# Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products: Aim 2

**NCT02707965**

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Abbreviated title: Characterization of epilepsy patients BEEP2b

Protocol Version: 5.10

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University of Maryland Baltimore
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620 W. Lexington Street, Second Floor
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Research Involving Human Subjects Committee (RIHSC)
U.S. Food and Drug Administration
White Oak Building 32, Room4286
10903 New Hampshire Ave
Silver Spring, MD 20993

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# PROTOCOL SUMMARY

## Abstract

This pilot study is exploratory research to characterize the "generic brittle" (GB) patient and to identify major causes for generic brittleness in epilepsy patients who are sensitive to antiepileptic drug (AED) formulation changes.
The primary aim of this BEEP2b study is to perform individual pharmacokinetic (PK) similarity testing of brand and generic AEDs in "probably GB" patients (N=24),who were selected on the basis of having GB-defining factors from the BEEP2a study, in order to confirm whether these factors are predictive of a generic brittle response to product switching. The study design involves a randomized, investigator-blinded, multiple-dose, complete four-way replicate crossover (i.e. RTTR and TRRT) design in which one brand and one generic will be compared in each patient from the patient's own AED regimen. Associated adverse events (i.e. seizures and side effects) will also be assessed. Bioequivalence (BE) will not be assessed. Rather, about nine AEDs are expected to be collectively evaluated. Generic brittleness anticipates that, for individual subjects, brand and generic may be the same or different, depending upon the underlying basis for generic brittleness. This exploratory research is focused on understanding individual patient attributes that contribute to GB, and is not focused on either product development or comparison of specific products.

## Lay Summary

Some epilepsy patients are described as GB when they have worsened seizures or side effects related to switching between brand name and generic, or between generic antiepileptic drug (AED) products. In concert with Aim 1 (protocol BEEP2a), this study will uncover possible reasons for patient problems with the drug switching. Factors that will be studied in GB epilepsy patients include physiologic, psychological, and genetic factors, including in this protocol whether brand and generic AEDs are pharmacokinetically similar in GB individuals.

## Study Summary

**Objectives:** The primary aim of this BEEP2b study is to perform individual PK similarity testing of brand and generic AEDs in a predefined cohort of "probably GB" patients (N=24) to test and further refine the working definition of GB. Associated adverse events (i.e. seizures and side effects) will also be assessed. From study BEEP2a, these N=24 patients will have shown the greatest potential strength of causation between physiologic, psychological, or genetic test abnormality and prior history of brittleness.

**Product Information:** Collectively across N=24 patients, about nine of the following 12 brand and generic products will be evaluated: oxcarbazepine tablet, divalproex sodium ER tablet, carbamazepine ER capsule and/or tablet, lamotrigine ER tablet, levetiracetam ER tablet, topiramate tablet and/or capsule, zonisamide capsule, phenytoin sodium capsule, levetiracetam IR tablet, and lamotrigine IR tablet.

**Study Duration:** 9 months

**Patient Population:** Focal or primary generalized epilepsy

**Sample Size:** 24
**Participation Duration:** approximately 18 weeks

**Location:** University of Maryland Medical Center
All clinical research procedures will occur at the University of Maryland Medical Center. Recruitment will be from BEEP2a study.

University of Maryland Medical Center (UMMC)
22 S. Greene Street
Baltimore, MD 21201

**Regulatory Status:**
An IND is not needed for this study. This is a pharmacokinetic study. CT.gov registration is NCT02707965.

**Types of Research:**
This is a clinical trial. The Types of research procedures involved in this pharmacokinetic study include the following:

- Sample (Specimen) Collection and/or Analysis (including pharmacokinetic analysis).
- Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).

**Risk Level:**
Greater than Minimal

## KEY ROLES AND CONTACT INFORMATION

### Key Roles

Principal Investigator (PI):
James E. Polli, PhD
Professor and Ralph F. Shangraw/Noxell Endowed Chair in Industrial Pharmaceutics
University of Maryland School of Pharmacy

Co-PI:
Tricia Ting, MD
University of Maryland School of Medicine
Department of Neurology, Division of Epilepsy, and
Georgetown University Department of Neurology

Study physician: Jeffery Fink, MD
Professor
University of Maryland School of Medicine

### Credentials of Investigators

[redacted]

