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Abstract:

Recently, the quality of generic metoprolol extended-release (ER) products has been called into question with reports of inconsistent effects when switching from the brand name product to a generic formulation. Problems with bioequivalence could have serious and widespread consequences given the high frequency of metoprolol ER use in the management of various cardiovascular disorders, including hypertension, coronary heart disease, heart failure, and cardiac arrhythmias. We hypothesize that both product- and patient-specific factors lead to variability in the pharmacokinetics and clinical response to different metoprolol ER formulations. The study objective is to provide the pharmacokinetic and clinical response data necessary to inform optimal bioequivalence metrics and criteria for generic metoprolol ER products to ensure availability of high quality generic alternatives. We will conduct a prospective, randomized, crossover trial of brand name and generic metoprolol ER formulations in hypertensive patients to compare pharmacokinetics and cardiovascular responses among equivalent labeled doses of each product. Responses will be compared between cytochrome P450 (CYP) 2D6 extensive and poor to intermediate metabolizers so that the impact of *CYP2D6* genotype on variable pharmacokinetics and clinical responses with metoprolol ER products can be determined. Responses will also be compared between patients taking and not taking a proton pump inhibitor for their clinical care given potential effects of a PPI on drug bioavailability. Following treatment with each metoprolol ER formulation, the patient will complete a 24-hour Holter study for determination of total heart beats and heart rate variability, a 24-hour blood pressure study, and a 24-hour pharmacokinetic study. Patient will also be administered an FDA-approved SmartPill capsule to monitor gastric pH in order to determine the effects of gastric pH on pharmacokinetics and clinical response. At the end of the 24-hour study period, patients will complete sub-maximal exercise treadmill testing to determine drug effects on exercise hemodynamics. This proposal is important because it will help elucidate factors contributing to variability in the pharmacokinetics and effectiveness of metoprolol ER products, which are among the most commonly prescribed agents in the U.S.

Introduction:

Background:

Metoprolol ranks among the top five most commonly prescribed medications, with an estimated 84 million prescriptions written in 2013.[1] Metoprolol is a β-1 selective agent indicated for the treatment of hypertension, angina pectoris, heart failure and post-myocardial infarction based on evidence that it reduces mortality and morbidity in these populations.[2-4] The extended-release (ER) formulation of metoprolol was approved in 1992, and is formulated as a succinate salt. Generic formulations of metoprolol ER became available in the late 2000s, and at least 3 products are currently marketed by various manufacturers: [redacted]. The availability of generic metoprolol ER offers a more affordable alternative for patients requiring β-blocker therapy. However, bioequivalence is essential to ensure that the quality of the generic product is similar to that of the brand name product.

The manufacturer of a generic product must provide data to the Food and Drug Administration (FDA) showing that the generic is bioequivalent to the brand name product. Bioequivalence is used as a surrogate for therapeutic equivalence and is defined under the Code of Federal Regulations Title 21 Part 320 (21 C.F.R. §320). The FDA proposes a two-pronged approach for testing bioequivalence consisting of *in vitro* dissolution testing and *in vivo* pharmacokinetic studies of the active substance. For the latter, two products are considered bioequivalent when any differences in the rate or extent of bioavailability of the active moiety are viewed as clinically insignificant (usually within 80% to 125% of the branded product).[5,6] Cross-over studies in healthy volunteers, where single doses of the reference and generic products are administered at the same labeled strength and under similar testing conditions, with quantification of area under the plasma concentration time curve (AUC) and peak plasma concentration (C_{max}), are the most frequently used *in-vivo* studies to establish bioequivalence, and this is what is recommended in the FDA's draft guidance for bioequivalence studies for metoprolol.[7] However, as acknowledged in a separate draft guidance dated March 2014, for extended release products, such as metoprolol ER, bioequivalence studies may not be sufficient to ensure similar safety and efficacy if the pharmacokinetic profiles of the two products differ. This draft guidance specifically cited differences in T_{max} as potentially problematic.[8] In this case, the guidance states that additional studies may be needed to ensure therapeutic equivalence between products.

Recently, the quality of generic metoprolol ER formulations has been called into question with reports of inconsistent effects when switching from the brand name to generic formulation. Whether this is actually a problem with bioequivalence and differences in therapeutic efficacy between products or is representative of the misperception that generic products are of poorer quality than the brand name formulation is unclear. However, if the products are truly not bioequivalent, this could **compromise clinical outcomes and impact the risk for adverse events following generic substitution**. A previous formulation of metoprolol ER (manufactured by [redacted]) was removed from the market after the FDA discovered failures in the process validation studies for metoprolol succinate tablets and variability among lots. The FDA recently issued a warning letter to [redacted], another manufacturer of generic metoprolol ER,

citing violations of good manufacture practice regulations and for adulterated drug products. These actions, in addition to the March 2014 draft guidance referenced above, point to a need to further investigate the bioequivalence of generic metoprolol ER products.

Factors potentially compromising bioequivalence of metoprolol products. For *in-vitro* dissolution testing of most products, including metoprolol ER, the FDA requests that testing be conducted using a US Pharmacopeia method and include at least 3 dissolution media (e.g. pH 1.2, 4.5, and 6.8 buffers) to demonstrate that the drug is stable in acidic stomach conditions and will release in the intestine.[7] However, even with comprehensive *in-vitro* testing, predicting *in-vivo* performance of drug can be challenging given that various physiological parameters can influence drug bioavailability. These include regional pH, bile acid and pancreatic secretions, luminal and mucosal enzymes, gastric emptying, intestinal permeability, gut transit time, and fluid volume. For *in-vivo* pharmacokinetic studies, the FDA recommends single dose studies in healthy volunteers because they are more sensitive in assessing drug release characteristics.[6] However, such studies may not necessarily reflect drug bioavailability after multiple drug doses in patients with disease. A combination of patient- and product-specific factors may compromise the dissolution and bioequivalence of generic metoprolol ER products. Specifically, concomitant medications or diseases that alter gut pH or transit time, and dietary factors that influence solubility could influence drug dissolution and bioavailability.[9] In addition, for modified-release products, such as metoprolol ER, there is a concern for alcohol-induced dose dumping, which can pose serious safety concerns.[10] In terms of product-specific factors, excipients in the product may lead to variability in pKa, solubility, stability, and molecular weight, which could potentially influence the degree to which alterations in physiologic conditions affect drug dissolution and bioavailability.[11]

Effect of *CYP2D6* genotype on metoprolol metabolism. Genotype may also impact the bioavailability of metoprolol. *O*-demethylation via the cytochrome P450 2D6 (CYP2D6) enzyme is the principal route of metoprolol metabolism, with metabolites having no significant β-blocking effect.[13] The gene for CYP2D6 is highly polymorphic, with over 100 alleles defined (http://www.cypalleles.ki.se). The *CYP2D6*1* and **2* alleles are associated with normal enzyme activity. Individuals with one or two copies of normally functioning alleles are deemed extensive metabolizers (EMs). The **9, *10, *17*, **29,* and **41* alleles occur secondary to nonsynonymous single nucleotide polymorphisms (SNPs) and lead to a reduction in enzyme activity. The **3*, **4*, **5*, **6, *7, *8, *11,* and **15* alleles are examples of loss-of-function alleles that occur secondary to frameshift mutations (**3, *6*), splicing defects (**4*), gene deletion (**5*), or other mutations. Individuals with one loss-of-function and one reduced-function allele are intermediate metabolizers (IMs), while those with two copies of loss-of-function alleles (e.g. **3* /**4*) are poor metabolizers (PMs). At the opposite extreme, duplication or multiplication of functional alleles confers the ultra-rapid metabolizer (UM) phenotype with marked increases in CYP2D6 activity. Frequencies of commonly described

CYP2D6 alleles are shown in **Table 1**. There is marked ethnic variability in the prevalence of CYP2D6 phenotypes, with the prevalence of PMs ranging from 0-10% and UMs ranging from 0-29%. In a multi-ethnic clinical trial population with hypertension, we found that 5% of participants were PMs, 7% were IMs, and 4% were UMs.[14]

Table 1. *CYP2D6* allele frequencies among ethnic groups[12]

CYP2D6 allele	European	African American	East Asian
**3*	1.3	0.3	0.0
**4*	18.5	6.2	0.4
**5*	2.7	6.1	5.6
**6*	1.0	0.2	0.0
**10*	3.2	4.2	42.3
**17*	0.3	18.2	0.0
**41*	8.6	9.4	2.0
**1xN*	0.8	0.4	0.3
**2xN*	1.3	1.6	0.4

Our group and others have shown that CYP2D6 PMs and IMs have several-fold higher plasma concentrations of metoprolol and a longer elimination half-life compared to EMs.[15-18] However the data suggest that *CYP2D6* genotype/phenotype may not significantly impact BP or adverse responses to metoprolol but may impact the HR response, and so may be important for some indications.[14,16-19] Additionally, because metoprolol is a high first-pass effect drug, differences in dissolution rate/absorption may impact the absolute bioavailability, and these differences in first pass effect between products may also differ by *CYP2D6* genotype. The effect of *CYP2D6* genotype on the bioequivalence of metoprolol products has not been examined and thus is important to define.

Significance:

Over 77 million Americans have hypertension, over 15 million have coronary heart disease, over 6 million have atrial fibrillation, and over 5 million have heart failure.[20] In addition, over 700,000 Americans suffer a new or recurrent myocardial infarction each year. Metoprolol is commonly used in the management of all of these diseases, and considered the standard of care for some, making it one of the most often prescribed medications in this country.

