a. We will perform at least 3 separate \textit{in vitro} tests per lot (chemical assay-potency, dissolution, impurity-content uniformity)
      i. each \textit{in vitro} test requires at least 12 tablets
      ii. duplicate for repeat testing if deemed necessary - estimate ~100 tablets required for \textit{in vitro} testing
   b. Calculations for the total tablet supply for the single dose study using 25 mg tablet size:
      i. \textit{in vivo} study: 54 subjects x 2 periods each gives 108 tablets divided by 4-6 sites. On average 18-22 tablets will be needed
per site with an approximate maximum of 36 (anticipated maximum 18 subjects at a single site). Since the products are sold in bottles of 100 tablets, we will purchase one bottle of each of the products selected for the *in vivo* study for up to 6 sites with 2 additional bottles purchased for storage for possible stability testing for 8 bottles per product (2 generics and 1 brand totals 24 bottles) purchased at the time of product selection after the *in vitro* testing is completed.

ii. *in vitro* testing: ~ 100 tablets will be needed for each lot (estimated above).

iii. The preference is to purchase bottles with 100 tablets of each of the lots selected for *in vitro* testing.

1. Purchasing the full number of tablets potentially needed for the complete study from all of the lots selected for *in vitro* testing was deemed wasteful and expensive given the increased number of study sites. Thus, the full quantity of tablets needed for the *in vivo* portion will not be purchased until the 3 study products are selected after the *in vitro* testing is completed.

2. Note: this approach risks the possibility that the selected product will not be available. However, this risk is deemed small since only a small number of bottles are needed and the purchase for the *in vivo* portion should be within 1.5 months of the initial purchase for the *in vitro* testing.

iv. Final estimate: 41 bottles (17 for *in vitro* and 24 for *in vivo* study) of 100 tablets (total 4100 tablets) of 25 mg size of lamotrigine.

6. All products will be stored in standard conditions once purchased throughout the duration of the study.

7. There will be extra tablets that are not used in the study. The extra tablets will be used for additional *in vitro* testing or discarded at the end of the study.
5.3. Study Medication Acquisition

For this study all study generic and brand products will be commercial stock of single lots obtained from a reliable distributor or the manufacturer (without mention of the study) and distributed through a central pharmacy. Individual subjects will receive, as each study dose, lamotrigine 25 mg. Although the dose recommended by the FDA guidance for individual product testing is 50mg (2x25mg), see: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm, 25mg was selected as the dose for this study to minimize the risk of adverse events. The subjects will receive standard release formulations of generic lamotrigine 25mg from each of the two most disparate generics and brand Lamictal® 25mg as the products tested.

5.4. Product Packaging and Labeling

The central pharmacy will order in bulk and stock, using optimal storage methods, an adequate supply from a single lot of each of the most disparate generic products and the brand product adequate for the entire in vivo study and in vitro testing (see Section 5.2). The central pharmacy will supply the study medication to each site in a standard package labeled with study identifying information. The labels will include the study name, medication name, Brand, Generic 1 or Generic 2, site name and date dispensed. The central pharmacy will provide the study medication sets (supply of Brand, Generic 1, and Generic 2) to the site prior to the first subject’s PK in-facility admission. The site will store the study medication packages in a secure location in an appropriate environment. At the end of the study, the site will count any unused doses and return these tablets to a central location for later access if necessary.

In the event a site runs out of tablets for a period (usage plus wastage), the site will request additional supply from the central pharmacy.
5.5. Product Storage and Stability

All study medications will be stored in a suitable environment to assure product stability throughout the trial. Since the study medications are approved drugs for treatment of epilepsy, storage requirements will be consistent with the instructions specified within the package inserts. All study medications will be stored at study sites in a cool, dry facility that is not subject to excessive light or heat. The study medications will be stored in a locked facility with access limited to authorized study staff.

5.6. Preparation, Administration and Dosage of Investigational Product

Adequate quantities of the bulk product will be obtained from each product manufacturer to ensure that a single lot is used to supply all periods for each product in each individual subject (see Section 5.2). At the onset of the study, prior to the first subject’s first admission for the PK in-facility admission, the central pharmacy will send the site three bottles (generic 1, generic 2, and brand), appropriately labeled containing ~60 tablets in each bottle, sufficient to enroll ~25 subjects with up to 10 wasted doses. (Note the target enrollment for each site is 9 subjects). During the entire study, each subject will receive two tablets from each bottle (one in each of two periods). When the tablets are administered to the subject by the site personnel, the site personnel will confirm the tablet is taken from the correct bottle based on the bottle labeling and additionally confirmed by checking the specific imprints on the tablets.

5.7. Accountability Procedures for the Study Medications

Each site’s study coordinator, pharmacy, or responsible and appropriate designate, is responsible for the accountability of all used and unused study medication (including wastage). Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all study drug supplies received, dispensed to study subjects, and destroyed or returned to the central location.

At the end of the study, all drug supplies and documentation will be reviewed and verified by the coordinating center. The site will send all unused study drug supplies to
the central location. The drug accountability form must be completed and sent to the coordinating center for archiving.

5.8. Concomitant Medications

5.8.1. Concomitant AEDs
During the study, subjects will be required to take the same concomitant AED products at the same dose as was being taken at the time of enrollment into the study. Blood samples for testing the concentration of concomitant AEDs will be obtained at the enrollment visit.

5.8.2. Other Concomitant Medications
There should be no changes to any prescription medications, herbals supplements, or over-the-counter medications during the study unless determined to be acceptable by the Independent Medical Monitor. No new prescription medications, herbal supplements or over the counter medications should be taken during the study except for those medications appearing on the acceptable use list (available in the manual of procedures) or determined to be acceptable by the Independent Medical Monitor. If new medications are taken, the Steering Committee will determine if these medications will confound or invalidate the data from that subject.
6.0 **Study Procedures and Assessments**

Examinations and subject contact will follow the schedule and procedures listed in Figure 2 and Table 2 and as described below.

6.1. **Screening and Enrollment**

Potential subjects will be identified from the clinical practices of the principal investigators and their Department of Neurology clinical practices, which each have a large population of people with epilepsy. Prescreening with reviews of medical records to identify potential subjects will be performed as appropriate. If additional subjects are needed, the recruitment may expand to each of the sites’ entire institutional practice, which includes many general neurologists. If further recruitment is needed, efforts can be extended to community neurologists’ practices. Initially word-of-mouth, including providing information about the study to colleagues, will be used to identify subjects and with expectation that some subjects will be referred by colleagues. If recruitment is slow (e.g. less than one-half of the study population is recruited by 6 months after a site is initiated) and further recruitment efforts are needed, publicizing the study through community organizations and possibly through IRB-approved general advertising may be undertaken. All advertising materials will be submitted to each local IRB and the RIHSC for review before distribution. In addition, if sites do not meet recruitment goals, the study may be expanded to include additional sites.

Potentially eligible subjects will have the study requirements discussed and will be screened for eligibility by local study coordinators and investigators. An approved IRB consent form is given to each subject and written informed consent is obtained at the screening visit. Prior to possible subject signing, the informed consent is thoroughly reviewed with the subject by a member of the research team. Emphasis is placed on the rationale for the study, procedures and study visits, and risks. Simple language will be employed prior to and during the review of the consent form. Subjects are encouraged to read the consent form closely and obtain clarification on any aspect of the study. Subjects will be given an opportunity to have any questions answered by a member of the research team. Subjects that are willing to participate in the study will sign the consent form. A copy of the signed, dated, and witnessed consent form is given to the
subject. Subjects, after signing the informed consent form, enroll in the study on chronic stable doses of their concomitant medications.

The enrollment visit will include a physical and neurological exam performed at the site by the investigator. Blood samples will be obtained for AED concentrations, electrolytes, renal and liver function tests and a CBC. A urine pregnancy test will be obtained in women of childbearing potential. The blood samples will be collected by venipuncture and consist of 9 ml of blood and a urine sample. Enrollment labs that are outside of the normal range will be reviewed by the principal or associate investigator(s) to determine subject’s eligibility and the need for further medical care by the subject’s primary care physician.

If circumstances permit, the screening and enrollment visit may occur on the same day.

The Steering Committee will adjudicate subject eligibility for enrollment into the study if the site investigators have any concerns.

6.1.1. Medication Regimen Determination and Medication/Event/Seizure Diary
At the enrollment visit, subjects will be provided a medication/event/seizure diary to be brought to each visit. The medication/event/seizure diary will specify the specific concomitant medication dose times (individualized for each subject). The site will individualize the subject medication regimen schedule. The time(s) the subject habitually takes their concomitant medication should be replicated in the study. This information will be recorded in the subject's study diary.

It is important for each subject to take their concomitant medications in the same relationship to food as is their habit, throughout the study; the only exception will be at the time of study dose administration during the PK in-facility admission as this will be given in the fasting condition. Missed or late concomitant medications should be entered into the diary.