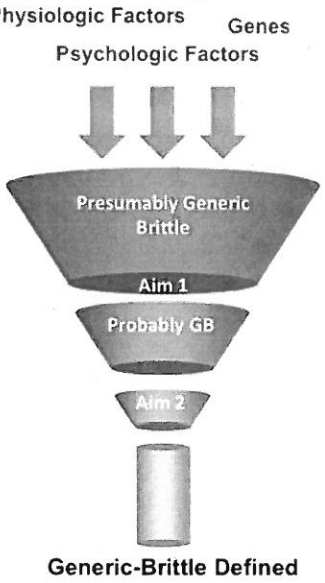
[redacted]

## Contact Information

[redacted]

## INTRODUCTION AND OVERVIEW

[redacted]




[redacted]

Patients at-risk for switchability problems may be subject to phenomena that predispose them to being GB, including physiologic factors, psychological factors, and pharmacogenetic factors. Physiologic factors such as age, drug interactions with polypharmacy, hepatic enzyme activity, and elimination rates may alter the PK of AEDs and amplify the effects of any formulation differences to clinical significance in at-risk individuals. Genetic variants for drug metabolism enzymes may not only influence pharmacokinetics and drug clearance, but also individual responsiveness to particular AEDs, a current focus of personalized medicine. Psychological factors may significantly influence adverse event reporting and tolerability to AED switching in the generic brittle. Patient attitudes and expectations may predispose to perceived problems with formulation switching. In the lamotrigine BEEP study, we gained excellent experience in the nocebo effect.

### Working Definition of GB Classification

[redacted] A final group of patients at greatest risk for being GB (Probably GB) will be defined by outcomes of standardized measures, and eligible for participation in BEEP2b.

[redacted]

[redacted]

**Probably GB** – requires an **abnormality in physiologic or psychologic measures**; or having a genetic variant in an AED response gene that has been validated; A list of subjects who are probably GB will be generated as a result of this study.

**Not GB** – based on having had neither problems with AED side effect(s) nor unanticipated breakthrough seizures on AED nor prior problems with generic AED substitution or switching.

[redacted]

In this BEEP2b protocol, individual PK profile similarity testing will be conducted in a small cohort (N=24) of epilepsy patients considered probably GB from BEEP2a. These patients will enroll in a replicate crossover comparison study of brand and generic formulations of their usual AEDs at steady-state. Bioequivalence will not be assessed. Figure 2 illustrates the individual pharmacokinetic comparison study.

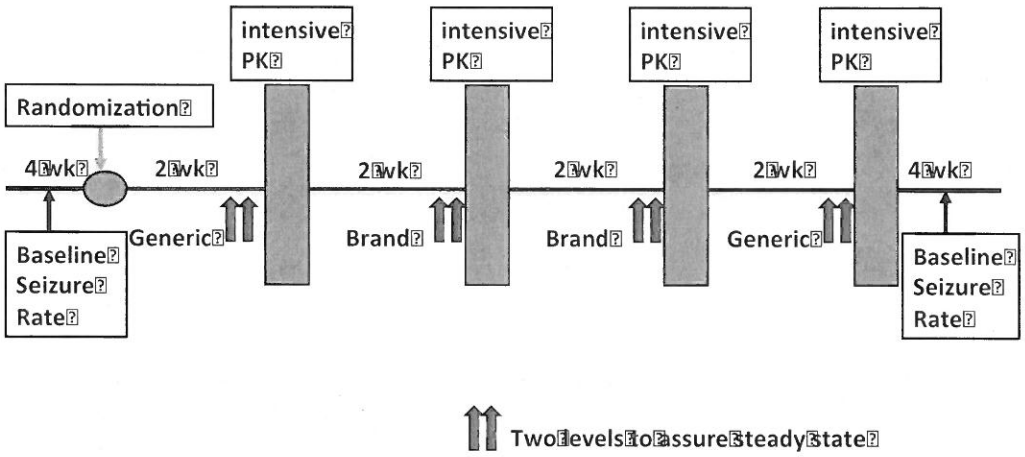
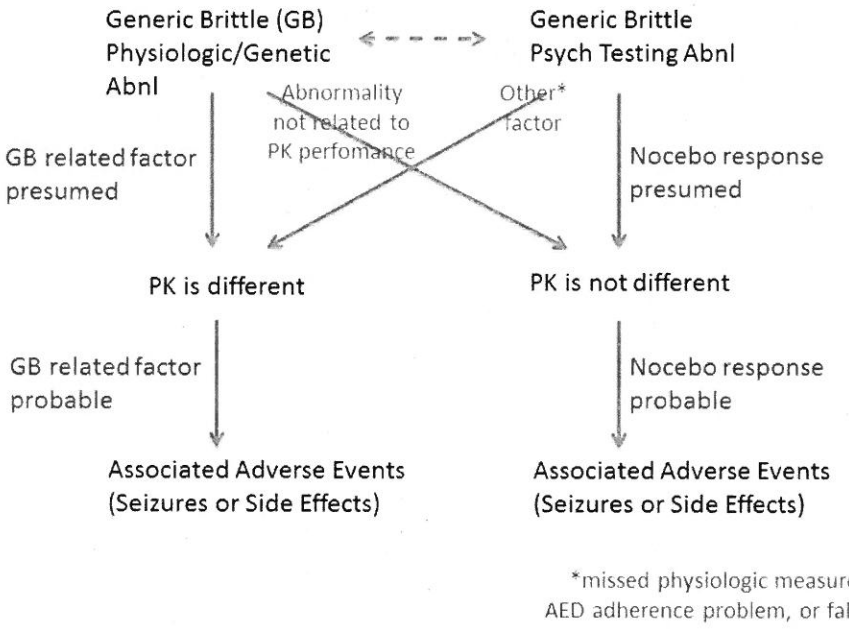