The **significance** of this project is that it aims to elucidate whether there are important differences in the pharmacokinetics and therapeutic efficacy of FDA-approved metoprolol ER products, and if so, to identify the patient- and product-specific factors contributing to differences. The line of research is important because differences in pharmacokinetics and therapeutic efficacy could increase the risk of therapeutic failure or adverse effects when patients switch from one metoprolol ER product to another. Metoprolol ER is considered the only appropriate metoprolol dosage form for treatment of heart failure, and the once daily dosing with metoprolol ER makes it a popular choice in the other conditions. As such, differences among metoprolol ER formulations could have far reaching consequences. Furthermore, knowledge gained from this study will help inform bioequivalence metrics and criteria for generic metoprolol ER products to ensure availability of high quality generic alternatives. [redacted]

Credentials of Investigators:

Investigator	Contact Information	Address	Statement of Qualifications
Larisa H. Cavallari	[redacted]	[redacted]	Dr. Cavallari (PharmD), Associate Professor, Dept of Pharmacotherapy & Translational Research and Director of the Center for Pharmacogenomics at the University of Florida (UF), [redacted].
Reginald Frye	[redacted]	[redacted]	Dr. Frye (PharmD, PhD) Professor and Chair, Dept of Pharmacotherapy & Translational Research at UF [redacted].
Yan Gong	[redacted]	[redacted]	Dr. Gong (PhD), Research Associate Professor, Dept of Pharmacotherapy & Translational Research at UF, [redacted]
Siegfried O.F. Schmidt	[redacted]	[redacted]	Dr. Schmidt (MD, PhD), Professor of Family Medicine at UF and Medical Director of Family Medicine at the UF Hampton Oaks clinic [redacted]
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David Estores Jr.	[redacted]	[redacted]	Dr. Estores (MD), Assistant Professor of Medicine and Director of Endoscopy at UF Health [redacted]
[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]	[redacted]

Research Facility:
Clinical and Translational Science Institute, University of Florida
Tel: 352-273-8700; Fax: 352-273-8703; Email: info@ctsi.ufl.edu

Enrollment visit will be conducted at:
UF Health Family Medicine at Hampton Oaks clinic
200 SW 62nd Blvd
Gainesville, FL 32607

Screening, follow-up outpatient visits, and overnight study visits will be conducted at:
Clinical and Translational Research Building
2004 Mowry Road
Gainesville, FL 32610

Overnight study visits may also be conducted at:
UF Health Shands Hospital
1600 SW Archer Rd
Gainesville, FL 32608

IRB Oversight:
University of Florida Institutional Review Board-1 (UF IRB-01)
Ruth K and Shepard Board Building
1300 Center Drive, Room 130
Gainesville, FL 32610

FDA RIHSC Oversight:
U.S. Food and Drug Administration
White Oak Building 32 Room4286
10903 New Hampshire Ave,
Silver Spring, MD 20993

Objectives:

Metoprolol succinate is widely used in the management of heart diseases and is available in generic formulations. However, there are mounting data suggesting potential issues with the bioequivalence and therapeutic equivalence of different generic metoprolol ER products, which could compromise clinical outcomes and impact the risk for adverse events with generic substitution. Studies used to establish bioequivalence between brand name and generic products are conducted in healthy volunteers rather than in patients

with underlying disease. Alterations in drug absorption or metabolic function secondary to disease processes or patient-specific factors, such concomitant therapies, may lead to variable response to products thought to be bioequivalent. Variation in gastric pH and product dissolution could further affect the bioequivalence of metoprolol products. Genetic polymorphism for CYP2D6, which is responsible for metoprolol metabolism, may provide additional contribution to variability in the pharmacokinetics and clinical response to metoprolol. **We <u>hypothesize</u> that both product- and patient-specific factors lead to variable pharmacokinetics and cardiovascular responses to metoprolol ER formulations**. **The <u>goal</u> of this project is to provide the pharmacokinetic and clinical response data necessary to inform optimal bioequivalence metrics and criteria for generic metoprolol ER products to ensure availability of high quality generic alternatives.**

Aim 1. Compare the pharmacokinetics and cardiovascular effects of brand name and generic metoprolol ER products in patients with hypertension. We will conduct a prospective, randomized, crossover trial of brand name and generic metoprolol ER and compare pharmacokinetics and cardiovascular responses with equivalent labeled doses of each product.

Aim 2. Determine the impact of gastric pH variation on the concentration-response relationship with different metoprolol ER products. Among patients in the Aim 1 study, we will examine the association between gastric pH, concomitant use of proton pump inhibitors, pharmacokinetics, and clinical response.

Aim 3. Examine the effect of *CYP2D6* genotype on the pharmacokinetics of different metoprolol ER products. CYP2D6 extensive and poor metabolizers will be preselected to participate in the Aim 1 study in order to examine the impact of *CYP2D6* genotype on variable pharmacokinetics and clinical responses with metoprolol ER products.

Regulatory Status:

An IND/IDE is not required to conduct this study.

Background (past findings and relevant literature):

[redacted] Data from selected publications relevant to the proposal herein are described below.

Comparison of metoprolol formulations in a heart failure population and relationship of clinical responses to pharmacokinetics. Based on questions at the time regarding differences in clinical outcomes for heart failure patients treated with immediate release (IR) versus ER metoprolol, we conducted a crossover study to evaluate possible mechanisms for the perceived differences in clinical outcomes by metoprolol formulation.[21] A total of 13 chronic systolic heart failure patients were randomized to a 2-way crossover study of equal total daily doses of the IR (generic metoprolol tartrate) and ER metoprolol ([redacted]) formulations. After 3-week treatment with each formulation, patients underwent pharmacokinetic evaluation at various time points during the dosing interval, 24 hour ambulatory BP monitoring, and 24-hour Holter monitoring. Metoprolol IR concentrations exceeded those of the ER formulation approximately 60% of the time, as shown in **Figure 1**. Despite this, both systolic and diastolic BPs were significantly lower for metoprolol ER versus IR over the entire 24-hr period **(Figure 2, left panel)**. These data demonstrate that the antihypertensive effects of metoprolol are unrelated to plasma drug concentration. These findings are consistent with our previous observations in patients with hypertension.[22] An explanation for the poor plasma concentration-response relationship may be due to the sigmoidal nature of the concentration response curve for β-blockers. Specifically, once maximal antihypertensive response is achieved (E_{max}), concentrations above this level do not result in any additional BP lowering effect.

[redacted]

We also observed greater HR variability with the ER formulation[21]. Mean 24-hr HR was similar between groups. However, the high to total frequency ratio (high-frequency HR variability) and the high to low frequency ratio were significantly greater with metoprolol ER versus IR. The low to total frequency ratio (low-frequency HR variability) was significantly lower for the ER formulation. These data are consistent with increased parasympathetic activity and decreased sympathetic activity (indicated by lower low-frequency HR variability) with metoprolol ER compared to IR. Reduced HR variability is an independent risk factor for increased mortality in heart failure.[23-25] Evidence that metoprolol ER is associated with increased HR variability suggests that this mechanism may contribute to the greater survival benefits observed with metoprolol ER over metoprolol IR in patients with heart failure. Importantly, the differences in HR variability were observed despite similar 24-hr HRs between products, indicating that HR variability is a better discriminator of clinical benefits between β-blockers.

[redacted]

Discordant β-blocker effects on BP and HR. Additional data from our group suggest that response rates to β-blocker therapy differ depending on the clinical response studied[26]. We initiated metoprolol in patients with hypertension, with clinic BP, ambulatory BP monitoring, and exercise treadmill testing assessed before and after treatment. Patients were classified as responders or nonresponders to metoprolol if the diastolic BP decreased by ≥10% or <10%, respectively. When classified based on clinic BP response, 71% of patients were considered responders to metoprolol. However, only 47% met this definition based on ambulatory data. In addition, BP response to metoprolol was not predictive of HR response. **As shown in Figure 3**, both responders and nonresponders to metoprolol based on BP data, had significant reductions in HR, whether measured at

rest or with exercise. These data suggest that patients with little to no BP reduction with metoprolol may still derive significant benefit from β-blocker management of disease where HR reduction is important, such as in atrial fibrillation, heart failure, and ischemic heart disease. Overall, these data highlight the importance of assessing multiple clinical endpoints to clearly define response to metoprolol.

Clinical response to metoprolol by CYP2D6 genotype. As part of the PEAR-2 study, we examined the influence of *CYP2D6* genotype on the efficacy and tolerability of metoprolol tartrate in a subset of 281 patients, including 73 enrolled from UF.[27] The *CYP2D6*2, *3, *4, *6, *10, *17*, and **41* alleles were detected via PCR and pyrosequencing using a PSQ HS96A SNP reagent kit. Additionally, copy number variation was estimated by the TaqMan Copy Number Assay (Life Technologies) and a pyrosequencing-based method[27]. Quantification of *CYP2D6* gene copy number was performed using CopyCaller Software (Applied Biosystems). Phenotypes were assigned based on genotype. Poor and intermediate metabolizers were found to have significantly greater HR response to metoprolol, consistent with these CYP2D6 phenotypes being the ones that result in the highest plasma drug concentrations **(Figure 4)**. In contrast, these impaired metabolism phenotypes were not associated with differences in the BP response or tolerability/adverse effects to metoprolol. Based on these data, we will enroll both PMs and IMs to compare against EMs.