The medication/event/seizure diary should be completed by the subject (or subject’s caregiver) on every day that there is an adverse event, seizure, or if a dose of a concomitant medication is late or missed, as soon as it is recognized. The subject (or
subject’s caregiver) is to record all other relevant events in the diary including medical care (physician/NP/PA office visit, ED visit, or hospitalization), medication change, injury, etc… The subject diary will be reviewed by the site coordinator at each visit; any entry concerning for an unexpected adverse event will be brought to the site investigator’s attention in a timely manner. The subject will be informed to contact one of the site coordinators or investigators as soon as possible (preferably within one day) for any serious adverse event. During each subject in-person visit, the site coordinator will assess the subject compliance with diary entries. If the site coordinator identifies subject non-compliance with diary entries, the study site investigator must assess the diary non-compliance. If, in the opinion of the site investigator, the subject non-compliance with diary entries could compromise the integrity of the study data, the subject must be withdrawn from the study. We recommend that subjects keep their calendars in the same location as their concomitant medications.

Subjects will be provided a new diary for each of the periods.

6.1.2. Study Periods

The study will consist of six 4-day PK assessment periods each separated by a 12-23 day washout interval (14 days preferred between PK studies). A pre-PK study phase of 2-30 days follows the enrollment visit to permit time for randomization and key laboratory results. Prior to the first PK period the results of the laboratory evaluation (CBC, electrolytes, renal and liver function, and pregnancy test, if applicable) must be consistent with eligibility. Each PK study period begins in the morning with a 12-14 hour admission to a PK facility for frequent pharmacokinetic sampling followed by 3.5 days of outpatient once-per-day PK sampling. Note that the PK facility admission will last up to approximately 14 hours providing for up to 2 hours prior to the PK sampling for admission plus a few minutes after the final sample collection to conclude the admission.

Upon discharge from each PK facility the subject will be provided a schedule for post-admission blood sampling and will return to the site for four further blood samples to be obtained at 24, 48, 72, and 96 hours (each plus/minus 4 hours, although within 1 hour of each scheduled time is strongly preferred) post the study medication administration. If reliable arrangements can be made by the site, blood sampling can be obtained by a trained and qualified phlebotomist at the subject’s home or at a qualified clinical
laboratory near the subject’s home. All blood samples, including those obtained off site, must be prepared and shipped per the central laboratory protocol. A wash-out period of at least 12 days up to a maximum of 23 days is required after each study medication administration (PK facility admission).

All samples, including the basic enrollment labs, concomitant AED levels, PK-admission levels and the 4 subsequent outpatient morning levels must be prepared and shipped per the central laboratory procedure; the central laboratory will do all laboratory analysis except for the urine pregnancy test, which will be performed at the site.
**Table 1: Sample PK Scheduling Options for Single-dose Study:**

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<thead>
<tr>
<th></th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thur</th>
<th>Fri</th>
<th>Sat</th>
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<tbody>
<tr>
<td>A</td>
<td>PK</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>96</td>
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<tr>
<td>B</td>
<td>PK</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

PK admission day
24, 48, 72, 96 – outpatient PK blood draws at 24, 48, 72, and 96 hours post dose +/- 4 hours

PK admission schedule examples illustrated in Table 1 are on Monday and Tuesday with the outpatient 24, 48, 72, and 96 hour (+/-4 hour) samples collected on the following three days. The Monday scheduling option permits all samples to be collected on weekdays. If arrangements can be made at the site and central laboratory, PK admissions and the outpatient 24, 48, 72, 96 hour samples are permitted on any day of the week.

Approximately 12-16 days following the final study period, the site will contact the subject by telephone for a closeout interview.

During the entire study the subjects should not change concomitant AEDs. Changes in any medications must be from the approved list or approved by the Independent Medical Monitor or Steering Committee.

If the subject develops an intercurrent illness requiring treatment (such as an infection treated with a several week course of antibiotics) and the treatment requires an unapproved drug (that can interfere with the study drug pharmacokinetics) or the illness causes physiological effects that could interfere with the pharmacokinetics (for example rapid GI transit time with diarrhea) or the subject receives a rescue dose of benzodiazepine within 7 days of the planned PK-facility admission, then the PK-facility admission can be delayed as long as the total period is 23 days or less to allow for the subject to be healthy or to recover from the rescue medication for at least 7 days. If the subject develops an illness during the PK sampling portion, that period will be excluded. A single make-up period is permitted, immediately following the invalid period (maintaining the same sequence of drug administration) following the same rules as the other periods.
**Study treatment procedures:** Subjects will meet study inclusion/exclusion screening (including medical history and examination) and consent during the enrollment visit (V0) and typically less than one week later (2-30 days) will receive a phone call confirming eligibility and the study schedule; the site will receive randomization sequence assignment prior to this call. Subjects will be admitted for consecutive 12-14 hour PK admissions, typically separated by 2 weeks (12-23 day range) during which they will receive a single 25mg tablet of lamotrigine of either generic 1, generic 2, or brand per the randomized sequence. The subject and study personnel will be blind to which is the predicted high or low generic. Blood samples for testing the concentration of all of the subjects concomitant AEDs will be obtained at enrollment (V0); full PK sampling studies will be performed during each in-facility admission at the beginning of each (12-23 day) study treatment period (V1, V6, V11, V16, V21, V26). During the 3.5 days after each of the PK admissions, the subjects will have outpatient lamotrigine samples (V2, V3, V4, V5; V7, V8, V9, V10; V12, V13, V14, V15; V17, V18, V19 V20; V22, V23, V24, V25; V27, V28, V29, V30). The subject will receive optional reminder phone calls 1-3 days prior to each PK admission (P2 – (may be combined with P1); P3, P4, P5, P6, P7). A single make-up period is permitted (P-M0, V-M1 (PK-admission); VM2, VM3, VM4, VM5 (24, 48, 72, 96 hour samples)). The make-up period must immediately follow the invalid period (beginning the day following any day of the prior period including up to day 23) and consist of a repeat of the specific study drug used in the invalid period. A subject can use the ‘make-up’ period to provide for a ‘holiday’ if personal scheduling requires it, but only if necessary for subject retention. However, only one ‘make-up’ period is permitted throughout the entire study and its use should be discouraged as it is important for as many subjects as possible to complete the study in 6 consecutive, valid periods. The subject will receive a close out phone call 14 (+/- 2 days after the final PK admission (P8).

If a subject withdraws from the study and requests, in writing, that no further use be made of his/her samples, the subject’s samples will be destroyed, with no further analysis performed on the samples, using the central laboratory’s procedure to destroy the samples that meets appropriate regulatory requirements. Data included in the analysis prior to receipt of this written request will not be altered.
Subjects will be required to take the same concomitant AED products at the same dose and schedule taken at the time of enrollment into the study. There should be no changes to any prescription or non-prescription medications during the study unless determined to be acceptable by the Independent Medical Monitor.

Procedures to be performed at screening, enrollment, and treatment visits are outlined in Figure 2 and Table 2 below:
Figure 2: EQUIGEN-Single Study Timeline:
<table>
<thead>
<tr>
<th>Visit #</th>
<th>V0</th>
<th>P1</th>
<th>V1</th>
<th>V6</th>
<th>V11</th>
<th>V16</th>
<th>V21</th>
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<td>PK5</td>
<td>PK6</td>
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</table>

**Visit #**

**Activity**

- Optional phone/text reminder
- 12 hour PK-facility admission
- 24 h draw
- 48 h draw
- 72 h draw
- 96 h draw

**Timeline (Day)**

- 1-3 days prior to PK-admit
- (12-23 days total to next PK-admit from dose)

**Washout Interval**

- 96 h draw
* - Washout interval between periods can be 12-23 days with a preference for 14 day periods, which is used for illustration in the above figure.

V – visit;
P - phone) contact
PK – pharmacokinetic facility admission for concentration-time sampling 24, 48, 72, 96 hour outpatient draws (+/-4 hours of scheduled time; preferred within 1 hour of scheduled time).

M – make-up
### Table 2: EQUIGEN-Single-dose Study Procedures:

<table>
<thead>
<tr>
<th>Procedures</th>
<th>V0 Enroll</th>
<th>P1 Random</th>
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<th>Period 2 V6</th>
<th>Period 3 V11</th>
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<th>Period 5 V21</th>
<th>Period 6 V26</th>
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</tbody>
</table>

* - V2, V3, V4, V5; V7, V8, V9, V10; V12, V13, V14, V15; V17, V18, V19, V20; V22, V23, V24, V25; V27, V28, V29, V30 (not shown in above table) are performed at 24, 48, 72, and 96 hours (+/4 hours) post dose of study drug given at the beginning of each PK admission and consist only of a blood draw for lamotrigine levels.

** - Study treatments and PK sampling studies may be extended up to 23 days for scheduling reasons (making intervals 12-23 days). In the table above, 14 day washout intervals, which are preferred and expected to occur for most subjects, are used for illustration.

*** - Only obtained in females of childbearing potential (regardless of contraception method).

**** - P2, P3, P4, P5, P6, P7 – subject-specific optional phone contacts (not listed in above table) reminding the subjects of the PK-admission visits.

***** - A single make-up period is permitted, if needed. It must immediately follow the invalid period, repeating the specific invalid period drug): P-M0 is a phone contact indicating a make-up period is needed (can occur during another visit†); V-M1 is the PK admit, equivalent to V1; Following the admission, the 24, 48, 72, and 96 hour samples are collected at VM2, VM3, VM4, VM5 (not listed in table).
6.1.3. Enrollment

At the enrollment visit, the subject must meet inclusion and exclusion criteria and provide informed consent through the process described above. Demographic data, medical history, psychiatric history, medication history, general physical examination, full neurological examination, and laboratory testing will be performed.