Figure 2. Individual pharmacokinetic comparison study with a randomized, investigator-blinded, multiple-dose, complete four-way replicate crossover (e.g. TRRT and RTTR) design in which brands and generics will be compared in each patient, with one AED from the patient's own regimen. Each period is two weeks in duration. With two weeks between screening and the start of "pre-study" baseline seizure rate assessment, the study will span about 18 weeks for any one subject. In addition, optional EEG monitoring may be done in subjects with large seizure frequencies (i.e. more than 30 per month); a 5-day ambulatory EEG is sampled in each of the first two treatment arms for seizure count validation.

The main outcome of this protocol is a more refined definition of GB through the PK comparison of brand and generic AED formulations in 24 patients who have been denoted to be probably GB. Generic brittleness anticipated that, for individual subjects, brand and generic may be the same or different, depending upon the underlying basis for generic brittleness. For example, a subject with a psychologic testing abnormality may exhibit a nocebo effect and hence brand and generic profiles can be expected to be similar.




[redacted]

## OBJECTIVES

The main outcome of this pilot study, in concert with BEEP2a, is to identify factors underlying generic brittleness in epilepsy patients, which is currently very poorly defined and understood.

### Study Aims

The primary aim of this BEEP2b study is to perform individual PK similarity testing of brand and generic AEDs in probably GB patients (N=24). Associated adverse events (i.e. seizures and side effects) will also be assessed. These N=24 patients will have shown the greatest potential strength of causation between test abnormality and prior history of generic brittleness in study BEEP2a. Individual PK similarity testing here is intended to assess whether the

proposed factors underlying generic brittleness are truly predictive of a generic brittle response to switching drug products. BE will not be assessed.

### Study Outcomes

This exploratory study will contribute towards a more refined definition of GB. Individual PK performance in patients, who were selected on the basis of having GB-defining factors from BEEP2a, will help confirm whether these factors are predictive. Moreover, prospective assessment of any seizures and side effects associated with formulation switching in this study will provide clinical correlation for any observed differences in PK, or in the absence of a PK difference, potential evidence for a nocebo response. Assessments of safety and efficacy in adverse event monitoring with AED switching will offer additional insights into defining generic brittleness. BE will not be assessed.

[redacted]