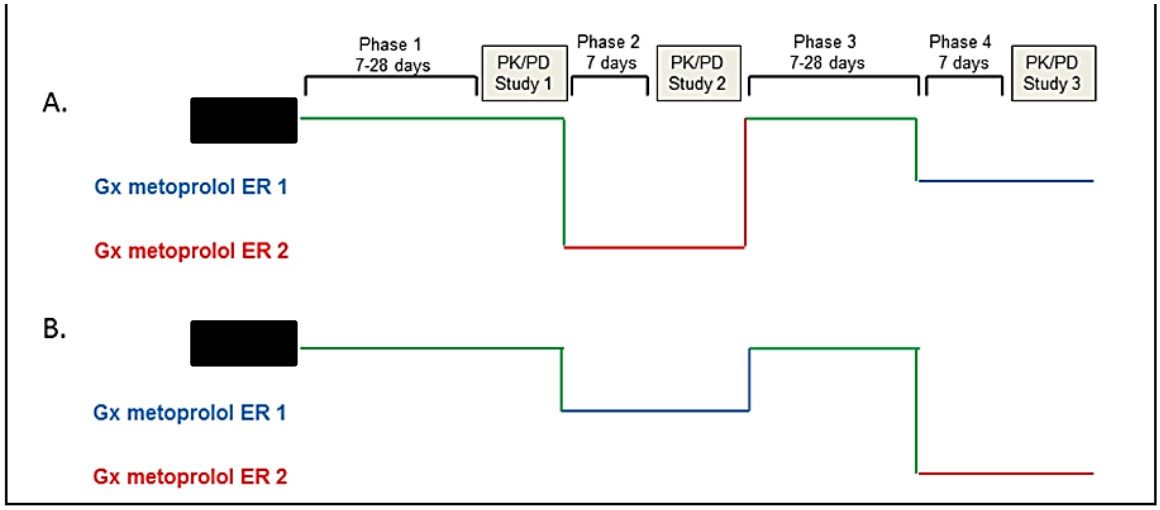
The lack of difference in BP and adverse responses is consistent with previous reports from our laboratory on metoprolol pharmacokinetics and response in heart failure and hypertensive patients.[28, 29] Consistent with our most recent report, in both of the previous studies we showed the expected differences in *S*-metoprolol concentration by CYP2D6 phenotype, but did not show differences in tolerability or response to metoprolol. Collectively, these data (and others in the literature for metoprolol and *CYP2D6*) suggest that *CYP2D6* genotype-derived phenotype is associated with dramatic differences in metoprolol pharmacokinetics and yet these differences translate into minimal differences in efficacious or adverse responses to the drug, with HR being the one response phenotype with a possible difference by *CYP2D6* genotype.[30, 31] The latter is also consistent with other data in the literature which document the strongest PK-PD relationship with the HR response.[31] Thus, the primary analyses by CYP2D6 phenotype will focus on pharmacokinetic differences between the formulations.

***Use of PEAR-2 patients to facilitate recruitment into this trial*.** Dr. Johnson was the PI for the PEAR (ClinicalTrials.gov identifier: NCT00246519) and PEAR-2 (ClinicalTrials.gov Identifier: NCT01203852) clinical trials of hypertensive patients. PEAR and PEAR-2 were funded by the NIH Pharmacogenomics Research Network, and both involved the enrollment of hypertensive patients at UF, Emory University and Mayo Clinic. PEAR enrolled 1701 patients, of whom 768 met all inclusion criteria and completed all aspects of the approximately 6 month clinical trial. PEAR-2 was recently completed (March 2014) and enrolled 836 patients, with 418 completing the trial. In the context of the proposed study, 127 patients completed the PEAR-2 trial at UF, of which we have complete metoprolol response data on 108 (the remaining 19 had a β-blocker contraindication and so were only studied on chlorthalidone). We have call-back information on these patients, and based on our 9 years of conducting hypertension clinical trials with the UF Department of Community Health and Family Medicine, we have established excellent rapport with these patients. In the PEAR trial (for which we studied atenolol), we studied β-blocker response in 312 unique hypertensive patients at UF, who also provided call back information. These patients will be targeted for recruitment specifically targeting those with known tolerability to metoprolol or atenolol based on experience from PEAR-2 and PEAR studies, respectively. We will further select patients based on CYP2D6 genotype, which is available from the PEAR studies, and clinical use of a proton pump inhibitor.

Study Design and Methods:

Study design. This will be a randomized, cross-over study of equal doses of different formulations of metoprolol succinate: [redacted], brand name metoprolol succinate; [redacted] generic metoprolol succinate product 1 (Gx metoprolol ER 1); and [redacted], generic metoprolol succinate product 2 (Gx metoprolol ER 2) in hypertensive patients as

Figure 5. Study design



illustrated in **Figure 5**. We anticipate that 50 patients may need to be enrolled to complete studies on a target of 38 patients.

Study Treatment Length. The 7 day duration was chosen for Phase 2 and 3 because there are multiple lines of evidence that the therapeutic effect of β-blockers is fully evident within a 7-day period.[32,33] Secondly, we have shown in our formulation crossover study that this is a sufficient period to document difference between formulations.[21]

Study population and eligibility requirements. The primary target for recruitment will be participants from the recently completed PEAR-1 and PEAR-2 studies who were recruited from the UF site and provided call-back information.

Inclusion criteria to enroll study participants include:

- Age 18-years or older
- Diagnosed with Essential Hypertension

Patients will be targeted for enrollment based on current treatment of their hypertension with a β-blocker or known tolerability to a β-blocker based on their previous participation in the PEAR studies. If necessary to meet enrollment targets, additional patients will be recruited from the patient population in the UF Health Family Medicine – Hampton Oaks clinic at UF, UF HealthStreet, UF Integrated Data Repository (IDR), Oak Hammock and through advertisements placed in local classified services. More detailed recruitment methods are described below under "Subject Selection and Recruitment". Patients enrolled in the PEAR studies provided consent for genotyping, and most of those from PEAR-2 have been genotyped for *CYP2D6* variants. Participants with the PM, IM, or EM phenotype will be enrolled based on *CYP2D6* genotype-derived phenotype. We anticipate that 40% to 60% of patients enrolled will be taking a proton pump inhibitor for clinical care, which will be taken into account in the data analysis.

Exclusion criteria: These criteria match those of PEAR studies and include the following:

- Documented secondary forms of HTN
- Known cardiovascular disease (including history of angina pectoris, myocardial infarction, coronary revascularization procedure, heart failure, or presence of a cardiac pacemaker)
- Known cerebrovascular disease (including stroke and TIA)
- Known peripheral vascular disease
- Diabetes mellitus (Type 1 or 2) (defined as a diabetes diagnosis in the medical record or fasting blood glucose ≥ 126 mg/dl or nonfasting blood glucose ≥ 200 mg/dl on screening laboratories)
- Systolic blood pressure (SBP) >170 mm Hg on screening visit
- Heart rate <55 bpm on screening visit (in the absence of treatment with a β-blocker)
- Renal insufficiency (serum creatinine >1.5 in men or >1.4 in women on screening laboratories)
- Liver enzymes (ALT and/or AST) >3 times the upper limit of normal on screening laboratories.
- Known Raynaud's phenomenon
- Current diagnosis of asthma or chronic obstructive pulmonary disease, unless patient is currently tolerating or has previously tolerated metoprolol
- Pregnancy or lactation
- Concomitant treatment with non-dihydropyridine calcium channel blockers (diltiazem or verapamil), digoxin, or clonidine because of additive HR suppression
- Concomitant treatment with catecholamine depleting drugs, reserpine or monoamine oxidase inhibitors
- Concomitant treatment with the potent CYP2D6 inhibitors quinidine, fluoxetine, or propafenone

With the exception of concomitant therapies listed in exclusion criteria, the use of other, non β-blocker, anti-hypertensives and other drug therapy will be allowed as long as therapy is held constant during study participation

Additional **contraindications**, which pertain to administration of the [redacted] **capsule** in Aim 2, include a history of any of the following, as documented in the electronic health record:

- History of gastric bezoars
- Swallowing disorders
- Strictures
- Fistulas
- GI obstruction
- History of gastrointestinal surgery within the past three months
- Severe dsyphasgia
- Crohn's disease
- Diverticulitis
- Any implantable electromedical device

Protocol. The protocol is described in detail below. Patients will be randomized at the baseline visit to one of two groups using the blocked randomization method with a block size of 4:

- Study group A
- Study group B

Both study arms consist of 4 metoprolol succinate treatment phases and 3 overnight study visits. Randomization will be stratified by *CYP2D6* genotype. [redacted] **will be administered in the first phase/period for all participants**. The rationale for this is that the problems with the generic formulation are reported after the switch from the brand name to generic product. Thus, we want to capture the switch from brand name to each generic.

Screening visit. Patients will be asked to come to the UF Clinical Translational Science Institute (CTSI) located in the Clinical Translational Research Building in Gainesville. After obtaining written, informed consent, the following will be done:

- Demographics, medical history and concomitant medication will be obtained,
- Vitals, Height and weight will be collected.
- The study nurse will draw 15 mL of blood total. 10 mL (2 teaspoonful) of venous blood for a basic metabolic panel, AST, and ALT and 5 mL (1 teaspoonful) of venous blood for genotyping. A urine pregnancy test will be done for women of childbearing potential.

In the absence of exclusion criteria from medical history, vitals and lab results, patients will be scheduled for the enrollment study visit within 2 weeks.

Enrollment visit. The enrollment visit will be conducted in the UF Health Family Medicine - Hampton Oaks clinic in Gainesville.

- The study physician will perform a physical exam on each patient.
- Patients meeting inclusion criteria will be randomized to study group A or study group B using a block randomization with a block size of 4.
- Patients will be provided with a supply of [redacted]. There will be no washout phase. Patients taking metoprolol succinate will be asked to stop taking their supply of drug and will be supplied with the same dose of the study drug to take instead for the duration of the study. The study physician may adjust metoprolol succinate doses up or down to achieve or maintain each patient's goal blood pressure. Patients taking a beta-blocker that is not metoprolol succinate on enrollment, will be switched to an "equivalent" [redacted] dose (i.e. 200 mg [redacted] daily for 100 mg atenolol daily; 200 mg [redacted] daily for 50 mg carvedilol daily, etc.), which will be determined by the study physician during the physical exam. The patient will be provided with up to a 2-week supply of study drug and asked to return once a week for a blood pressure check and additional supply of study drug, if necessary, until the first overnight pharmacokinetic (PK)/pharmacodynamic (PD) visit. Patients not currently taking a β-blocker will either have [redacted] added if not at goal BP, or [redacted] substituted for another antihypertensive medication. In either case, [redacted] will be started on 50 mg/day. This is within the recommended initial dose range in the drug labeling of 25-

100 mg/day. [redacted] will be provided by the Investigational Drug Service (IDS), and patients will be instructed to take their [redacted] dose at 9 A.M. each morning.