Subjects (and, if applicable, the subject’s caregiver) will be provided and instructed in a medication/event/seizure diary, which should be brought to every visit. The medication/event/seizure diary will specify the specific dose times for the concomitant medications (individualized for each subject). Adverse events (including timing, duration and severity) recorded in the diary will be assessed and recorded by study personnel at the enrollment visit and each PK-visit. The relationship of each dose to food will be determined so that for the duration of the study the subjects will be advised to take each dose of their concomitant medications in approximately the same relationship to food. Subjects will be instructed on the importance of adherence to dosing schedules and to completing medication/event/seizure diary logs.

Upon enrollment, the subjects enter a 2-30 day pre-study interval during which the enrollment visit laboratory studies will be processed and confirmation of eligibility to enroll will be made. Upon enrollment, no changes in concomitant medications are permitted, except as above. The sites can plan the subject PK-period schedule at either the enrollment or the randomization visit.

The subjects are required to provide all of their concomitant medications including AEDs. The site investigator can prescribe these medications for the subject if they do not have an adequate supply with standard prescribing using a commercial pharmacy following standard clinical care. The subject (with or without insurance coverage) is responsible for obtaining and paying for all medication provided by a commercial pharmacy.

The subjects will record in their diary when all new refill prescription bottles are used including the manufacturer of each medication.
6.2. Randomization

The randomization phone-visit will be conducted by study site personnel and completed via a phone contact 2-27 days following enrollment (at least one day prior to the first PK-admission, which is V1 minus 1-28). The randomization phone-visit consists of confirmation that the subject is eligible to continue in the study based on the laboratory evaluation and other enrollment information, randomization to one of the three study sequences, and scheduling (or confirming) the date for the first PK-admission.

There are six test periods performed in one of three sequence orders (Section 3.0). During two test periods the subject will receive the brand study drug (Lamictal®) (from the same lot in each period) as the reference product (B) and during the other four test periods the subject will receive the two disparate generic forms of the study drug (lamotrigine) made by different manufacturers (two periods for each generic; G1, G2). The test order (Table 3) is based on a combination of FDA recommended sequences for examining individual bioequivalence. Subjects will be randomly assigned to sequence 1, sequence 2, or sequence 3 using the statistician developed method as detailed in the MOP. Subjects who do not complete the first three periods will be replaced. This schedule will provide adequate time for the key laboratory study results.

Table 3: Randomization Sequences

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G1, G2, B, G1, B, G2</td>
</tr>
<tr>
<td>2</td>
<td>G2, B, G1, G2, G1, B</td>
</tr>
<tr>
<td>3</td>
<td>B, G1, G2, B, G2, G1</td>
</tr>
</tbody>
</table>

G1 = “high generic; G2 = “low” generic; B = brand

6.3. Follow-up Procedures and Assessments

6.3.1. Study Medication Administration

This study is not blinded as to product, but the site personnel will be blind to which is the predicted high and which is the predicted low generic product. The site personnel will open the study medication bottle, confirm the medication is correct (see below), place it in an opaque container (small envelope) and give the medication to the subject in a
manner that the subject does not see the tablet so that the subject is masked to the specific tablet (i.e. subject places envelope to mouth and pours tablet into mouth without seeing it). The packaging and all extra tablets will be kept and returned to a central location at the end of the study. The site personnel will confirm the correct tablet is administered by checking that both the bottle label and markings (imprints) on the tablet are correct and recording the information on a CRF. The subject will take the study medication with 150 ml's of water to swallow the tablet. Concomitant medications can be taken with small sips of water at other times during the fasting portion as required by the subject's medication regimen. If a subject is unable to swallow the tablet and spits it out or vomits at any time during the 12-hour PK facility admission, the period will be invalid. A single make-up period is permitted and must immediately follow the invalid period and repeat the invalid period study drug. Replacement study medication will be obtained from the appropriate bottle stored at the site. Note that if the subject vomits after the discharge from the PK facility, but during the time interval that PK samples are still being collected, the study period remains valid.

All subjects will receive the study medication in the fasted state. Before the PK admission, the subjects will fast for approximately 10 hours prior to the dose (during the preceding night beginning at about 9 pm or 11 pm) and until 4 hours after the dose given the following morning. The test product will be administered in the morning as soon as the admission evaluation is completed. A catheter for sample collection will be placed by qualified site personnel (including IV trained technicians, nurses, or physicians). The time that the test product is administered is recorded to the nearest minute and the subsequent blood sampling time is calculated. After administration of the dose the subjects are required to sit in an upright position for the first 4 hours (bathroom breaks are permitted if necessary). Standardized meals will be administered at approximately 4 and 10 hours post-dose. A snack will also be provided during the day. In the event of difficulty with the catheter or by subject preference, samples can be collected by venipuncture.

The subject is required to bring all concomitant medication for the day to the PK facility admission. The concomitant medications will be administered per the subject’s usual routine during the PK admission; the only exception can be at the time of study dose administration during the PK admission as this will be given in the fasting condition.
6.3.2. Medication Adherence
Adherence to concomitant medications will be assessed by subject diary.

6.3.3. Pharmacokinetic Testing
Pharmacokinetic (PK) testing will be performed on the first day of each study period in the PK facility using a catheter for subject comfort (although venipuncture can be used if there are problems with the catheter or by subject preference) and for 3.5 subsequent days following discharge with a venipuncture. With each sample collection through the catheter, a small amount of blood ~0.5 ml will be withdrawn and discarded to clear the line. Each lamotrigine level sample collection will consist of 2 ml of blood that will be allowed to clot for at least 30 minutes and then centrifuged with the serum transferred to an aliquot tube within 8 hours of sample collection. Each of the outpatient samples will consist of 4 ml of blood and similarly centrifuged with serum transferred to an aliquot tube within 8 hours. Samples can be kept at room temperature through the day, but need to be frozen to minus 70 C or colder within 24 hours of collection. The frozen samples can be sent to the central laboratory in monthly batches using a courier service. The catheter will be flushed with saline after each sample collection.

All lamotrigine level samples will be collected into no additive draw red top tubes. The concomitant AED levels sample will be collected into a 4 ml no additive draw red top tube. The chemistries will be collected into a gold top serum separator 5 ml tube. The CBC will be collected into a 4 ml EDTA purple top tube.

A central laboratory will perform all lamotrigine level assays (as well as all the other clinical laboratory measurements done in this study except for the urine pregnancy tests which will be performed at the sites). Each site will prepare and ship all samples according to the central laboratory protocol.

The PK-study period is a total of 4 days (with a 12-23 day washout interval between study mediation doses).

The PK sampling, obtained by trained and qualified site personnel, will be used to determine AUCs and C\text{max} by sampling just prior to each dose, then every 20 minutes for
the first 4 hours after the dose, then at 4, 4.5, 5 and 6 hours and then every 2 hours up
to 12 hours (8h, 10h, 12h) after the study dose. Following removal of the catheter and
discharge from the PK-facility, outpatient samples will be obtained at 24 hours, 48 hours,
72 hours, and 96 hours (+/-4 hours) after the administration of the study drug using
venipuncture technique. (Times: immediately pre-dose-trough= time 0, 20m, 40m, 60m,
80m, 100m, 120m, 140m, 160m, 180m, 200m, 220m, 4h, 4.5h, 5h, 6h, 8h, 10h, 12h;
24h, 48h, 72h, 96h = 23 samples total). The times of all of the blood sample collections
will be recorded to the nearest minute using a clock synchronized to standard time. The
sampling while in the PK-facility should be within plus or minus 5 minutes of each time
specified; the 4 outpatient samples should be obtained within 1 hour of the scheduled
times, but up to +/- 4 hours are permitted to optimize subject retention. All deviations
from the protocol timing will be noted on the case report form and will be accounted for
in the statistical analysis. The total amount of blood during each PK session will be equal
to about 14 teaspoons (66.5 milliliters) calculated as 2 ml for each sample with 0.5 ml
wasted for each sample and 3 ml wasted with catheter insertion and 4 ml for each of the
4 outpatient draws (2.5ml*19 + 3ml + 4ml*4 = 66.5ml per PK session). The initial
laboratory testing at the screening visit will be 13 ml (4 ml CBC, 5 ml chemistries, 4 ml
concomitant AED levels). The total amount of blood drawn through the entire study will
be about 83 teaspoons (412 milliliters). If a make-up period is performed, an additional
66.5 ml will be drawn for a maximal possible total of 96 teaspoons (478.5 milliliters). For
reference, this amount is approximately equal to the quantity of blood drawn during a
standard blood donation by the Red Cross.

If 51 subjects complete all 6 periods and one-half (25 of the subjects) use a make-up
period, then the total number of lamotrigine levels in the study will be: 51x23x6 + 25x23
= 7613. In addition, for 54 enrolled subjects there will be 54 laboratory evaluations
including CMP and CBC and, for an average of 1.5 concomitant AEDs sampled at the
enrollment visit, there will be ~54x1.5 = 81 concomitant AED levels all performed in the
central laboratory. Also, for ~25 females of child bearing potential there will be 25x2 = 50
urine pregnancy tests performed at the site in a qualified laboratory.