## STUDY DESIGN AND METHODS

### Study Design

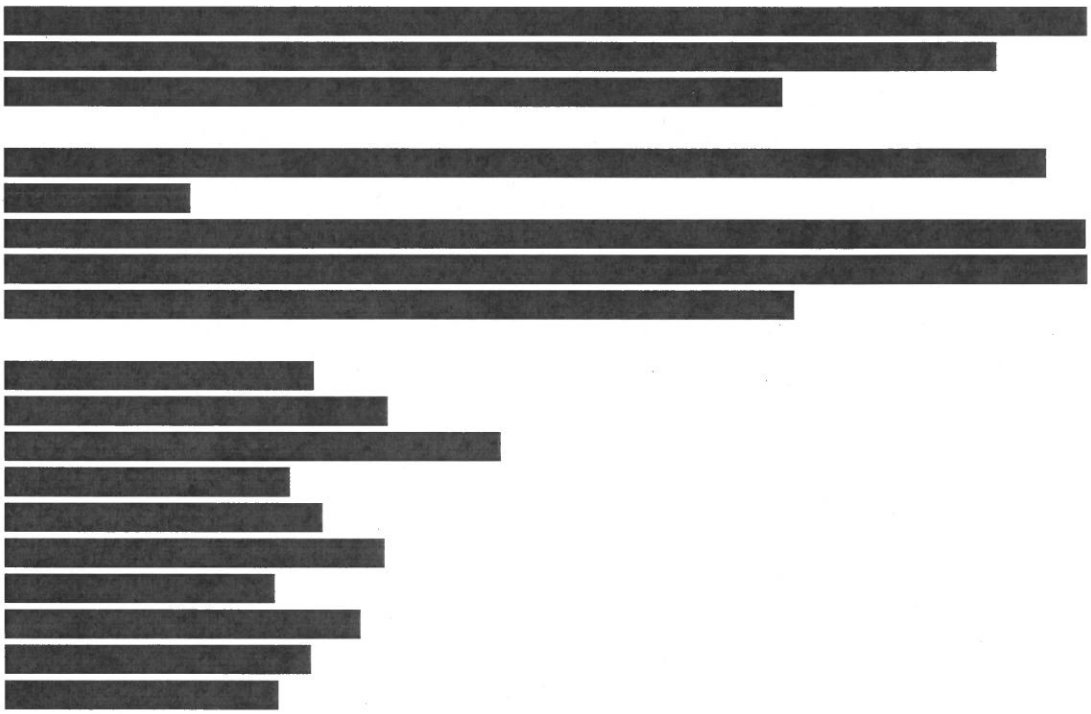
This is a replicate design, two treatment, four period, investigator-blinded, multiple-dose pharmacokinetic comparison study. This study is exploratory and a final draft definition of BG is expected. Figure 2 (above) illustrates the overall design of this individual pharmacokinetic comparison study. In each patient, brand and generic will be compared, evaluating an FDA-approved AED from their own regimen. Only a single AED will be evaluated in each patient in order to optimize feasibility, adherence and, thereby, safety. For example, if a patient is on three AEDs (which is common), one of these AEDs will be evaluated (i.e. brand and generic compared via steady-state PK profile comparison). Total daily doses of study drug will amount to patient's usual daily doses divided into their usual dosing frequency. It is expected that different AEDs will be studied in individuals, such that collectively about eight or nine different AEDs will be studied.

Approximately nine drug products are expected to be examined in these probably GB patients. The 12 possible drug products (across eight drug substances) are: oxcarbazepine tablet, divalproex sodium ER tablet, carbamazepine ER capsule

and/or tablet, lamotrigine ER tablet, levetiracetam ER tablet, topiramate tablet and/or capsule, zonisamide capsule, phenytoin sodium capsule, levetiracetam IR tablet, and lamotrigine IR tablet. Periods will be two weeks in duration, to allow for steady-state to be achieved.

Parent drug in plasma will be the analyte. Additionally, for oxcarbazepine, its active metabolite 10-monohydroxy derivative (MHD) will also be quantified as additional data.

One eligibility requirement is that a patient must be taking at least one of the above AED drug products.



## STUDY ENROLLMENT AND WITHDRAWAL

### Eligibility

All adult epilepsy patients who are eligible may enroll in this study. Vagus nerve stimulation and intermittent benzodiazepine use (e.g. lorazepam, diazepam, clonazepam) are not exclusion criteria.

Epilepsy patients determined to be probably GB (following completion of Aim 1 (BEEP2a) will be eligible for BEEP2b enrollment. **Probably GB** – requires an abnormality in physiologic or psychological measures; or having a genetic variant in an AED response gene that has been validated.

The following criteria for laboratory and neuropsychological testing abnormalities will be employed to identify patients as probably GB and eligible for the BEEP2b individual pharmacokinetic assessment. Any single physiologic lab or psychological measure considered of potential clinical significance by virtue of meeting the results criteria below, or any single genetic variant identified, will identify a patient as probably GB.

Inclusion Criteria

1. Subject previously completed BEEP2a study, found to be probably GB, and able to provide informed consent or subject's legally authorized representative is able to provide informed consent.
2. Subject is male or female between 18 and 76 years of age inclusive.
3. Subject has a diagnosis of epilepsy including focal or primary generalized epilepsy.
4. Subject is taking at least one study antiepileptic drug for the treatment of epilepsy.
5. Subject is an acceptable candidate for venipuncture.
6. Subject is willing to be switched between brand and generic drug.
7. Subject is willing to stop all non-routine OTC medications for 24 hours prior to and during pharmacokinetic study visits.
8. Subject is willing to maintain stable doses of all other AEDs, including Vagus Nerve Stimulation parameters for the duration of the study.