- Patients will be asked to bring their study medication pill bottle and leftover pills to each study visit for pill counts to assess adherence.
- Patients will be provided with a home BP monitor and appropriate sized cuff. Patients from PEAR-1 and PEAR-2 underwent extensive training by research personnel on the use of the home BP monitor. Patients will be provided additional training as needed and instructed to monitor BP at home upon arising in the morning and just before retiring in the evening daily (with the exception of overnight study visits) until the study is completed.
- Patients will be instructed to contact the study nurse for a BP check if their home BP monitor shows two consecutive resting BP measurements taken 5 minutes apart >170 or <100 mmHg for SBP and/or >110 mmHg for diastolic blood pressure (DBP), or pulse <50 beats/minute at any time during the study. The dose will be reduced by half for a systolic BP <100, symptoms of hypotension, or pulse <50BPM following initiation of therapy. Home BP data will be collected using the Microlife 3 AC1-PC (Minneapolis MN), set in triplicate mode. Each activation of the device will lead to the measurement of BP in triplicate, and the HR and BP readings are electronically recorded and time-stamped. The data will then be downloaded by the study coordinator when the study participant reports to the clinical research center (CRC) for BP checks during dose titration or for overnight studies.

The schedule of events is shown below in **Table 2**.

Table 2. Schedule of events

	Screening	**Enrollment**	**Dose Titration[a] followed by Phase 1**	**PK-PD #1 / Phase 2**	**PK-PD #2**	**Phase 3**	**Phase 4**	**PK-PD #3**	**Follow up**
Visit[f]	1	2	3 (3a, 3b, 3c)	4	5	6 (6a, 6b, 6c)	7	8	9 (9a, 9b, 9c)
Study week	**0**	1-2	2 to 5	2 to 6[b]	3 to 7[b]	4 to 12[c]	4 to 13	5 to 14[c]	6-15
Informed consent	**X**								
Demographics	**X**								
Medical History	**X**								
Body Weight	**X**								
Height	**X**								
Sitting Vital Signs	**X**	**X**	**X**			**X**	**X**		**X**
Basic metabolic panel	**X**								
AST/ALT	**X**								
Genetic whole blood sample	**X**								
Urine Pregnancy Test	**X**								
Concomitant Medication	**X**			**X**	**X**			**X**	
Physical Exam		**X**							
Inclusion/ exclusion		**X**							
Randomization		**X**							
Dispense Study Drug		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**[d]
Medication compliance			**X**	**X**	**X**	**X**	**X**	**X**	
PK sample				**X**[e]	**X**[e]			**X**[e]	
Holter monitor				**X**	**X**			**X**	
Ambulatory BP monitoring				**X**	**X**			**X**	
pH monitoring				**X**	**X**			**X**	
Treadmill exercise				**X**	**X**			**X**	
Adverse events assessment			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study drug tapering								**X**	**X**

a: Includes up to 3 weekly visits for dose titration to 100 mg qd, 150 mg qd, and 200 mg qd as tolerated or until BP <140/90 mm Hg

b: Study week is dependent on duration of Toprol XL treatment in Phase 1, which many range from 7 to 28 days
c: Study week is dependent on duration of Toprol XL treatment in Phase 3, which many range from 7 to 28 days
d: Study drug will be dispensed for patients undergoing dose tapering
e: Immediately before the dose (baseline) ± 5min, then 30min ± 5min, 60min ± 5min, 2hr ± 10min, 3hr ± 10min, 4hr ± 10min, 6hr ± 20min, 8hr ± 20min, 12hr ± 30min, 16hr ± 30min, 20hr ± 30min, 24hr ± 30min after the dose
f. Study visits window +/- 2 days

Phase 1. Phase 1 will consist of treatment with [redacted] for 7 to 28 days. The range in duration of Phase 1 is to allow for β-blocker up-titration if needed to achieve a BP < 140/90 mm Hg and to allow flexibility in scheduling the first overnight visit. Patients not on a β-blocker prior to the study (i.e. patients starting [redacted] 50 mg/day) will be asked to come to the CRC in the Clinical and Translational Research Building (CTRB) each week for a BP check and dose titration to a maximum dose of 200 mg/day or BP <140/90 mm Hg. At least one titration visit, documenting BP < 140/90 mm Hg, will be required before scheduling the first PK/PD study visit. This optimized dose will be used for all PK-PD visits.

Patients will be reminded at each visit to take their [redacted] dose at 9 A.M. each morning and to continue to monitor their BP at home with the monitor provided as described above. At the end of Phase 1, patients will be asked to stay overnight at the CRC or the UF Health Shands Hospital for the first pharmacokinetic (PK)/ pharmacodynamics (PD) study visit. A pill count will also be conducted during this visit and subsequent visits to ensure patient adherence.

PK/PD study visit. Subjects will be instructed to abstain from caffeine and alcohol beginning at 8 P.M. the night before the study and for the entire study day, and fast (no food or beverage except water) beginning at 12 midnight before the study. Patients will be asked to wear and/or bring comfortable clothing and shoes suitable for walking on a treadmill. Patients will arrive to the CTSI CRC or at Shands Hospital at the University of Florida the morning of their scheduled visit.
The following will be placed:

- Holter monitor for determination of total 24-hour heart beat and HR variability
- ambulatory BP monitor for 24-hour blood pressure
- an indwelling venous catheter for a 24-hour pharmacokinetic study

Patients will not be allowed to shower while wearing the monitors, but can do other normal activities. Patients will be asked not to leave the unit until completion of the study the following day. Patients will be given a [redacted] standardized meal to eat before taking the [redacted] to initiate post-prandial motility. Immediately afterward, participants will be asked to swallow a disposable SmartPill® capsule [redacted], designed to continuously measure pH and motility as it moves through the gastrointestinal track until it is excreted.

Patients will be provided a regular diet, or any diet appropriate to their needs, for the duration of the overnight stay. Patients will be given a similar type of diet for each subsequent PK/PD visit to minimize any impact of meals on the pharmacokinetics of the metoprolol formulation.

At the end of the 24-hour study period, the Holter monitor, ambulatory BP monitor, and venous catheter will be removed. Patients will be given another dose of their metoprolol succinate 2 hours before their scheduled submaximal exercise treadmill test. Patients will be taken to the Shands Heart Center where they will undergo a submaximal exercise treadmill test. The PD studies will conclude following completion of their treadmill testing. Details of each PK and PD measurement are described below.

Phase 2. At the end of the first overnight study visit, the patient will be crossed over to the first generic metoprolol succinate formulation to which they are randomized. A 7-day supply of the generic product will be supplied by the IDS at the same dose as the final dose of [redacted] for the patient in Phase 1. The overnight PK/PD studies will be repeated at the end of Phase 2.

Phase 3. Patients will then be placed back on [redacted] at the same dose as determined in Phase 1. [redacted] will be dispensed in 7 day supplies, and patients will come to the CRC for BP checks each week and another 7 day supply of study drug until Phase 4. The range in length of Phase 3 treatment is to allow flexibility in scheduling the final overnight study visit after Phase 4. During Phase 3, data collection from the Holter monitor or the ambulatory blood pressure monitor may be repeated on an outpatient basis to replace erroneous or missing data collected during PK/PD Study Visit 1 (Phase 1). This repeated data collection will only be necessary if there were errors in heart rate variability or ambulatory blood pressure data collection during Phase 1, and the patient agrees to wear the monitor(s) as an outpatient during Phase 3.

Phase 4.
After Phase 3, patients will come to the CRC for a BP check. They will be given a 7-day supply of the final generic product for Phase 4, at the same dose as determined in Phase 1, followed by the final overnight PK/PD studies. After the overnight PK/PD studies, patients taking metoprolol or any other β-blocker prior to study enrollment will be placed back on their pre-study medication. On the other hand, patients who were not on a β-blocker before study enrollment, will have the metoprolol dose reduced by 50% initially as part of a weekly tapering regimen, and will be restarted on any medication that was withdrawn or dose adjusted on study enrollment.

Follow-up study procedures. Patients will be scheduled for a follow up visit for a BP check at the CRC one week after the last overnight study visit. Patients will be asked to return the SmartPill® data recorder to the study nurse at this visit. Patients who are undergoing a metoprolol taper will have their metoprolol dose reduced by 50% each week until completely withdrawn, with an outpatient visit for a BP check scheduled with each dose reduction. Patients will be asked to continue to measure BP in the A.M. and P.M. and to call the study nurse for a BP check in the CTSI if two consecutive resting SBP measurements are above 170 or below 100 mmHg, and/or DBP measurements are above 110 mmHg when taken at least 5 minutes apart, or pulse below 50 BPM. The study nurse will call the patient between 3 to 5 weeks after the final overnight study visit for a safety check, which will include asking about home BP readings and the occurrence

of any adverse effects. This will end the patient's study participation. Patients may keep the home blood pressure monitor after the study for their personal use.