All samples, including the basic enrollment labs, concomitant AED levels, steady state
levels, and PK-admission levels will be drawn by trained and qualified phlebotomists or
trained and qualified health care providers including nurses or physicians and prepared and shipped per the central laboratory procedure; the qualified central laboratory will do all laboratory analysis except for the urine pregnancy test, which will be performed at the site’s qualified laboratory.

If during the study, the subject experiences an unacceptable adverse event or the investigator is concerned about subject safety on the product being tested, then the site investigator is responsible to assure that the subject receives appropriate medical care and the subject must be withdrawn from the study.

If the subject experiences a seizure exacerbation, rescue medications can be administered from the approved list (which includes benzodiazepines) for as many doses and days as the site investigator or other care providers deem necessary for subject safety. The PK facility admission should be delayed if the subject uses rescue medications during the 7 days prior to planned admission. There must be 7 days between last rescue medication use and the PK admission. Use of rescue medications should be recorded by the subject in the medication/event/seizure diary.

If the PK period (4 days of blood sampling) is determined to be invalid, the study period can be repeated as a ‘make-up’ period for a maximum of one time.

6.3.4. History, Physical and Neurological Examination
A complete history, physical and neurological examination will be completed by the site investigator and recorded in the subject’s case report form at the enrollment visit. At each PK-facility admission vital signs (HR, BP, RR, and temperature), a focused history, focused general physical exam to assess for an intercurrent illness (that could affect the pharmacokinetic measurements such as gastroenteritis), and a focused neurological exam specifically assessing for signs of medication toxicity will be performed. If an intercurrent illness is present the PK facility admission can be postponed. The history and exams at the PK facility admission can be performed by the site investigator or a qualified surrogate (including a trained CTC, nurse, physician’s assistant or nurse practitioner) who is involved in the implementation of the study. In all women of childbearing potential, a urine pregnancy test will be performed at the enrollment visit and the final PK-admission visit. If a urine pregnancy test is positive at any time, the
subject must be withdrawn from the study and encouraged to follow up with a healthcare provider. The results of each history and exam will be recorded in the subject’s case report form.

6.3.5. Assessment of Seizure Frequency and Adverse Effects
Seizure frequency will be monitored by subject maintained diaries. Adverse events will be monitored by subject maintained diaries and interviews.

During the PK facility admission, the subjects will record in their medication/event/seizure diary any adverse events or seizures they experience.

6.3.6. Closeout visit phone contact
The subject will be contacted by site personnel, typically by phone, for a closeout interview 12 to 16 days following the final PK session. During this interview adverse effects will be assessed including ongoing and new. Additionally, the subject will be asked which set of periods they thought that they were on the predicted high generic and which set of periods they thought they were on the predicted low generic.

6.4. Follow-up Termination Procedures
At the conclusion of the study, the subjects will continue on their usual medication regimen. The subjects have the right to obtain any data collected about them. The subjects and their physicians will be informed of the results of the study at such time as the Independent Medical Monitor allows disclosure. The study team will analyze the data from all the subjects except for data obtained from samples after subject withdrawal, if the subject provides a written request to no longer use his/her samples; data included in the analysis prior to receipt of this written request will not be altered. Each site will be provided with an IRB approved letter that will be distributed to subjects informing them of the outcome of the study. All individual data will remain confidential.

Assessment of Study Objectives
6.5. Primary Outcome

The primary outcome measures for the study will be AUCs and $C_{max}$ for the brand and disparate generic products.

6.6. Methods and Timing for Assessing, Recording, and Analyzing Outcome Measures

The subjects will be assessed as above at each outpatient study visit and PK facility admission. On the first day of each study medication period a 12-hour pharmacokinetic (PK) sampling will be performed at the site PK facility followed by 3.5 days of daily sampling. The PK sampling will be used to determine AUCs and $C_{max}$. This procedure is repeated for each of the 6 periods.

Seizure frequency and adverse events will be monitored by subject maintained diaries.

6.7. Laboratory Assay:

The bioanalytical measurements will be performed in accordance with the principles of Good Laboratory Practice (GLP). A quality monitoring system is in place. All samples will be stored in a secure location and all data will be maintained and transferred in a HIPAA-compliant manner.

The in vitro analyses will adhere to USP guidelines and standards.

An LC-MS/MS analytical method will be used for the lamotrigine analysis. This method was selected to achieve low-end specificity and sensitivity at 10 ng/ml or lower with a linear range from 10 to 2000 ng/ml. Throughout the study appropriate calibration and validation of the assay (pre-study and during study) including specificity, intra-assay precision, intra-run accuracy, inter-run precision, inter-assay accuracy, and stability will be maintained.

The lamotrigine analysis consists of serum samples extracted with acetonitrile and internal standard. The samples will then be injected onto a reverse phase HPLC column and separated using a gradient of acetonitrile with 0.2% formic acid and 2mM
ammonium formate. Eluted peaks will be detected on a tandem mass spectrometer using a turbo-ion spray source and multiple reaction monitoring. For the analyte and internal standard a precursor ion along with one product ion will be monitored. A calibration curve allows for quantitation of results.

**Incurred Sample Reanalysis (ISR)** $^{31, 32}$

**ISR Sample Size**
A minimum of 5% of all incurred lamotrigine samples will be re-analyzed either during the course of the study or after study completion to ensure that the assay results meet reproducibility standards.

**ISR Approach**
A two phase approach will be used to ensure that the assay is reproducible. In the first phase, each time an analytical run is set up samples will be randomly selected from the immediately previous analytical run for re-analysis. As batch size may vary with workload, a minimum of 1 sample and a maximum of 4 samples will be selected from the previous run. After study completion, a minimum of 2 samples will be randomly selected from each subject in the study and re-analyzed. The total number of samples re-analyzed in the course of the study will represent no fewer than 5% of the entire volume of samples received for testing during the study and will represent randomly selected samples from every subject.

**ISR Acceptance**
The ISR will be completed prior to the issuance of the final study report. A minimum of 67% of the samples re-analyzed should have a CV of 20% or less in order to demonstrate assay reproducibility.

Analysis of the lamotrigine samples will be conducted by the laboratory without information on treatment.

All blood samples obtained for lamotrigine levels in this study will be stored in stable conditions until up to 2 years after the publication of the results of this study. Thereafter they will be destroyed by the central laboratory using the laboratory’s procedure that
meets all applicable regulations including the HIPAA regulation to maintain subject confidentiality.

Assessment of Safety

6.8. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The Coordinating center assures through standard procedures, regular reviews and audits, that data are submitted according to the study requirements. Each clinical site is responsible for reporting all adverse events to the Coordinating center. Routine reporting of data from study visits and laboratory tests is expected within 5-7 days. Serious adverse events are to be reported within 24 hours of the site personnel becoming aware of the SAE. Study investigators must report serious adverse events to their local ethics Review Committee (or IRB) promptly in accordance with local regulations or policies, in addition to providing the information to the Coordinating center.

6.9. Monitors

6.9.1. Independent Medical Monitor

The Independent Medical Monitor will assess study data with particular consideration of subject safety. The Independent Medical Monitor will review accumulated data on a regular basis, but will convene ad hoc meetings of the Steering Committee to address any significant problems related to subject safety brought to the attention of the Independent Medical Monitor by any study subject or investigator. The Independent Medical Monitor will review the accumulated data and consider whether a protocol modification is necessary. If changes in the protocol are indicated, recommendations will be made to the sponsor who will consider and act on such recommendations in a timely manner.

In addition to the routine review of cumulative reports of other study events, toxicities, and study results, the Independent Medical Monitor will review all serious adverse events, which will be reported by sites immediately upon learning of them. The Independent Medical Monitor will then report to the FDA and the Steering Committee within 24 hours.
6.10. Study Stopping Rules

The Independent Medical Monitor will confer an emergency session with FDA and members of the Steering Committee if any of the following criteria are met:

If any subject death occurs during the study,
Any life-threatening seizures or life-threatening adverse events occur in a subject during the study,

Once an emergency session has occurred, recommendations will be forwarded to the FDA Project Officer. The final decision to terminate a study will be made by the sponsor, after taking recommendations of all parties into consideration, and in accordance with the requirements of the FDA, OHRP or other regulatory agencies. If a decision is not made within 7 days of the notification by the Independent Medical Monitor an automatic suspension of further enrollment to the study will take effect.

6.11. Safety Monitoring

This section defines the types of adverse events to report and outlines the procedures for appropriately collecting, grading, recording, and reporting the adverse events.

6.11.1. Definitions

All adverse events (AE) and serious adverse events (SAE) observed under this protocol will be reported in accordance with Federal and FDA requirements for the duration of the study.

- **Adverse Event (AE) or Medical Event:**
  An adverse event is a new, undesirable medical event or occurrence or worsening of an existing condition (including an abnormal laboratory finding) in a subject that occurs during treatment and throughout the study, whether or not it is considered study related.

- **Serious Adverse Event:**
  We define a serious adverse event (SAE) as any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but is not limited to, any of the following events:

  1. **Death:** A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy whether or not considered treatment-related must be reported.
2. Life-threatening: Any adverse therapy experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).