Exclusion Criteria

1. Subject has any medical condition, including a progressive neurological condition, which in the opinion of the investigator, could jeopardize the subject's health or would compromise the subject's ability to participate in the trial.
2. Subject has a history of alcohol or drug abuse, which in the opinion of the investigator, could jeopardize the subject's health or would compromise the subject's ability to participate in this trial.
3. Subject has a history of previous or current significant psychiatric disorder that would interfere with conduct of the study.
4. Subject is pregnant or lactating.
5. Subject has severe liver impairment as assessed by alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥10 times the upper limit of normal (ULN).
6. Subject has severe renal impairment as assessed by creatinine clearance lower than 30mL/min, using the Cockcroft-Gault formula.
7. Female subjects of childbearing potential will not be eligible to participate who are unwilling or unable to use a medically acceptable method of contraception throughout the entire study period and for one week after the study is completed. Medically acceptable methods of contraception that may be used by the subject and/or her partner are: condom with spermicide, diaphragm with spermicide, IUD without progesterone, vaginal spermicidal suppository, surgical sterilization of their partner(s) or abstinence.
8. Subject is not willing or able to be adherent to study protocol (e.g. study medication dosing and any interacting comedication).

## Enrollment

It is anticipated that N=36 subjects will be screened so that at least N=24 subjects will be completed. Subjects will be recruited from subjects who completed BEEP2a study and found to be probably GB. Probably GB requires an abnormality in physiologic or psychologic measures; or having a genetic variant in an AED response gene that has been validated.

All BEEP2a subjects found to be probably GB and who have indicated a willingness to be contacted about this protocol (i.e. BEEP2b) will be contacted and asked about their willingness to be screened. Subjects who indicate a continued willingness to be screened will be provided an appointment for screening at UMMS. During the consenting and screening process, no coercive statements will be made to encourage subject participation. No advertisements will be used.

## Informed Consent Forms

[redacted]

## Withdrawal

[redacted]

[redacted]

[redacted]

## STUDY SCHEDULE AND PROCEDURES

### Study Schedule

[redacted]

### Study Procedures

All study procedures are research-related. There are a total of 15 or 16 study visits over approximately 18 weeks. The first visit (visit 1) is a screening visit to assess if the subject is willing and eligible. If a subject is eligible, he or she will record a 4 week "pre-study" baseline seizure and adverse event diary prior to the second visit. Diary entries will include date and time of events and documentation of days of no seizure occurrence. The second visit (visit 2) is the medication pick-up, where the subject will pick up their medication for the first study arm. The next 12 visits involve blood draws to allow for pharmacokinetic assessment of drug levels, across the four study arms. Eight of these 12 visits will be short (about 30 minutes in duration) to allow for drug trough level measurement and assessment of pharmacokinetic steady-state. Four of these 12 visits will involve 6, 12, or 24 hour PK sampling, one for each of the study arms. Duration of sampling will equal the patient's study AED dosing interval (i.e. 6 hr if drug is given three-times-a-day, 12 hr if drug given every 12 hr, or 24 hr if drug given once daily). The four arms reflect a full replicate design to compare two products (i.e. brand and generic), where each subject takes each product (at steady-state) twice. After visit 14, patients will resume taking the medication that their physician has prescribed. The last visit (visit 15) will occur about 4 weeks after arm 4 to collect patient final seizure diary (about 30 minutes), to collect "post-study" baseline seizure rate. A possible one extra visit is if blood samples cannot be collected to measure study drug levels on visit 5, 8, 11, or 14. The participant may be asked to visit one additional time, so all blood pharmacokinetic samples are collected.

Subjects will be randomized into one of two sequences: sequence T (test, reference, reference, and finally test) or sequence R (reference, test, test, and finally reference). Each of the four arms (or periods) will be about two weeks in duration. During the study, subjects will receive their ongoing therapeutic drug regimen. Study medication (brand or generic) will be dispensed to the subject at

the start of each study arm, per randomization. Study medication will be dispensed by the UMMC investigational drug pharmacy.

[redacted]

Subject ID Number

[redacted]

Screening: Visit 1

[redacted]

At this visit, the HIPAA and consent forms will be reviewed with the subject by a member of the research staff; they will be signed and dated.