Detailed description of PK/PD study procedures:

Ambulatory BP monitoring. On admission to the CRU, patients will be fitted with a SpaceLabs 90227 OnTrak ambulatory BP monitor (Spacelabs Healthcare, Snoqualmie, WA) and a MindWare Mobile Cardio/GSR holter monitor (MindWare Technologies LTD, Gahanna, OH). The ambulatory BP monitor will be programmed to randomly measure BP 4 times per hour during the day (6 A.M.-11 P.M.) and 2 times per hour during the nighttime (11 P.M.-6 A.M.), as in previous trials.[21,19,34,35]

Pharmacokinetic studies**.** The metoprolol dose will be administered between 8 A.M and 12 P.M. A 6-ml blood sample will be drawn from the venous catheter into EDTA collection tubes at the following times: immediately before the dose (baseline), and at 30 mins ± 5 mins, 60 mins ± 5 mins, 2 hrs ± 10 mins, 3 hrs ± 10 mins, 4 hrs ± 10 mins, 6 hrs ± 20 mins, 8 hrs ± 20 mins, 12 hrs ± 30 mins, 16 hrs ± 30 mins, 20 hrs ± 30 mins, and 24 hrs ± 30 mins after the dose. A total of 72 mls (almost 5 tablespoonfuls) of blood will be drawn from the catheter during the overnight study visit. Blood will be immediately centrifuged, and the plasma separated and stored at -20ºC or -80 ºC until analysis. Metoprolol enantiomer concentrations will be determined by a validated chiral high-performance liquid chromatography tandem mass spectrometric method, modified based on a fluorescence detection method previously published by our group.[22]

pH monitoring. The [redacted] Capsule and GI Monitoring System offers a noninvasive, nonradioactive, well tolerated means of assessing gastrointestinal pH and motility. The SmartPill is an ingestible, single-use capsule and is FDA-cleared to aid in the evaluation of gastrointestinal motility conditions. As it moves through the GI tract, it wirelessly and continuously transmits data to a recorder worn on the belt or lanyard for up to 5 days or when it passes with a regular bowel movement. Dr. Estores (Co-Investigator) has extensive experience in gastrointestinal and esophageal pH monitoring via a number of techniques.[36-42] Most relevant to this proposal, he has experience with wireless capsule systems to monitor pH in both the research and clinical settings.[36,40] Immediately after ingesting a [redacted] participants will be given a [redacted] capsule to swallow, and fitted with the wireless Data Recorder to wear on a belt or lanyard until the [redacted] capsule passes with a regular bowel movement. The participant will be discharged with the Data Recorder to be worn at all times except while bathing or sleeping. The recorder should be removed while bathing and placed close by where it will not get wet. While sleeping, the participant will be instructed to place the data recorder under the pillow or on a nightstand by the bed. The [redacted] is expected to pass within 5 days of ingestion, and participants will be asked to return the Data Recorder at the next scheduled study visit.

Exercise treadmill. Patients will undergo submaximal graded exercise testing to gradually reach 85% of their maximum predicted exercise HR calculated as: 0.85 * (220-age). A 12-lead ECG will be placed to monitor HR and conduction during exercise, and

a BP monitor will also be placed. HR will first be recorded in the supine, sitting, and standing position after at least 5 minutes of rest between readings. Treadmill exercise will begin at 1.7 mph with a 0% incline. The speed and slope of the incline will be increased as shown below.

Table 3. Submaximal Exercise Treadmill Testing (Modified Bruce protocol)

	Stage Time (min)	Speed (mph)	Grade (%)
Pretest			
Supine	-	0	0
Standing	-	1.0	0
Warm-up	-	1.0	0
Exercise			
Stage 0	3:00	1.7	0
Stage ½	3:00	1.7	5
Stage 1	3:00	1.7	10
Stage 2	3:00	2.5	12
Stage 3	3:00	3.4	14
Stage 4	3:00	4.2	16
Stage 5	3:00	5.0	18
Stage 6	3:00	5.5	20
Stage 7	-	6.0	22
Recovery	-	1.5	0

Product Information:

	Product				
	[redacted]	**Metoprolol succinate** [redacted]	**Metoprolol succinate** [redacted]	[redacted] **capsule**	[redacted]**r**
Chemical name	di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propranol] L-(+)-tartrate	di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propranol] L-(+)-tartrate	di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propranol] L-(+)-tartrate	Contains sensors which transmit pH and pressure measure-ments to a data receiver [redacted]	[redacted]

Drug information	Selective beta-1 blocker for treatment of hypertension, heart failure and angina pectoris	Selective beta-1 blocker for treatment of hypertension, heart failure and angina pectoris	Selective beta-1 blocker for treatment of hypertension, heart failure and angina pectoris	FDA-cleared ingestible, disposable capsule; [redacted]	FDA-cleared Standardized meal similar to a granola bar [redacted] to be consumed immediately before ingesting the [redacted] capsule
Formulation	Extended release tablet	Extended release tablet	Extended released tablet	Ingestible, disposable capsule	Nutritional bar
Manufacturer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
# of doses to be administered	14-56 doses (7-28 doses during 1st phase of study and then 7-28 doses in 3rd phase of the study)	7 doses	7 doses	3	3
Planned maximum dosage	200 mg	200 mg	200 mg	Not applicable	Not applicable
Duration of subject exposure	14-56 days	7 days	7 days	Up to 15 days (takes up to 5 days for the capsule to pass)	3 bars to be consumed over course of study

Duration:

The estimated study duration ranges between 6-15 weeks. This includes the drug treatment duration of 4 to 10 weeks plus 1-2 weeks between then enrollment and screening visit, and 1-3 additional weeks for follow up.

Location:

The study will be conducted in the UF Health Family Medicine – Hampton Oaks clinic for the enrollment visit, UF CRC in the CTRB for the screening visit, and the CRC or UF Health Shands Hospital for overnight visits for PK/PD studies.

Subject Selection and Recruitment:

Subjects will be recruited among participants in the recently completed Pharmacogenomic Evaluation of Antihypertensive Responses-2 (PEAR-2) study from the University of Florida site. Participants in PEAR-2 previously provided a genetic sample, and the target population will be selected based on cytochrome P450 (CYP) 2D6 genotype, targeting at least 10 patients with the PM or IM genotype and remained of patients with the EM genotype. Participants will be targeted for enrollment based on current treatment of their hypertension (HTN) with a β-blocker, or known tolerability to a β-blocker based on their previous participation in PEAR-2.

Inclusion of Women and Minorities**:** The investigators have no planned limitations to enrollment based on race or ethnicity. However, based on the population demographics of the PEAR-2 study, from which subjects will be recruited, the subjects will primarily be non-Hispanic whites or African Americans. Specifically, the PEAR-2 subjects enrolled from the University of Florida site were 58% whites, 43% African Americans, and 3% Hispanics. We anticipate enrolling 50 subjects with a similar number of men and women and similar ethnic and racial representation as subjects from PEAR-2.

Strategies/Procedures for Recruitment. Many strategies will be used for recruitment: **1.)** Patients in the PEAR-2 study who provided call-back information and meet eligibility criteria will be contacted by a study investigator to assess interest in study participation. If a sufficient number of patients cannot be recruited from among those enrolled in PEAR-2, investigators will screen patients from PEAR-1 for eligibility. Those meeting eligibility criteria will be contacted by a study investigator to assess interest in study participation. If a sufficient number of patients cannot be recruited through the PEAR-1 and PEAR-2 studies, patients with hypertension will be recruited by other methods including: **2.)** The UF Health Family Medicine – Hampton Oaks clinic via an IRB-approved flyer placed in clinic waiting rooms and clinical rooms. **3.)** HealthStreet will be an additional mechanism for patient recruitment. HealthStreet will be provided with an IRB-approved flyer and information to give to participants that may be interested in the study. Potentially interested patients may call a number provided on the postcard. **4.)** Potential participants will also be identified by accessing the IDR provided through the NIH-funded i2b2 tool, which provides UF researchers access to a HIPAA-compliant and IRB-approved data set. Our query for the i2b2 data set will identify cohorts that meet our inclusion and exclusion criteria. **5.)** Advertisements will be placed with classified advertisements services including [redacted]. **6.)** [redacted] will be provided with an IRB-approved flyer and information to give to participants that may be interested in the study. Potentially interested patients may call a number provided on the flyer.

For all avenues of recruitment, a study investigator will follow-up with potentially interested patients to describe the study. Interested patients will be invited to the study center to further discuss the details of participation with an investigator, as described under the Screening Test and Interview section below.

Screening Tests and Interview Prior to Subject Enrollment:

Candidates who express interest in study participation will be invited to the UF Health Family Medicine - Hampton Oaks clinic to meet with the study team and further discuss the details of participation. At this visit, the study objectives, procedures, and risks of participation will be explained in detail. After the candidate has been given an opportunity to ask questions, the candidate will be asked to sign the informed consent form, which will contain language appropriate to satisfy the rules and regulations surrounding HIPAA requirements. The signed informed consent will become part of the subject's medical record and will serve as documentation of the patient's willingness to participate. Patients will then be screened at the CRC for exclusion criteria (stated in the study population and eligibility criteria) based on a complete medical history, BP and HR assessment, and lab results. Patients without exclusion criteria will be scheduled for the enrollment study visit within 14 days where they will complete the physical exam with the study physician and if eligible, they will be randomized and begin the study.

Study Drug Management

Patients will be provided with a supply of [redacted]. There will be no washout phase. Patients taking metoprolol succinate will be asked to stop taking their supply of drug and will be supplied with the same dose of the study drug to take instead for the duration of the study. The study physician may adjust metoprolol succinate doses up or down to achieve or maintain each patient's goal blood pressure. Patients taking a beta-blocker that is not metoprolol succinate on enrollment, will be switched to an "equivalent" [redacted] dose (i.e. 200 mg [redacted] daily for 100 mg atenolol daily; 200 mg [redacted] daily for 50 mg carvedilol daily, etc.), which will be determined by the study physician during the physical exam. The patient will be provided with up to a 2-week supply of study drug and asked to return once a week for a blood pressure check and additional supply of study drug, if necessary, until the first overnight pharmacokinetic (PK)/pharmacodynamic (PD) visit. Patients not currently taking a β-blocker will either have [redacted] added if not at goal BP, or [redacted] substituted for another antihypertensive medication upon physician's discretion. In either case, [redacted] will be started at 50 mg/day. This is within the recommended initial dose range in the drug labeling of 25-100 mg/day. [redacted] will be provided by the Investigational Drug Service (IDS), and patients will be instructed to take their Toprol XL dose at 9 A.M. each morning. Dosage strength will be established during Phase 1 and will remain the same throughout the study duration. If further blood pressure management is needed during the study, the study physician will be consulted.