3. In-patient hospitalizations or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to hospital or ER longer than 24 hours. Prolongation of existing hospitalization is defined as hospital stay longer than originally anticipated for the event or development. Hospitalization (scheduled or unscheduled) for a pre-existing condition which has not worsened or pre-planned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups are **not** considered SAEs.

4. Persistent or significant disability or incapacity (substantial disruption of the subject’s ability to conduct normal life functions)

5. Pregnancy.


7. An event that required intervention to prevent permanent impairment or damage.

(This terminology is from Section B.2 on the FDA MedWatch form. For a copy of the current MedWatch Form 3500, see the list of PDF forms on the Web at: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.)

- **Pregnancy:**
  Any pregnancy that occurs during the study will be reported as a serious adverse event and the subject will be withdrawn from the study.

- **Unexpected Adverse Event:**
  An adverse event is “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, or the investigator’s brochure.

- **Toxicity Grading:**
  The site will assign toxicity grades to indicate the severity of adverse experiences and toxicities. We will use The National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE) for application in adverse event reporting. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatment-related toxicities. The NCI-CTCAE provides a term and a grade
that closely describes the adverse event. Each participating site will receive copies of the grading scales and event descriptions.

Sites will record adverse events not included in the NCI-CTCAE listing and grade them 1 to 5 according to the General Grade Definition provided below:

**Table 2: Adverse events grading:**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Mild</th>
<th>Transient or mild discomforts (&lt; 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Moderate</td>
<td>Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe</td>
<td>Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening</td>
<td>Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required; hospitalization, or hospice care probable.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
<td>Death</td>
</tr>
</tbody>
</table>

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE website: [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html).

**6.11.2. Relationship to Procedure Definitions**

The Investigator will provide the determination of the likelihood that the study medication is associated with the AE.

- **Associated:** There is a reasonable possibility that the adverse event may have been caused by the study medication and/or procedure. This definition applies to those adverse events considered definitely, probably, or possibly related to the
procedure.

1. **Definitely related:** An adverse event that follows a temporal sequence from administration of the study medication; follows a known response pattern to the study medication; and, when appropriate to the protocol, is confirmed by improvement after stopping the study medication and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the subject’s clinical state or by other therapies.

2. **Probably related:** An adverse event that follows a reasonable temporal sequence from administration of the study medication; follows a known response pattern to the study medication, is confirmed by improvement after stopping the study medication; and cannot be reasonably explained by the known characteristics of the subject’s clinical state or other therapies.

3. **Possibly related:** An adverse event that follows a reasonable temporal sequence from administration of study medication and follows a known response pattern to the study medication, but could have been produced by the subjects’ clinical state or by other therapies.

• **Not associated:** an adverse event for which sufficient information exists to indicate that the etiology is not related to the study medication.

• **Unrelated:** an adverse event that does not follow a reasonable temporal sequence after administration of the study medication and most likely is explained by the subject’s clinical disease state or by other therapies. In addition, a negative rechallenge to the study medication would support an unrelated relationship.
6.11.3. Adverse Events Collection Procedures
Adverse events and other problems will be evaluated from the onset of the event until the time the event resolves or is medically stable or until 30 days after the subject completes study treatment, whichever comes first.

Adverse events may be discovered through any of these methods:
- Observing the subject
- Questioning the subject, which is done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records or subject diaries

6.11.4. Recording and Reporting Procedures
The study will provide a multi-page adverse event case report form (CRF), which will allow the submission of all adverse events through a single reporting mechanism. Serious adverse events will require additional information reported on additional pages. Source documents can be scanned and attached to the adverse event CRF as well. The investigator treats subjects experiencing adverse events appropriately and observes them at suitable intervals until their symptoms resolve or their status stabilizes.

- SAE Recording and Reporting Procedures
Serious adverse events will be recorded on the adverse event e-CRF. All sites are obligated to report SAEs within 24 hours of their occurrence and/or the site staff's knowledge of the event to the Independent Medical Monitor and the FDA. The following attributes must be assigned:
  - Description
  - Date of onset and resolution (if known when reported)
  - Severity
  - Assessment of relatedness to study medication
  - Action taken
  - Follow up

The site investigator must apply clinical judgment to determine whether an adverse
event is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator must suspend any trial procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

After subsequent review by the Independent Medical Monitor and the ethics review committee, or IRB and the FDA IRB, the sponsor may suspend further trial treatment or procedures at a site. The study sponsor and the Independent Medical Monitor retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

A subject may also voluntarily withdraw from treatment due to what the subject perceives as an intolerable adverse event, or for any other reason. If a subject voluntarily withdraws, they will be asked to continue scheduled evaluations and receive appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject’s condition becomes stable.

- **Reporting Criteria**

  1. Site Investigators are notified by site staff.

  2. An Adverse Event Form is completed and submitted by the site. Information regarding a Serious Adverse Event report must be recorded in the subject’s medical chart.

  3. Serious Adverse Event follow-up reports should include hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment, and any other pertinent information regarding the event. Reporting should not be delayed in order to provide these documents.

  4. The Serious Adverse Event Form will be completed in the event of a death. This will be transmitted along with other supporting data (e.g., death certificate, medical notes, etc).

- **Notifying the Sponsor**

The site will provide the Coordinating center with data for SAEs as defined per the protocol on an ongoing basis. The Independent Medical Monitor is responsible for notifying the sponsor, simultaneously with his or her completing a report in the electronic
data system. This reporting should happen within 24 hours of site awareness of the SAE. Events that are serious, related to therapy, and unexpected must be reported to the FDA within 15 days. All reports of death or life threatening events must be reported to the FDA within 7 days. The Independent Medical Monitor will insure that all events meeting these criteria that are reported to the Coordinating center are forwarded to the FDA within these time periods.

- **Notifying FDA and the Independent Medical Monitor**

  The Coordinating center will provide the Independent Medical Monitor with listings of all SAEs on an ongoing basis. Furthermore, the Coordinating center informs the FDA of expedited reports of SAEs as described above.

- **Notifying the Institutional Review Board**

  The site investigator will ensure the timely dissemination of all AE information, including expedited reports, to the IRB in accordance with applicable local regulations and guidelines.
7.0 **Statistical Considerations**

The statistical considerations summarized in this section describe the plan for data analysis of this study.

7.1. **Primary Analysis**

A random-effects linear model of the log-transformed $C_{\text{max}}$ measures will be fitted. All data from all subjects and all periods will be used to fit the model. As independent variables, the model will include: two dummy variables representing the three products (B, G1, and G2), two dummy variables representing the three sequences, and 5 dummy variables representing the six periods. The intercept and the regression coefficients corresponding to the two dummies representing the products will be treated as random coefficients. All other regression coefficients will be treated as fixed effects. Because LTG is inducible, a dummy variable representing subjects receiving versus those not receiving concomitant hepatic enzyme inducing AEDs will also be included as an independent variable of the model. An interaction term between this variable representing induction and the variables representing the generic products will also be examined. To account for the possibility of study center effects, two dummy variables representing the three centers will also be included as independent variables in the random-effects linear model. Also, to account for the possibility that period effects may vary across centers, additional analyses will include interaction terms between the dummies representing the centers and the dummies representing the periods.

To examine average bioequivalence between the two disparate generics, a 90% confidence interval for the difference in mean log-transformed $C_{\text{max}}$ between the two generics will be computed; if this interval lies within the interval $(\log(0.8), \log(1.25))$ provided by the [2001 FDA Guidance, Statistical Approaches to Establishing Bioequivalence](#), then the two generics will be considered as average bioequivalent.

This model will also provide all within-subject variances and subject-by-formulation interaction variances that are needed to examine individual bioequivalence between each generic and the brand according to FDA guidelines. Since subjects with missing data will also be included in analyses, restricted maximum likelihood will be used to estimate variance components as recommended by the FDA guidelines.
Studentized residuals from linear contrasts will be computed in order to investigate subject-by-formulation interaction outliers.26

SAS PROC MIXED will be used to fit the above model by using essentially the same code recommended in the 2001 FDA Guidance, Statistical Approaches to Establishing Bioequivalence (page 34). It should be noted that the above analyses closely follow the FDA guidelines for bioequivalence analyses, and that the above model will provide simultaneously all the parameters that are needed to perform all the planned average and individual bioequivalence analyses that will compare the three formulations and to perform the outlier analyses.

Analogous statistical analyses will be performed using the log-transformed AUC.

The PK data modeling to determine the pharmacokinetic parameters will be performed with Pharmacokinetic Solutions software or comparable software. The area under the plasma concentration time curve to time 96 hours (AUC96) and extrapolated to infinity (AUC∞) over each dosing interval will be determined using a non-compartmental model. Cmax and Tmax will be determined for each dosing interval by visual inspection of individual concentration-time data.

7.2. Sample Size and Power

For testing the null hypothesis of non-average bioequivalence for Cmax between the two lamotrigine generics, using the 3-sequence 6-period design, a sample size of 45 subjects will provide a power of 90%, provided that the real separation for Cmax between the two generics is at most Δ=5%. This 5% is the “standard” separation suggested by FDA guidelines for power analyses in average bioequivalence studies (2001 FDA Guidance, Statistical Approaches to Establishing Bioequivalence, page 28). This power was computed through Monte-Carlo simulations (SAS program available upon request) by using a lamotrigine intra-subject variance for the log of Cmax of 0.0907, which was provided by the study of Thompson et al (2008),16 and an assumed treatment-by interaction variance of 0.04. Since the lamotrigine intra-subject variance for the log of
AUC was smaller than 0.0907 (0.0787), there is at least 90% power for investigating the null hypothesis of non-average bioequivalence for AUC between the two generics by using the 3-sequence 6-period design, provided that there is a real separation for AUC of at most $\Delta = 5\%$.