Demographic information will be obtained. A brief physical exam with a medical/medication history, including smoking and alcohol, will be conducted at the GCRC. Subjects will be asked whether they are currently taking the brand name or a generic formulation. Blood pressure, pulse and respiration, and weight will be obtained. Clinical safety labs of serum chemistries will include hepatic and renal function tests (i.e. creatinine, BUN, AST, ALT, and total bilirubin), as well as a screening Point of Care hemoglobin test using 1 drop of blood to test for anemia assessment. Amount of blood drawn is approximately 10cc. Screening labs that are outside of the normal range will be reviewed by study physician to determine subject's eligibility and the need for further medical care. Subjects may request copies of lab values. Female subjects will be asked if they are pregnant, trying to become pregnant, breast-feeding, and willing to use certain methods of contraception throughout the entire study period and for one week after the study

is completed. Female subjects of childbearing potential will have a urine pregnancy test, as well as asked if they are breast-feeding. If a subject is pregnant or breast-feeding, they will not be enrolled. The subject will be asked if they are willing to stop any OTC (over-the-counter) medications for 24 hours before and during each study visit, starting with visit 3. The subject will be asked if they are willing and able to fast overnight for some morning visits. The subject will be asked if they are willing and able to follow study requirements, such as reliably take study medications as directed (i.e. TID, or every 12 or 24 hr), reliably take certain other medications that may impact drug pharmacokinetics (e.g. carbamazepine, phenytoin, valproate, phenobarbital, primidone), and attend all appointments at the GCRC facility. Subjects whose study AED medication is given once daily will be asked if they are willing to stay overnight.

[redacted]

Medication Pick Up Visit: Visit 2

Visit 2 involves the subject picking up study medication for the first study arm, where the subject will start study dosing the next morning. [redacted]

[redacted]

[redacted]

Blood Sample Visits for Study Arm 1

After taking study medication for most of arm 1, subjects will return to the GCRC for blood sampling for subsequent plasma analysis of drug concentration. Visit 3 and 4 will be on the second-to-last day of arm 1, in order to obtain two trough levels (i.e. Cmin) in this multiple dose design, in order evaluate if subject is at a pharmacokinetic steady-state. For example, for subjects taking study drug every 12 hours, Troughs will be collected at about 7AM and 7PM. Visit 5 is the 6, 12, or 24 hr pharmacokinetic visit. Visits 3-5 involve two days, although also involve an overnight stay in the GCRC (or nearby hotel) and part of a third day for subjects taking once daily study AED (i.e. subjects providing blood samples over 24 hr).

For visits 3 and 4, study medication will also be administered immediately after blood sampling (e.g. first and second doses for subjects taking study drug TID). Subjects who are taking study drug only once daily, only one trough level will be obtained, and there will be no visit 4.

Subjects will be requested to arrive at the GCRC by about 7AM for visit 3, after an overnight fast of 10 hours (except water), and arrive prior to taking that morning's dose. Vitals (blood pressure, pulse and respirations) will be taken. Female subjects of childbearing potential will have a urine pregnancy test, as well as asked if they are breast-feeding. If a subject is pregnant or breast-feeding, they will be removed from the study. Subjects will be asked about their health, medication compliance, and about other medications, including OTC drugs and any nutritional supplements. If inclusion/exclusion requirements are met, a blood sample (4-7cc or about 1 teaspoon) will be collected by individual needle stick into a green top on visit 3. Subjects will be administered their morning medication dose with 240 ml of water, and instructed to return by about 7PM for visit 4, without regard to meals. At visit 4, subjects will be asked about their medication compliance and about other medications, including OTC drugs and any nutritional supplements. Venipuncture will be used for a single blood sample. Subjects will be administered their evening medication with 240 ml of water, and instructed to return by about 7AM tomorrow for visit 5. Since subjects need to return in about 11 hours for visit 5, they would have been previously offered to stay in a near-by hotel for this evening. The offer would be for the study to pay for a room, and room only.

They will be encouraged to eat dinner within the next hour. They will be encouraged to drink water before going to bed and after waking up, but not after about 6AM of the morning of visit 5.

Visit 5 will be on the on the last full day of arm 1 and involves collecting blood at various times over 6, 12, or 24 hours. Visit 5 will last about 6, 12, or 24 hours, respectively, plus 1 hour. Like the prior day morning visit, subjects will be requested to arrive at the GCRC by about 7AM, after an overnight fast of 10 hours prior (except water), and arrive prior to taking that morning's dose. Vitals (blood pressure, pulse and respirations) will be taken. Subjects will be asked about their health, medication compliance, and about other medications, including OTC drugs and any nutritional supplements. Preferably, an IV catheter is inserted for drawing blood. Otherwise, venipuncture technique may be used for blood sampling. After a trough blood sample is taken (i.e. time zero), subjects will immediately be administered their morning dose with 240 ml of water. Four hours after taking the morning dose, or approximately 11AM, a lunch will be served. No breakfast will be served. For subjects who are providing samples for 12 or 24 hours, an afternoon snack will be served three hours later, or at approximately 2PM, and dinner will be served three hours later, or approximately at 5PM (i.e. immediately after 10 hr blood draw). Meals and snacks include beverages.