Risk/Benefit Ratio:

Potential Risks: Risks are those associated with venipuncture, placement of an indwelling venous catheter, treatment with metoprolol, administration of the [redacted], exercise treadmill testing, and genetic information disclosure.

i. Venipuncture. The risks of placing a catheter in your arm for drawing blood include discomfort at the site of puncture; possible bruising and swelling around the puncture site; uncommonly, faintness from the procedure, and rarely an infection. The total amount of blood drawn during the entire study is 25 tablespoonsfuls (less than 1 pint).
ii. Metoprolol. Risks with metoprolol include hypotension (over response), continued HTN (under response), bradycardia, and worsening of asthma or bronchitis. Hypertension from under response increases the risk of acute coronary syndrome and stroke. Metoprolol may also cause the side effects of fatigue, impotence, dizziness, light-headedness, drowsiness, lethargy, tiredness, depression, diarrhea, nausea, vomiting, and vivid dreams.
iii. [redacted] capsule. The risks associated with taking the [redacted] are capsule retention and aspiration. These risks are greatest in patients with gastrointestinal obstruction or severe dsyphasgia, and such patients will be excluded from participation. If a [redacted] capsule is in the body during an MRI test, there is a risk of damage to the GI tract. Subjects will be warned of this risk and the importance of avoiding an MRI until the capsule has passed.
iv. BP monitoring. There are no risks associated with wearing an ambulatory BP or Holter monitor. However, these devices may be uncomfortable and disturb sleep.
v. Exercise treadmill testing. Side effects of the exercise treadmill test can include shortness of breath, light headedness, hypotension, or abnormal heart rhythm. In rare cases, these side effects can be serious or life-threatening. Medical staff trained in emergency response will be present for the studies. Also possible are direct injuries such as bruises, sprains, and strains and indirect problems such as worsening of pain from arthritis.
vi. Genetic study risks. Genetic study risks include those related to confidentiality surrounding the genetic information and the chance that the genetic information could in some way expose the patient to increased risk regarding employment or that future life, health, disability or long term care insurance providers could potentially use this genetic information to deny, limit or raise rates for insurance coverage.

Potential Benefits

Study participation may not result in any direct benefit for the participant. However, risks associated with participation are minimal, and there are potential societal benefits from this study. Specifically, the results of this study may help the FDA better understand which factors should be considered in bioequivalence studies of metoprolol succinate, leading to safer and more effective generic alternatives.

Alternative Treatment

The alternative is not to participate in the study. Patients who do not want to participate in this study can receive a blood pressure lowering medication via a prescription from their doctor and can obtain a blood pressure monitor from their local drug store to monitor blood pressure at home.

Adequacy of Protection Against Risks

i. Protection from venipuncture. Venipuncture will be performed by a trained and experienced phlebotomist or nurse using standard techniques, and venous catheter insertion will be performed by a trained and experience nurse using standard techniques.

ii. Protections from antihypertensive drug therapy risks. Several measures will be in place to protect from adverse effects with metoprolol. First, patients already taking a β-blocker or with known tolerability to a β-blocker based on their previous participation in PEAR-2 will be targeted to minimize the likelihood for adverse drug effects. Second, we will exclude populations are most at risk for adverse effects with metoprolol (e.g. patients with heart disease, bronchospastic disease). Third, patients will undergo laboratory screening at baseline, and patients with elevated blood glucose, serum creatinine, or liver enzymes (ALT, AST) will also be excluded to minimize risk. Regular laboratory testing is not part of standard of care with use of this long established drug, and thus will not be done after the initial screening. However, as an additional important measure of safety, throughout the period of metoprolol therapy, patients will be encouraged to monitor their BP at home and report any SBP >180 mmHg or <100 mm Hg, DBP >110 mm Hg, or HR <55 bpm. At each study visit, BP will be checked, home BP data will be assessed, and patients will be evaluated for adverse effects, including symptoms of hypotension. Patients experiencing intolerable adverse effects at any time will be discontinued from the study immediately. All study medication will be stopped, and patients will be placed back on any blood pressure medications adjusted or stopped at the beginning of the study. The patient's primary physician will be contacted for follow-up

iii. Protections from [redacted] risks. Patients with gastrointestinal obstruction or severe dsyphasgia, who are at the highest risk for capsule retention and aspiration will be excluded. Patients will be instructed to immediately report any unusual symptoms and will be warned of risk of damage to GI tract if an MRI is done before the capsule is passed.

iv. Protections from exercise treadmill testing. Medical staff trained in emergency response will be present for the studies.

v. Protections against risks from genetic study participation. Genetic testing results will not be provided to any of the patients, and thus will not be included in the patient's medical record, and will not be available to insurance providers. All data will be stored in a secure, password protected database with access limited to key investigators only. All records will link only a code number and no patient specific identifiers will be used.

Payment for Participation:

Patients will receive a [redacted] gift card at the completion of each overnight study visit and a [redacted] gift card after the enrollment visit, screening visit, each outpatient visit needed for medication adjustment repeating, holter monitor on an outpatient basis, or repeating ambulatory blood pressure on an outpatient basis, for a total compensation up to [redacted] for patients completing all study procedures. Parking at both the clinic and CTRB is free, and the patient will be provided with a home blood pressure monitor at the baseline visit, which they may keep after study participation ends.

If a patient withdraws on his/her own before completing the 24-hr PK and PD studies, or if the patient is withdrawn by study investigators prior to completing the 24-hr PK and PD studies because of an adverse event or intolerance to the procedures, he/she will receive [redacted] for that study visit. If the patient withdraws on his/her own or is withdrawn by study investigators after completing the 24-hr PK/PD studies but before completing the exercise treadmill test, he/she will be compensated in the amount of [redacted]

Patients will be responsible for paying income taxes on any payments provided by the study that total [redacted] or more or if the patients is a nonresident alien. Payment will be processed through the University of Florida Accounts Payable department and the University must report the amount received to the Internal Revenue Service (IRS).

Adverse Event Reporting:

Women of child bearing potential will be instructed to use an acceptable method of contraception during study participation.
Monitoring for documentation of an adverse event, whether anticipated or unanticipated, is the responsibility of the principal investigator who will maintain oversight but may delegate collection of information related to this function to other study team member. In term of SAFETY monitoring, all adverse events spontaneously reported, elicited, or observed by the investigators will be recorded.

All Serious Adverse Events, should they occur, whether study-related or expected, will be documented on a Case Report Form, under Adverse Event section in the Patient's binder, reported by the principal investigator to the IRB within five (5) working days. The principal investigator will follow the reporting requirements for serious and unexpected adverse events outlined in the UF IRB Adverse Event Evaluation and Reporting Guide. All unanticipated, serious, fatal and/or life-threatening adverse events will be reported to the UF IRB. Aggregate reports of adverse events will be prepared on an annual basis or at the end of the study, whichever may occur earlier and forwarded to the IRB at annual review.

In addition, the principal investigator will report to the RIHSC (FDA IRB) through the FDA Sponsor any unanticipated problems involving risk to human subjects or others 45 CFR 46.103(b)(5)(i). Per the RIHSC definition, the following adverse events will be reported to the RIHSC within 10 working days of the discovery of the event:

- An adverse event that is not expected, i.e. not listed in the informed consent document or the investigator's brochure;
- An expected adverse event that occurs at a greater frequency or duration than expected;
- Any adverse event that would require modification of the protocol and/or informed consent document.

Data Safety Monitoring. According to the UF IRB assessment for potential risk for subject form (Appendix N), our study is considered low risk in that it meets the following criteria: the study is therapeutic but the agent to be studied has a known safety profile and is to be used for an indication and population already approved by the FDA. Expected adverse events are of low severity and reversible with low chance of serious harm. Thus, a DSMB is not required and we do not feel that it is necessary since we are targeting patients who have demonstrated tolerance to beta-blocker therapy and are excluding those at increased risk for adverse effects with metoprolol. In addition, metoprolol has a wide therapeutic index and will be titrated up with close monitoring for those not on a beta-blocker at baseline.

Data Safety Monitoring Plan. Planned assessments for individual patient safety are as follows:

Safety Assessment	*Criteria leading to alteration or discontinuation of subject participation*	*Personnel responsible for assessment*
Home blood pressure measurement	*Subject is instructed to contact study nurse for any SBP > 170, DBP > 110, or HR <50 on 2 consecutive measurements at least 5 minutes apart for a BP/HR check.*	*Subject measures BP. Reports high values to research nurse; who reports to study physician.*
	Manual. 15 minutes of rest prior to HR measurement. *If HR <55 bpm on screening visit in absence of treatment with a β-blocker, the subject is withdrawn.* *If HR<50 bpm during beta-blocker treatment, reduce the dose by half*	

Resting heart rate measurement	*Manual. 15 minutes of rest prior to HR measurement. If HR <55 bpm on screening visit in absence of treatment with a β-blocker, the subject is withdrawn. If HR<50 bpm during beta-blocker treatment, reduce the dose by half*	
Pregnancy test	*Test done in CTSI lab.* *If positive, subject is withdrawn*	*CTSI Lab Technologist* *Study nurse or PI withdraws subject*
Blood glucose	*If fasting blood glucose ≥ 126 mg/dl or nonfasting blood glucose ≥ 200 mg/dl, subject is withdrawn*	*Drawn by CTSI nurse. Physician evaluates labs for subject inclusion.*
Serum creatinine	*If SCr >1.5 in men or >1.4 in women, subject is withdrawn*	*Drawn by study nurse. Results checked by study nurse or PI. Study nurse or PI withdraws subject.*

The study physician, Dr. Schmidt, and study PI, Dr. Cavallari, will evaluate adverse events for seriousness, expectedness, severity, and relationship to study intervention. An adverse event will be defined as any untoward occurrence (physical, psychological, behavioral) that occurs during the course of the study regardless of its causal relationship with the treatment being studied. The IRB will confirm the causative relationship afterward.