7.3. **Statistical Methods in Secondary Analyses**

The effects of age, gender and concomitant enzyme inducing AED on average bioequivalence will be investigated by including interaction terms in the above model between these variables and the dummy variables representing the formulations. If the regression coefficient for one of the interaction terms is significant, we will conclude that the corresponding variable affects significantly the bioequivalence between the two formulations compared by the dummy variable involved in the interaction. High and low groups of enriched population will be compared analogously.

Safety analyses will use outcomes of all subjects that enrolled in the study regardless of adherence to the protocol. Additional listings or specific investigations into event rates may be conducted as requested by the Independent Medical Monitor.

Reported adverse events will be listed by MedDRA term, frequency, severity, and association to drug product. Incidence rates will also be calculated by drug product (generic or brand) and by manufacturer of the generic products.

7.4. **Handling of missing data:**

To examine whether missing data affected conclusions regarding average bioequivalence, the linear mixed model will also be fitted by using only subjects with complete (6-period) data. The confidence intervals for the fixed treatment-effect parameters computed with only subjects with complete data will be compared with those computed with all subjects. If all confidence intervals for corresponding fixed-effect parameters overlap, we will conclude that missing data did not affect our conclusions, and conclusions will be reported by using the model fitted with all subjects. If at least one pair of corresponding confidence intervals does not overlap, conclusions based on the model fitted with only the subjects with complete data will be reported, and a due note describing the restricted sample size will accompany the conclusions.
8.0 **Human Subjects Protection**

All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study. The subjects will have an opportunity to review the consent document carefully and ask questions regarding this study prior to signing. They will be informed that they may withdraw from the study at any time without prejudice to themselves. All procedures and follow-up recommended are those considered standard of care in the community.

8.1. **Risks and Benefits**

Study subjects enrolled in this protocol will be subject to those risks and hazards associated with administration of the study drug (lamotrigine), staying for 14 hours in a pharmacokinetic facility, the blood draws, and with switching products of AEDs.

Subjects will be given reasonable compensation for each visit and completed period of the study for travel, parking, and the time spend during the pharmacokinetic facility admission.

8.2. **Risks of Therapy**

It is possible that a subject may experience study drug (lamotrigine) adverse effects (with the most common including dizziness, headache, double vision, muscle coordination problems, nausea, blurred vision, drowsiness, and rash) or an increase in seizure frequency or intensity. If the subject experiences a worsening of seizures and the site investigator chooses to give the subject rescue therapy (for example a benzodiazepine) it is possible that the subject will suffer an adverse reaction to the rescue treatment. Additionally a subject may experience an allergic or idiosyncratic reaction to the study medication, lamotrigine, which in chronic administration has caused life-threatening serious rashes in up to 0.3% of people. Since this is a low-dose, single-dose (times six) study, the incident of rash, including life-threatening rash, is anticipated to be lower. For any safety concerns, the site investigator has the authority to intervene and if necessary withdraw the subject from the study. Given that all the medications that will be used in this study (lamotrigine brand and A-rated generic products) are approved by the FDA as interchangeable with no additional concerns for safety, no other treatment
emergent risks are anticipated. Subjects may experience hunger associated with the fasting required overnight and the morning of each of the six in-center pharmacokinetic sessions. Subjects may experience discomfort associated with the blood draws. Subjects may experience symptoms associated with blood loss, although the total volume of blood removed will be less than indicated as safe by the Red Cross.

8.3. Institutional Review Board

This clinical study will be reviewed and approved by the Institutional Review Board (IRB) representing each participating institution prior to enrolling subjects and must be reviewed again on an annual basis. The review must include the protocol, the informed consent document, and any other materials that will be provided to prospective subjects (e.g., advertisements). Each reviewing IRB must be registered with OHRP. A list of IRB voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Institution’s Assurance of Compliance, must be kept available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials.

All enrolled subjects must sign an IRB approved consent form. The principles of informed consent are described in 21 CFR Part 50. Subjects enrolled at a collaborating institution must sign the informed consent approved by that institution prior to participation in the study.
9.0 Confidentiality

The Investigator must ensure that the subject’s anonymity is maintained. Blood samples will be retained for analysis of drug and metabolites as well as other products that could affect the way the body handles drugs until the study is formally concluded and a final report is completed. No tissue or other samples will be stored for this study. All medical records will be kept confidential and will only be reviewed by the participating investigators, their staff representatives and designated Coordinating center staff or their representatives during site visits or safety reviews. Data will be kept in password-protected computers held at the Data management center. Only study investigators, Data management center staff and Coordinating center staff will have access to the study data. Names will not appear on any of the data forms or copies of medical records (i.e. hospital discharge summaries) reported to other locations. A study registration number will identify the subject on study related case report forms and other documents. No subject identifiers will be used in any publication of the study results. The investigators and his or her organization will take all necessary steps to protect the confidential nature of all study data, such as materials, data, reports, programs, and information.
10.0 **Compensation**

Subjects will not be paid for taking part in this research study, but will be reimbursed for expenses including travel, parking, and time. During participation the study drug (lamotrigine) will be provided free of charge. For this study, sites will recompense subjects $25 for the enrollment visit, $225 per completed inpatient PK-admission and $25 per each completed outpatient visit for blood samples for travel, parking, and time. Additional compensation of up to $25 per visit will be provided to subjects that travel greater than 30 miles (total; meaning 15 miles each direction) to the site for time and travel (using the IRS standard business mileage rate applied to the portion of the travel over 30 miles). Thus, a subject completing 6 periods will receive $1975 (1 x $25 plus 6 x $225 plus 24 x $25); if the subject travels a substantial distance to each visit, the subject can receive up to an additional $750 (30 x $25). The make-up visit can result in $325 ($225 plus 4 x $25) plus an additional $125 (5 x $25) for substantial travel.

Study subjects are being offered overnight stay in a hotel on or near campus for the night before the inpatient pharmacokinetic sampling. Subjects are being asked to arrive at the study site early in the morning on the pharmacokinetic sampling day. The overnight hotel stay is to avoid delays in starting the study procedures due to weather, traffic, distance or other delays. The staff of the inpatient research facility may be unable to complete the study per protocol if the subject is substantially late arriving to the inpatient research facility. If a subject chooses to stay at the hotel, they will be offered $20 reimbursement to cover the cost of their evening meal.

All payments will be disclosed in the consent form.
11.0 Data Sharing

At the end of the funding period for the trial, the investigators will follow the FDA guidelines for release of data.
12.0 References


13.0 Appendix 1:

Preliminary Data: Determining Magnitude of AED Concentration Change to Qualify for the Enriched Population

We determined that the enriched population for secondary analysis should include, in addition to subjects who had previously reported loss of seizure control or worsening of adverse effects associated with an AED product switch, subjects who experienced asymptomatic, unexpected changes in AED concentrations while receiving the switched (mainly generic) product. Preliminary analysis was conducted to determine parameters for an “unexpected” change in AED concentration. We can calculate an individual standard deviation ($SD_i$) and individual coefficient of variation ($CV_i$) if a subject has 3 or more AED concentrations on the baseline product, and changes in AED concentrations on the switched product can be compared using the $SD_i$ or $CV_i$. However, if a subject has only one or two AED concentrations on the baseline product, the determination of an “unexpected” change in AED concentration must use population data. To estimate expected variations in a population of subjects receiving AEDs, data from several randomized controlled trials were obtained from the sponsors, and data from clinics of three of the investigators were also analyzed.