For subjects who are providing samples for 24 hours, an evening snack will be served four hours later, or at approximately 9PM. Breakfast will be served 10 hours later (i.e. immediately after 24 hr blood draw), or at approximately 7AM.

Subjects will fast between meals or snacks, except for water. However, no water is allowed 1 hour before and after drug administration. When determined to be medically necessary, a small snack can be provided to subjects. For example, if subjects with diabetes show signs of low blood sugar, orange juice and crackers with peanut butter can be administered, including during the morning fast period.

For any one study drug, 11 or 14 PK blood levels will be drawn at scheduled times. The first sample is immediately prior to drug administration. For medication that is dosed TID, the 10 remaining times are: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 hr. For medication that is dosed every 12 hours, those 11 sample times are used, as well as 8.0, 10.0, and 12.0 hr (i.e. total of 14 sample times). For medication that is dosed every 24 hours, the 14 times are: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hr. All blood samples (4-7ml) will be collected in a heparinize green top tube, placed on ice immediately, centrifuged (>2000 rpm at +4 degrees for 10 min) within 15 minutes of collection to produce plasma, split into two plasma aliquots then frozen at -20 degrees C,

[redacted]

At the end of visit 5, subjects will be given study medication for arm 2. As for other study arms, the dispensed container will have enough study for 20 days, but the subject will be scheduled to visit in about two weeks. The next visit will be on the second-to-last day of the arm, which will be day 11-17 of the arm (i.e. in 12-18 days). The subject will be instructed to bring back all unused study medication at the next visit, visit 6. Subjects will be reminded of future visits, prior to that appointment. Subjects will be reminded to keep a diary of when they take study medication. Subjects will also be reminded to record any seizures, along with any drug side effects or AEs.

For subjects taking study drug TID or every 12 hr, round 2 starts the following day (i.e. the following morning after leaving visit 5 at the GCRC). For subjects taking study drug once daily, round 2 starts immediately after the 24 hr blood collection.

[redacted]

Blood Sample Visits for Study Arm 2

Arm 2 is designed the same as arm 1, and involved visits 6, 7, and 8. For each subject, the study procedures and timing of events over these two or three days will be the same as visits 3, 4, and 5 in arm 1. As in arm 1, visits 6 and 7 will be on the second-to-last day of arm 2, and will each be about 30 minutes. Subjects will be requested to arrive at the GCRC by about 7AM for visit 6, after an overnight fast. Vitals will be taken. Female subjects of childbearing potential will have a urine pregnancy test, as well as asked if they are breast-feeding. If a subject is pregnant or breast-feeding, they will be removed from the study. Subjects will be asked about their health, medication compliance, and about other medications. If inclusion/exclusion requirements are met, a blood sample (4-7cc or about 1 teaspoon) will be collected by individual needle stick into a green top for subsequent drug trough concentration measurement. Subjects will be administered their morning dose with 240 ml of water. Subjects who are taking study drug TID or every 12 hours will be instructed to return by about 1PM or 7PM, respectively, for visit 7, without regard to meals. Subjects who are taking

study drug only once daily, there will be no visit 7 and will be instructed to return by about 7AM for visit 8.

At visit 7, subjects will be asked about their medication compliance and about other medications. Venipuncture will be used for a single blood sample. Subjects will be administered their evening dose with 240 ml of water. A hotel room will have been offered for the evening between visit 7 and 8. As in arm 1, visit 8 will be on the last day of arm 2 (i.e. the next morning) to collect a 6, 12, or 24 hour pharmacokinetic profile. For subjects taking study drug only once daily, visit 8 will span into part of a third day and require an overnight stay in the GCRC or at a nearby hotel.

### Blood Sample Visits for Study Arms 3 and 4

Arms 3 and 4 are designed the same as arm 1. Arm 3 will involve visits 9, 10, and 11. Arm 4 will involve visits 12, 13, and 14. Per sequence assignment, there will be switching between brand and generic across the four arms. [redacted]

### Visit 15

The final visit is for the patient to return the final post-study baseline seizure diary (about 30 minutes long). Diary entries will include date and time of seizures and adverse events and documentation of days of no seizure occurrence. It will be about 4 weeks after arm 4.