Analysis of the Study:

Aim 1: Compare the pharmacokinetics and cardiovascular effects of brand name and generic metoprolol ER products in patients with hypertension:

Heart rate variability and 24 hour HR. Data will be analyzed by an expert in analysis of heart rate variability data who will be blinded to the metoprolol formulation the patient was taking and to patient genotype and other characteristics. For holter monitor analysis, one 5-min epoch from each hour of the quartile will be selected based on absence of a significant number of ectopic beats and artifact. Spectral measures of HR variability will be calculated over each 5-min epoch. These absolute measures will consist of: high-frequency variability (parasympathetic activity), low-frequency variability (primary sympathetic activity), and total variability.[43] Ratios of HR variability will include: high to low (parasympathetic/sympathetic balance), high to total (normalized measure of parasympathetic activity), and low to total (normalized measure of sympathetic activity). Spectral measures of HR variability will be compared between brand name and each

generic treatments (and over quartiles of the day for HR variability) using an analysis of variance model with measures repeated on 2 factors (treatment and quartile). Treatment order will be included as a covariate in the model to test for any differences in response based on the sequence of drug administration. Significance levels will be adjusted for violation of the assumption of compound symmetry using the Greenhouse-Geiser correction.

24 hour ambulatory and home BP data. Data will be analyzed by an investigator blinded to the metoprolol formulation the patient was taking and to patient genotype and other characteristics. The BP data will be analyzed as previously described.[35] 24 hour ambulatory data will be cleaned for artifactual readings and then hourly averages taken. These data can be used with the PK data for PK/PD modeling. Additionally, these data, along with the AM and PM home BP data across multiple days will be analyzed to create a composite BP, as previously described.[35] Composite BP will be compared between brand name and each generic product over each of the 24-hour recording periods using analysis of variance for repeated measures, with measures repeated on treatment and time of day.

Pharmacokinetic and pharmacometric modeling. Data will be analyzed by an investigator blinded to the metoprolol formulation the patient was taking and to patient genotype and other characteristics. A non-compartmental analysis will be performed in Phoenix® WinNonlin® (version 6.1 or higher, Pharsight, www.pharsight.com) to determine the basic pharmacokinetic parameters of generic metoprolol succinate 1, generic metoprolol succinate 2 and [redacted] following oral administration. Log-transformed values of the key pharmacokinetic parameters (AUC, C_{max}) for each drug product will then be used for bioequivalence testing. Ratios of geometric means and arithmetic means as well as respective 90% CI (0.8-1.25 limits) will be computed for each drug product. Bioinequivalence is declared when the 90%CI for PK parameters of the test product is completely outside the limits of 80-125% of the reference (brand name) product. In addition, a fully-parametric population pharmacokinetic (pop-PK) model will be developed in NONMEM® (version 7.2 or higher, ICON Development Solutions, Ellicott City, MD, USA) to simultaneously estimate the population pharmacokinetic parameters characterizing the absorption, distribution, metabolism, and elimination of metoprolol succinate as well as the interindividual and residual variability associated with them. The developed pop-PK model will then be linked to the corresponding pharmacodynamic (PD) endpoints to: i) characterize the dose-concentration-response relationship of all three drug products on both a patient level as well as a population level and ii) to determine if potential differences in PK between drug products translate into statistically significant differences in the dose-concentration-response relationship. We will also include treatment with a proton pump inhibitor and *CYP2D6* genotype as parameters in the model.

Power analysis**.** Due to the cross-over design, each participant will have responses to 3 different metoprolol ER products. The comparisons we are most interested in are the paired comparisons between the brand name and each of the two generic products.

Table 4. Data for power calculation

Effect size	N	HR variability, SD =1,479, mean=13,886		T_{max} (hr), SD =2.3, mean=6		AUC, SD=993, mean=3230		C_{max}, SD = 34, mean=163	
		Δ	Δ %	Δ	Δ %	Δ	Δ %	Δ	Δ %
0.5	41	740	5%	1.2	19%	497	15%	17	10%
0.53	**38**	784	6%	1.22	20%	526	16%	18	11%
0.6	29	887	6%	1.4	23%	596	18%	20	13%
0.65	25	961	7%	1.5	25%	645	20%	22	14%
0.7	22	1035	7%	1.6	27%	695	22%	24	15%
0.8	18	1183	9%	1.8	31%	794	25%	27	17%
0.9	15	1331	10%	2.1	35%	894	28%	31	19%
1	13	1479	11%	2.3	38%	993	31%	34	21%
1.1	11	1627	12%	2.5	42%	1092	34%	37	23%
1.2	10	1775	13%	2.8	46%	1192	37%	41	25%

In determining the sample size needed for the Aim 1 analysis, we used the reported mean and standard deviation of all the endpoints: T_{max} (6 ± 2.3 hr), AUC (3260 ± 993 ng*hr/mL), C_{max} (163 ± 34 ng/mL), and HR variability (13,886 ± 1,479 ms^2).[33,34] With a sample size of 38, at an alpha level of 0.025 (0.05/2 comparisons), using a 2-sided paired t test, we would have >80% power to detect a 20% difference in T_{max}, 16% difference in AUC, and 6% difference in HR variability (Table 2). We will target 50 total patients for enrollment to allow for drop-outs.

Aim 2: Determine the impact of gastric pH variation on the concentration-response relationship with different metoprolol ER products

[redacted] data. Data will be analyzed by an investigator blinded to the metoprolol formulation the patient was taking and to patient genotype and other characteristics. Analyses of [redacted] data will be performed via [redacted] software ([redacted]). Only data during the time of the 24-hour studies will be used for analysis. Mean intragastrointestinal pH for every hour and 24 hours will be obtained from the raw pH data. Data on gastric transit time and pH will be explored as potential covariates for the PK/PD model developed in Specific Aim 1, particularly with respect to their influence on the rate and extent of metoprolol absorption from the 3 different formulations. Additionally, we will use the median pH value to create a dichotomous variable for pH and then test for differences between formulations. For example, the mean difference in C_{max} for generic #1 versus the reference product will be compared between the two pH groups using analysis of covariance controlling for effects of baseline characteristics.

Power analysis: According to a prior study using the [redacted],[44] the mean (SD) gastric pH among healthy subjects without GI diseases was 2.79 (1.39). Based on these data, at an alpha level of 0.025, with 38 subjects, we will have >80% power to detect an effect size of ≥ 0.65 (variability in gastrointestinal pH of ≥ 0.9 unit) between subjects. Therefore this sample size should provide us with adequate interpatient variability in pH to assess

whether pH is contributing to any differences in pharmacokinetics for the various metoprolol ER formulations.

Aim 3 Examine the effect of *CYP2D6* genotype on the pharmacokinetics of different metoprolol ER products

Genotype data. We will determine whether formulation differences are greater within a CYP2D6 phenotype group. Since CYP2D6 would be expected to only affect the pharmacokinetics, and not the PK-PD relationship, then analyses will first include comparison of the deltas in the various PK parameters between the generic versus reference product in PMs/IMs versus EMs. For example, the mean difference in C_{max} for generic #1 versus the reference product will be compared between the CYP2D6 phenotype groups using analysis of covariance controlling for effects of baseline characteristics. Secondary analyses will compare the PK-PD relationships across formulations between the two CYP2D6 phenotype groups. In addition, *CYP2D6* genotype will be explored as potential covariate for the PK/PD model developed in Specific Aim 1 to determine if the rate and extent of oral metoprolol absorption is changed as a result of e.g. altered first-pass metabolism in the liver or in the gut.

Power analysis. We plan to recruit a total of 50 participants to allow for drop-out, with a target of 38 who complete all studies. We will target enrollment of at least 10 PMs/IMs and the remainder EMs. This will be possible due to targeted recruitment of participants with known genotypes. According to a meta-analysis of 13 studies,[45] the PK parameters such as C_{max} and AUC in PMs were at least doubled compared to EMs: 2.3 fold for C_{max} and 4.9 fold for AUC. For IMs, C_{max} was 1.6-fold higher and AUC was 2.5-fold higher compared to EMs. Based on the information presented in this meta-analysis, we estimated the mean and standard deviation of C_{max} and AUC for 200 mg of metoprolol to be: C_{max}: 312 ± 338 and AUC: 1462 ± 1522 for EMs, C_{max}: 512 ± 572 and AUC: 3692 ± 4491 for IMs; C_{max}: 710 ± 504 and AUC: 7106 ± 3478 for PMs. For comparison of PK parameters across formulations between the CYP2D6 phenotype groups, with at least 10 PMs/IMs and the remainder of the study population composed of EM individuals, at alpha of 0.05, we would have >80% power to detect effect size of ≥ 1.2, which is equivalent to Cmax difference of 405 (1.3 fold) or AUC difference of 1754 (1.2 fold). These numbers were smaller than those differences reported in the meta-analyses.[15]

Data Management/Confidentiality of Data/Records:

Case Report Form (CRF) will be used for each subject. To protect the participant's right of privacy, the Patient Identification Number will identify patients' individual records related to the study and will be stored in locked cabinets with limited access, and electronic files will be kept in secured database. A de-identified dataset from the database using a patient identification number will then be shared with statistician for analysis. During the study, data will be analyzed as it becomes available by Dr. Larisa Cavallari. No early closure is planned because of the limited scope and projected low risk of the study.

If subject consents to banking, samples from the study subjects will be stored at the Center for Pharmacogenomics Laboratory with limited access for authorized personnel only. All samples will be identified by a code that can be linked to the patient's identity only by the reference information file and separately on the secure server with limited access and password protected. After completion of the study, all left over samples from subjects who consented to banking will be stored in the Center for Pharmacogenomics. All other samples and data will be destroyed upon completion of the study according to the University of Florida's Human Subjects Protections requirements.

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UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study?