Data from a Randomized Controlled Trial of Lamotrigine (LTG):
AED concentration data were obtained from Glaxo Smith Kline from a randomized, unblinded trial comparing a Lamictal® immediate release (IR) to a Lamictal® extended release (ER) product. Each of 44 subjects received a 12-hour pharmacokinetic sampling at the end of a two week period while receiving LTG-IR, a two week period while receiving LTG-ER, and a one week period while receiving LTG-IR. Subjects were categorized as receiving, in addition to LTG, neutral concomitant drugs, inhibitor concomitant drugs, or inducer concomitant drugs. Trough AED concentrations from sampling during the weeks the subjects received the IR product were used to calculate coefficient of variation for the individual subject ($CV_i$) and for a mean $CV_{pop}$ for the population for the group receiving inducer concomitant drugs, neutral concomitant drugs, and inhibitor concomitant drugs. (CVs are defined as 100 times the SD divided by the mean and are used analogous to a percent as a measure of dispersion.)
Appendix 1 - Table 1: Distribution of Coefficients of Variations for LTG Concentrations

<table>
<thead>
<tr>
<th>Group (all IR)</th>
<th>n</th>
<th>Mean (CV&lt;sub&gt;pop&lt;/sub&gt;)</th>
<th>S.D. of CVs</th>
<th>Median CV</th>
<th>Min CV</th>
<th>Max CV</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; Percentile CV&lt;sub&gt;pop75&lt;/sub&gt;</th>
<th>90&lt;sup&gt;th&lt;/sup&gt; Percentile CV&lt;sub&gt;pop90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
<td>14</td>
<td>12.4</td>
<td>13.4</td>
<td>7.0</td>
<td>1.3</td>
<td>50.8</td>
<td>21.5</td>
<td>22.7</td>
</tr>
<tr>
<td>Induced</td>
<td>12</td>
<td>24.8</td>
<td>27.3</td>
<td>14.3</td>
<td>1.4</td>
<td>89.7</td>
<td>29.3</td>
<td>67.4</td>
</tr>
<tr>
<td>Inhibit</td>
<td>13</td>
<td>8.9</td>
<td>4.0</td>
<td>8.8</td>
<td>4.1</td>
<td>17.4</td>
<td>10.4</td>
<td>13.9</td>
</tr>
</tbody>
</table>

We chose to use the 75<sup>th</sup> percentile as the CV<sub>pop</sub> (designated - CV<sub>pop75</sub>) for each of the three groups as an approximation of the expected dispersion, and multiply this value by two to approximate the limits of variation expected for LTG concentrations. Thus, a subject with 1 or 2 LTG concentrations before a product switch will qualify if one or more LTG concentrations obtained after the switch are beyond 2 times the CV<sub>pop75</sub> for the appropriate group (induced, inhibited, or neutral).

For example, a subject receiving monotherapy Lamictal as the baseline product has trough plasma concentrations of 8.2<sup>μg/mL</sup> and 9.2<sup>μg/mL</sup> each drawn in the early morning 10-12 hours after the last dose giving a mean of 8.7 <sup>μg/mL</sup>. Following a product switch to generic lamotrigine, the subject has a steady state plasma concentration of 4.8<sup>μg/mL</sup> also drawn in the early morning as a trough level 10 hours after the last dose, which is 3.9<sup>μg/mL</sup> different from the mean on the brand Lamictal. Using the criteria above, the CV<sub>pop75</sub> is 21.5 multiplied by 2 equals 43% multiplied by the mean on the baseline (8.7<sup>μg/mL</sup>) equals 3.74<sup>μg/mL</sup>. The subject’s difference of 3.9<sup>μg/mL</sup> is greater than the criteria difference of 3.74<sup>μg/mL</sup> meaning that this subject would qualify for the trial’s enriched population. The other inclusion criteria (as per section 4.1.3.c.ii) are also met as at least one of the baseline levels is equal to or greater than 4 <sup>μg/mL</sup> and the level on the switched product is at least 2 <sup>μg/mL</sup> different from the mean of the baseline levels. In addition, the baseline levels of 8.2<sup>μg/mL</sup> and 9.2<sup>μg/mL</sup> can be used because the difference of 1<sup>μg/mL</sup> is less than 21.5% (CV<sub>pop75</sub> from Table 1) times the mean of 8.7<sup>μg/mL</sup> which equals 1.8<sup>μg/mL</sup>.

For the study, the following multipliers of the mean baseline level will be used to define the criteria difference required to qualify for subjects with one or two baseline levels:
Appendix 1 - Table 2: Multiplies for population level criteria

<table>
<thead>
<tr>
<th>Group</th>
<th>2 times CV&lt;sub&gt;pop75&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral (no inhibitors or inducers)</td>
<td>43%</td>
</tr>
<tr>
<td>Induced (e.g. PHT, CBZ, PB, PRM)</td>
<td>58.6%</td>
</tr>
<tr>
<td>Inhibited (VPA)</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

A subject receiving both inducing and inhibiting concomitant drugs will be categorized in the inducing group, the most conservative categorization. Concomitant AEDs considered neutral are TPM, OXC, GBP, PGB, LEV, ZNS, VGB, LAC, RUF, and benzodiazepines.
14.0 Appendix 2 - ANDA Data:

ANDA AUC and Cmax data under fasting conditions for lamotrigine used to select the manufacturers of the products for in vitro testing:
Bioequivalence (AUC) of 25 lamotrigine generic formulations: point estimates and 90% CI under fasting conditions
Bioequivalence (Cmax) of 25 lamotrigine generic formulations: point estimates and 90% CI under fasting conditions.
15.0 Appendix 3: Most Disparate Product Selection:

**Bioequivalence study data:** The ANDA average bioequivalence data were obtained for approved generic AED products from the FDA Center for Drug Evaluation and Research (CDER), Office of Generic Drugs. Separate fasting and fed BE studies were performed for most generic products. Key data for test and reference products were the geometric mean ratios (GMRs) and their 90% confidence interval (CI) for the maximum concentration (Cmax) and for the area under the plasma concentration time curve (AUC) calculated to the last measured concentration (AUC$_{0-t}$), and extrapolated to infinity (AUC$_{0-\infty}$).

**Ranking based on ABE data:** Comparison of the ABE data on the products was performed as the first step to determine the most disparate products using the following scheme. The ideal disparate products had the 90% CI completely below or above the reference for both the mean Cmax and AUC compared to the brand product (that is they do not include 100%). Rankings were initially based on the mean. For those with similar means, the products with the greatest distance of the lower or upper bounds of the CI from reference 100% received the highest ranks. However, the ranking was done even for those products that overlapped 100% with the products with the smallest overlap having the higher ranks. The products were ranked based on both CIs and means for both the Cmax and AUC. The decision to weigh the Cmax or AUC more heavily was based on the expert opinion of the steering committee.

For example, using the illustrations in Figure 1 in section 2.1, the products in C would be ranked #1 for both the low and high groups. The top two products in D would be ranked 2nd in each group because the means are most different and the low and high ends of the CI, which overlap, are closest to 100%.
Appendix 3 - Table 1: Most Disparate Generics based on ANDA data (Ranked by Steering Committee May 2011):

<table>
<thead>
<tr>
<th>LTG 25 mg (1 or 2)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mylan 76630a</td>
<td>Roxane 77392 &gt;</td>
</tr>
<tr>
<td></td>
<td>Apotex 78625</td>
<td>Sandoz 78409</td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mylan 76630a</td>
<td>Zydus 77633, Roxane</td>
</tr>
<tr>
<td></td>
<td>Apotex 78625</td>
<td>77392, Aurobindo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78956, Taro 79204,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wockhardt 78982</td>
</tr>
<tr>
<td>AUC</td>
<td>Fed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mylan 76630,</td>
<td>Sandoz 78645, Zydus</td>
</tr>
<tr>
<td></td>
<td>Sandoz 78409</td>
<td>77633, Roxane 77392,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taro 78525 &amp; 79204,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Torrent 78947</td>
</tr>
<tr>
<td>Cmax</td>
<td>Fed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandoz 78409,</td>
<td>Taro 78525, Torrent</td>
</tr>
<tr>
<td></td>
<td>Mylan 76630</td>
<td>78947, Zydus 77633,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sandoz 78645 &gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upsher Smith 78310</td>
</tr>
<tr>
<td>OVERALL - LTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mylan 76630 and</td>
<td>Roxane 77392, Taro</td>
</tr>
<tr>
<td></td>
<td>Apotex 78625</td>
<td>79204 &amp; 78525,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aurobindo 78956 and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zydus 77633</td>
</tr>
</tbody>
</table>

Final selection of candidate products based on ABE data: The steering committee by consensus selected the following several products as predicted to be most disparate based on ABE data for additional study using *in vitro* testing.

Lamotrigine predicted low:
  - Mylan 76630 and Apotex 78625

Lamotrigine predicted high:
  - Roxane 77392, Taro 79204 & 78525, Aurobindo 78956 and Zydus 77633
16.0 : Appendix 4: FDA Investigation of ANDA Data and Excipients to Select Most Disparate Products:

Selection of Disparate Generic Lamotrigine ANDAs for EQUIGEN Study

Summary

Generic lamotrigine products are available in two dosage forms: tablet and chewable/dispersible tablet. Lamotrigine tablet is the subject of the EQUIGEN study. There are total 21 Abbreviated New Drug Applications (ANDAs) approved for lamotrigine tablets up to Mar 2012. Four of them are discontinued. Thus, 17 lamotrigine tablet ANDAs are considered for the selection of the most disparate products using the following scheme:

1) Use differences in bioequivalence data under fasting and fed conditions to prescreen ANDAs for further selections

Further selections are based on
2) Differences in impurity and dissolution profile
3) Formulation differences
4) Differences in dissolution profile, manufacturing process, bioequivalence study site and strength, and years on the market

The upper and lower confidence interval (CI) of AUC for these 17 ANDAs varied between 92.43 and 114.10 with a range of point estimates of 0.98 to 1.09. The upper and lower CI of Cmax varied between 91.72 and 115.75 with a range of point estimates of 0.97 to 1.09. The ANDAs are ranked initially based on the geometric mean ratio of Cmax and AUC. For those with similar means, the products with the greatest distance of the lower or upper bounds of the CI from reference 100% received the highest ranks. Based on these rationales, 9 ANDAs are considered for further evaluation. The upper and lower confidence interval (CI) of AUC for the 9 ANDAs varied between 94.43 and 114.10 with a range of point estimates of 0.98 to 1.09. The upper and lower CI of Cmax of these 9 ANDAs varied between 91.72 and 115.75 with a range of point estimates of 0.97 to 1.09.