## Laboratory Procedures

### Clinical Laboratory Evaluations

At screening, approximately 10cc of blood will be used for clinical safety labs of serum chemistries of study participants. Clinical Laboratory tests will include:

- creatinine
- BUN
- AST
- ALT
- total bilirubin

- anemia
- pregnancy test for a woman of child-bearing potential

## Pharmacokinetic Specimen Handling and Storage

[redacted]

## Risks

[redacted]

[redacted]

[redacted]

[redacted]

## Risk/Benefit Ratio

[redacted]

Subjects may not receive any benefit by participating in this study. Characterization of generic brittle patients might lead to a means of prevention of generic drug switchability problems. The data collected from this study will not be used for any clinical decisions.

## Payment for Participation

[redacted]

[redacted]

## STATISTICAL CONSIDERATIONS AND ANALYSIS

### Study Subjects

This is an exploratory study to characterize probably GB epilepsy patients. [redacted] we anticipate about N=24 subjects who will be eligible for this protocol (i.e. probably GB, along with other I/E criteria).

### Data Analysis

For each patient, PK measurements will be compared of generic verse brand drug.

PK comparisons will include AUC0-last_ss (via the linear trapezoidal method); Cmax_ss; Cmin_ss; Tmax_ss (if the maximum value occurs at more than one time point, Tmax_ss will be the first time point with this value); and fluctuation index from 100 ×(Cmax_ss – Cmin_ss)/Cave_ss, where Cave_ss is the ratio of AUC0-last_ss/tau. Regarding subscripts, ss refers to steady-state, and 0-last_ss refers to the time from 0 hr to the last time point.

For each patient, their PK similarity will be denoted as either similar or not similar; where similar will require each Cmax_ss ratio and AUC0-last_ss ratio of generic versus brand to be within the range of 80-125%. Using routine regression methods, both forward and backward regression will be used to assess for associations between independent variables (e.g. physiological, psychological, genetic factors) and the dependant variable (i.e. PK similar or PK not similar).

Additionally, for each patient, ratio of generic versus brand for mean AUC0-last_ss, Cmax_ss, and Cmin_ss will be computed and simply characterized as being within or outside a range of 80-125%. The intra-subject variability will be calculated as well. However, these PK parameters will not be statistically compared between brand and generic due to limited sample size.

Number of seizures and AEs during brand or generic product administration will be tabulated as a secondary outcome.

In considering these BEEP2b PK observations along with BEEP2a outcomes, a descriptive analysis and interpretation of this exploratory study is intended to summarize data features. [redacted]

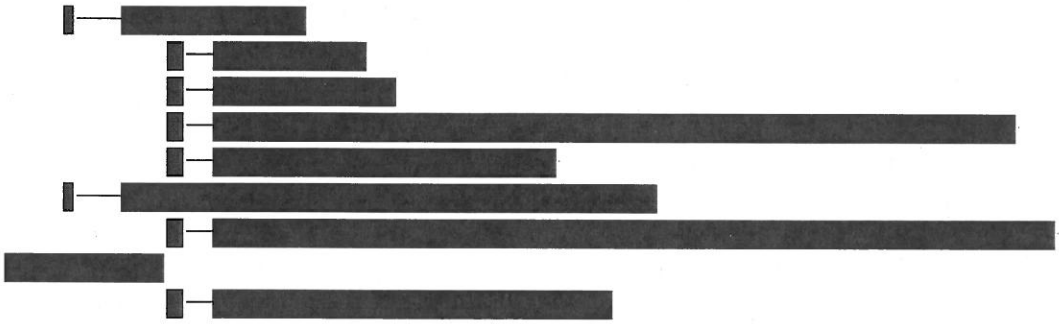
## STUDY OVERSIGHT

### Adverse Event Reporting

[redacted]

### Serious Adverse Event Reporting

[redacted]



### Monitoring

## ETHICAL CONSIDERATIONS

### Institutional Review Board (IRB)

### Ethical Conduct of the Study

### Subject Information and Consent

[redacted]

Subject Confidentiality

[redacted]

Student and Employees of the University of Maryland and the UM Medical Center

[redacted]

[redacted]

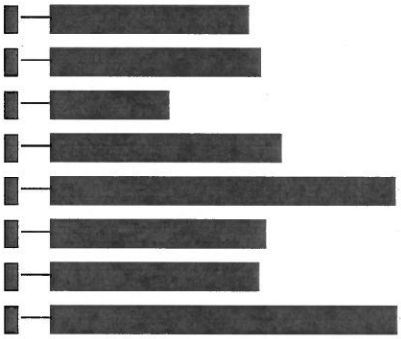
### Study-Related Injuries

[redacted]

## DATA MANAGEMENT

### Data management

[redacted]



### Confidentiality of data/records

[redacted]

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