The 9 ANDAs have comparable drug product impurity profiles. Several ANDAs which has slightly wider dissolution specifications are ranked higher in the lamotrigine predicted low group. If possible, the lamotrigine predicted high and low ANDAs are preferred to differ most in formulation composition, manufacturing process, BE study sites and strength.

Considering all the above mentioned factors, the following ANDAs are selected as the most disparate ANDAs for the EQUIGEN study.

Lamotrigine predicted low: ANDA 78625 (1st choice), ANDA 78645 (2nd choice),
Lamotrigine predicted high: ANDA 76708 (1st choice), ANDA 78525 (2nd choice)

ANDA 78625 and ANDA 76708 are both approved in 2009 and epilepsy patients may have similar exposure time to these products. Under fasting condition, the CI of AUC for ANDA 78625 is between 95.48 and 101.43 with a point estimate of 0.98 while the CI of
AUC for ANDA 76708 is between 102.0 and 113.8 with a point estimate of 1.08; the CI of Cmax for ANDA 78625 is between 93.81 and 100.57 with a point estimate of 0.97 while the CI of Cmax for ANDA 76708 is between 100.8 and 105.8 with a point estimate of 1.04. ANDA 78625 is composed of microcrytalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, colorants, and ANDA 76708 is composed of mannitol, powdered cellulose, L-hydroxypropyl cellulose, hydroxypropyl cellulose NF, magenesium stearate, and talc. ANDA 76708 and ANDA 78625 also differ in manufacturing process, BE study sites and strength.

The document below summarized the details of the ANDA selection.

**Step 1: Ranking based on average bioequivalence (ABE) data**

Both FDA OGD and the EQUIGEN Steering Committee conducted a ranking of lamotrigine ANDAs based on average bioequivalence data of ANDAs. FDA ranked the ANDAs initially based on the geometric mean ratio of Cmax and AUC. Data from fasting study are weighed more than the fed study. For those with similar means, the products with the greatest distance of the lower or upper bounds of the CI from reference 100% received the highest ranks. In addition, the study with point estimate not including 1 are weighted more. Based on the above rationales, FDA considered the following ANDAs for further evaluation:

Lamotrigine predicted low: ANDA 78625, ANDA 78645, and ANDA 90607
Lamotrigine predicted high: ANDA 76708, ANDA 77783, and ANDA 77710

The steering committee selected the following several products as predicted to be most disparate based on similar rationales except that fasting study data and the study with point estimate not including 1 were not weighed higher.

Lamotrigine predicted low: Apotex 78625
Lamotrigine predicted high: ANDA 78525, ANDA 78956 and ANDA 77633

To have a comprehensive analysis evaluation, both FDA and EQUIGEN steering committee’s preliminary selections are combined and carried forward for further evaluation. The ANDAs are:

Lamotrigine predicted low: Apotex 78625, ANDA 78645, and ANDA 90607
Lamotrigine predicted high: ANDA 76708, ANDA 77783, ANDA 77710, ANDA 78525, ANDA 78956, and ANDA 77633

**Step 2: Ranking based on drug product impurity and dissolution profile**

1 The steering committee initially included discontinued product and chewable product in the selection, and they are eliminated from the list. In addition, the recently approved ANDAs were not included in evaluation by the steering committee.

2 The drastic difference between the steering committee and FDA’s selection on lamotrigine predicted high is because that FDA weighed the study with point estimate not including 1 higher.
The 9 ANDAs have comparable drug product impurity profiles. Several ANDAs have dissolution specifications which allow slightly slower dissolution than the RLD. They are ranked higher in the lamotrigine predicted low group.

Step 3: Ranking based on difference in drug product composition

Table 1 summarized the formulation compositions and tablet appearance of RLD and generic lamotrigine tablets. The weight of generic lamotrigine tablets ranged from 200 mg to 350 mg. The tablet shapes are available in round, capsule, shield, and trigonal. Of them, ANDA 76708 differs most from the RLD, and also from the ANDAs of the lamotrigine predicted low group. Due to this formulation difference, ANDA 76708 was ranked higher in the lamotrigine predicted high group.

Table 1. Formulation composition of lamotrigine tablets

<table>
<thead>
<tr>
<th>Application</th>
<th>Formulation Compositions</th>
</tr>
</thead>
<tbody>
<tr>
<td>20241 (RLD)</td>
<td>Microcrystalline cellulose, Lactose, povidone, sodium starch glycolate, magnesium stearate, colorant</td>
</tr>
<tr>
<td>78625</td>
<td>Microcrystalline cellulose, Sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, colorants</td>
</tr>
<tr>
<td>78645</td>
<td>Microcrystalline cellulose NF, povidone USP, sodium starch glycolate, low-substituted hydroxylpropyl cellulose, colloidal silicon dioxide, colorants and magnesium stearate.</td>
</tr>
<tr>
<td>90607</td>
<td>Lactose monohydrate, sodium starch glycolate, povidone, talc, magnesium stearate</td>
</tr>
<tr>
<td>76708</td>
<td>Mannitol, powdered cellulose, L-hydroxypropyl cellulose, Hydroxypropyl cellulose NF, Magnesium stearate, Talc,</td>
</tr>
<tr>
<td>78956</td>
<td>Microcrystalline cellulose, Lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, colorants</td>
</tr>
<tr>
<td>78525</td>
<td>Lactose monohydrate, microcrystalline cellulose, povidone, Croscarmellose sodium, Crospovidone, magnesium stearate, colorants</td>
</tr>
<tr>
<td>77633</td>
<td>Microcrystalline cellulose, lactose monohydrate, Povidone, sodium startch glycolate, magnesium stearate</td>
</tr>
<tr>
<td>77783</td>
<td>Lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, povidone, magnesium stearate, colorant</td>
</tr>
<tr>
<td>90170</td>
<td>Lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, colorants</td>
</tr>
</tbody>
</table>

Step 4: Ranking based on ANDA manufacturing process, bioequivalence study strength, site, and year of approval
Other factors considered in the ranking of disparate lamotrigine ANDAs are manufacturing process, bioequivalence study strength, site, and year of approval. Fig 1 listed the distribution of the year of approval of 9 ANDAs selected in step 1. ANDAs approved in earlier years may have higher market share and more patient experiences, thus they are generally ranked higher compared to those of recently approved ANDAs. Fig 2, 3, and 4 listed the distribution of manufacturing process, BE study sites, strength of 9 ANDAs selected, respectively. If possible, the lamotrigine predicted high and low ANDAs are preferred to differ in manufacturing process, BE study sites and strength.

Disparate Lamotrigine ANDA selection

Based on all factors considered in step 1, 2, 3, and 4, the following ANDAs are recommended as the most disparate ANDAs for the EQUIGEN study.

Lamotrigine predicted low: Apotex 78625 (1st choice), ANDA 78645 (2nd choice),
Lamotrigine predicted high: ANDA 76708 (1st choice), ANDA 78525 (2nd choice)

ANDA 78625 and ANDA 76708 are both approved in 2009 and epilepsy patients may have similar exposure time to these products. Under fasting condition, the CI of AUC for ANDA 78625 is between 95.48 and 101.43 with a point estimate of 0.98 while the CI of AUC for ANDA 76708 is between 102.0 and 113.8 with a point estimate of 1.08 (Table 1); the CI of Cmax for ANDA 78625 is between 93.81 and 100.57 with a point estimate of 0.97 while the CI of Cmax for ANDA 76708 is between 100.8 and 105.8 with a point estimate of 1.04 (Table 1).

ANDA 78625 is composed of microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, colorants, and ANDA 76708 is composed of mannitol, powdered cellulose, L-hydroxypropyl cellulose, hydroxypropyl cellulose NF, magnesium stearate, and talc. ANDA 78625 and ANDA 76708 also differ in manufacturing process, BE study sites and strength.
Fig 1. Year of Approval of 9 ANDAs selected

![Pie chart showing the year of approval of 9 ANDAs selected: 2009, 2010, 2011.]

Fig 2. Manufacturing process of 9 ANDAs selected

![Pie chart showing the manufacturing processes of 9 ANDAs selected: Wet granulation, Direct Compression.]
Fig 3. Bioequivalence study sites of the 9 ANDAs selected

Bioequivalence Study Sites of the 9 ANDAs selected

- India
- Canada
- US

Fig 4. Bioequivalence study strength of the 9 ANDAs selected

Bioequivalence Study Strengths of the 9 ANDAs selected

- 25 mg
- 200 mg
- 25*2 mg
Table 1. BE data of selected disparate lamotrigine ANDAs

<table>
<thead>
<tr>
<th>Selections</th>
<th>Fast</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC PE</td>
<td>CMAX PE</td>
</tr>
<tr>
<td>Low 1st</td>
<td>78625</td>
<td>0.98</td>
</tr>
<tr>
<td>Low 2nd</td>
<td>78645</td>
<td>1.02</td>
</tr>
<tr>
<td>High 1st</td>
<td>76708</td>
<td>1.08</td>
</tr>
<tr>
<td>High 2nd</td>
<td>78525</td>
<td>1.03</td>
</tr>
</tbody>
</table>