Open-Labeled Pharmacokinetic and Pharmacodynamic (PK-PD) Studies of Metoprolol ER

3. Who do you call if you have questions about this research study?

Principal Investigator: Larisa Cavallari, PharmD at (352) 273-8245

Other research staff: Study Physician: Dr. Siegfried Schmidt at (352) 265-9475

4. Who is paying for this research study?

The sponsor of this study is the Food and Drug Administration (FDA)

5. Why is this research study being done?

The purpose of this research study is to compare the quality and effectiveness of two generic versions of a blood pressure lowering medication, called metoprolol succinate, to the brand name version of this medication ([redacted]). The study will also look at the effect of genetic makeup on drug response. Genetic makeup is what determines a person's body traits, such as height and eye color. Genetic makeup differs from person to person, which is why one person's body traits are different from another person's. Genetic makeup can also determine how the body breaks down a drug. This can cause drug effects to differ from person to person.

You are being asked to be in this research study because you are currently being treated for high blood pressure and/or you previously participated in the Pharmacogenomic Evaluation of Antihypertensive Responses trials (PEAR-1 or PEAR-2).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

Regular visits to your doctor for blood pressure checks and occasional blood work is part of your normal clinical care for your high blood pressure. Checking your blood pressure at home may also be part of your normal care. Your normal clinical care should continue. Things will be done during your participation in this study that would not be considered part of normal clinical care. While you would normally have your blood pressure monitored by your doctor, we will monitor it in more ways. We will also look at drug levels in your body and your heart rate during exercise.

7. What will be done only because you are in this research study?

If you are18 years of age or older, and agree to participate in the study, it will involve a minimum of 7 study visits (possibly up to 15 visits) occurring over a 6-15 week period. Three (3) of the visits will involve an overnight stay, and each overnight stay will take about 28 hours. Other study visits are expected to be 30 minutes to 1 hour. There will be 4 periods of drug treatment of various lengths of time. You will be given

a study medication for your blood pressure called [redacted] for periods 1 and 3. You will be given a generic form of [redacted] (Generic Drug A or Generic Drug B) for periods 2 and 4. During the time you are in the study, your metoprolol succinate treatment will be managed by the study physician and your other blood pressure medications may be adjusted to control you blood pressure. Any other medical conditions will continue to be managed with your primary care physician.

The first visit (screening visit) and outpatient visits will occur at the Clinical Research Center (CRC) at the UF Health Clinical and Translational Research Building (CTRB) at 2004 Mowry Rd, Gainesville, FL 32610. The enrollment visit will occur in the UF Health Family Medicine - Hampton Oaks at 200 SW 62nd Blvd, Gainesville, FL 32607. Overnight visits will occur in the CRC at CTRB or at UF Health Shands Hospital at 1600 SW Archer Rd, Gainesville, FL 32608.

Screening Visit

If you agree to participate by signing this form, the study nurse will draw 3 teaspoonfuls (15 mL) of blood from a vein in your arm. Two teaspoons (10 mL) will be drawn for basic blood work and one teaspoon (5 mL) will be drawn for genotyping. The study nurse will collect your medical history and the list of your current medication. The study nurse or the Clinical Research Center Nursing staff will check your vitals (blood pressure, heart rate, respiration rate, temperature) and height and weight. If you are a woman of childbearing potential, we will perform a urine pregnancy test. This will end the screening visit. If you still qualify for the study after initial testing, the study nurse will call you to schedule the enrollment visit.

Enrollment Visit

The study nurse will check your vitals and the study physician, Dr. Siegfried Schmidt will perform a physical exam and discuss your medical history with you. If you are eligible to participate you will be randomized to one of two groups like flipping a coin. You or the researcher cannot choose which group you will be assigned to:

- Study Group A- start with [redacted], switch to [redacted] metoprolol succinate, switch back to [redacted], then switch to [redacted] metoprolol succinate.
- Study Group B- start with [redacted] switch to [redacted] metoprolol succinate, switch back to [redacted], then switch to [redacted] metoprolol succinate.

Each study group will consist of treatment with Toprol XL for 2 periods, treatment with [redacted] metoprolol succinate for one period, and treatment with [redacted] metoprolol succinate for one period. The generic drug periods will be in a different order for each study group. After the enrollment visit, you will be provided up to a 2-week supply of study drug to begin the first of four treatment periods.

Period 1

You will be provided with the blood pressure medication called [redacted] (metoprolol succinate). You will take this study medication for 7-28 days. The length of time you take the medication will depend on your blood pressure level and when you are able

to come in for the first overnight study visit. If you are taking metoprolol succinate or a drug like metoprolol succinate before the study, it will be stopped. You will be started on [redacted] at a dose that should have the same effect on your blood pressure. Also, your dose of metoprolol succinate may be adjusted up or down to achieve or maintain your goal blood pressure. If you are not taking metoprolol succinate or a drug like metoprolol succinate before the study, [redacted] will be started at a low dose of 50 mg/day. It may be necessary to reduce the dose or stop another blood pressure medicine so that you can safely take the study medication. By signing this consent form, you are providing permission for Dr. Larisa Cavallari or Dr. Siegfried Schmidt to talk to your doctor before adjusting any of your medications. You may be asked to return for an outpatient visit once a week for up to 3 study visits for a blood pressure check and increase in the dose of your study medication. At least one titration visit, documenting BP < 140/90 mm Hg, will be required before scheduling the first overnight study visit. You will need to take your study medication each morning at 9AM. Metoprolol succinate extended-release tablets should be swallowed whole and not chewed or crushed.

You will be provided a home blood pressure monitor. The study nurse will show you how to use the monitor. You will be asked to take your blood pressure each morning when you wake up and each evening when you go to bed. If your systolic blood pressure (top number) is above 170 or below 100, diastolic blood pressure (bottom number) is above 110, or heart rate (pulse) is less than 50 for 2 measurements in a row taken about 5 minutes apart, you should contact the study nurse for a BP check visit as soon as possible. You should bring your home blood pressure monitor and study medication pill bottle with any leftover pills each time you come for a study visit. Your study nurse will provide you with the dates and times you will need to come in for each study visit.

Overnight study visit

After taking your study medication for 7- 28 days, you will be asked to come to the CRC or to UF Health Shands Hospital at 7:30AM for an overnight visit. You should bring comfortable clothing and shoes for the exercise treadmill test. The overnight visit will last approximately 28 hours. You should not consume caffeine or alcohol beginning at 8PM the night before your study visit and during the entire overnight study. You should not eat or drink anything except for water after 12 midnight the night before your study visit. We will ask you to stay on site until the following morning after completion of the study. If you leave before completion of the visit, you may be withdrawn from the study. You will not be allowed to shower during the overnight stay.

At the beginning of the overnight visit, you will have a blood pressure cuff placed on your arm and electrodes (small, flat, sticky patches) placed on your chest. The electrodes will be attached to a monitor that you may clip to your belt or wear around your neck to check your heart rate. The cuff will be attached to a monitor that can be worn on your waist. The monitor will take your blood pressure at random times 4 times per hour between 8 AM and 11PM, two times per hour between 11PM and 6 AM, and 4 times per hour between 6AM and 8AM. You will also have a catheter placed in a vein in your arm so that blood can be drawn. A little over 1 teaspoonful (6

mL) will be drawn 12 times during the overnight visit for a total of about 1/3 cup or 5 tablespoonfuls (72 mL). The times of the blood draw are around 9 AM, 9:30 AM, 10 AM, 11 AM, 12 PM, 1 PM, 3 PM, 5 PM, 9 PM, 1 AM, 5 AM, and 9 AM the following day.

You will be provided with a "[redacted]" (similar to a granola bar) to eat around 8:30 AM. You will be asked to swallow a "[redacted]" capsule with water right after you finish the [redacted]. The "[redacted]" capsule is a blue and clear oblong pill that is little larger than a vitamin pill. Both the [redacted] and "[redacted]" capsule are cleared by the Food and Drug Administration. You will be given a special recorder to chart the progress of the "[redacted]" capsule as it moves through your body. The recorder will chart the pH (acidity) of your stomach and intestines. The recorder should remain within 2 feet of you and can be worn on a belt clip or lanyard (cord) around your neck. Approximately at 9 AM, you will be given a dose of your study medication. Actual times may vary depending on your time of arrival, blood draws, and/or intake of [redacted].

You will also be provided with a menu of meals to select from during your overnight stay. The menu includes a variety of meals including vegetarian options. The same food options you chose for the first overnight visit will be provided to you for the second and third overnight visits.

The blood pressure monitor, heart rate monitor, and catheter in your arm will be removed around 9AM the following morning. You will be asked to take your next dose of study medication approximately at 9AM. You will be taken to the Shands Heart Center, located in the Shands hospital, for an exercise treadmill test around 11AM. The actual times may vary depending on a time of treadmill availability, but we will inform you as soon as we know. Small areas on your chest will be cleaned, and electrodes (small, flat, sticky patches) will be placed on these areas. The electrodes will be attached to an electrocardiograph monitor (ECG or EKG) that charts your heart's electrical activity. A blood pressure cuff will be placed around your arm. You will be asked to start walking on the treadmill. The speed and slope of the treadmill will be increased every 2 to 3 minutes. You may feel like you are walking uphill. The total exercise time will last between 7 and 12 minutes. Your heart's electrical activity, heart rate and blood pressure will be monitored before, during, and after the test. You will also be asked how you are feeling at regular intervals during the test. At the end of the test, you will be asked to walk slowly for a couple of minutes to cool down. Your heart's electrical activity, heart rate, and blood pressure will continue to be monitored until they return to pre-test levels. The electrodes will then be removed. You will be provided with up to a 2-week supply of the next study drug to begin taking at 9 AM the next day.

[redacted] *Capsule*

The "[redacted]" capsule will naturally pass during a bowel movement within 3 to 5 days. You can remove the recorder after you notice the "[redacted]" capsule has passed in your stool or after 5 days. You will be able to resume most of your usual activities while wearing the recorder, but should avoid excessive exercise. The

recorder should be worn at all times except during bathing and sleeping. The recorder should be kept within 2 feet of you when you are not wearing it. Remove the recorder before bathing and place it somewhere nearby where it will not get wet. You may place the recorder under your pillow or on your nightstand while sleeping. You will be asked to return the recorder at your next study visit (next overnight study or outpatient visit depending which occurs first).

Period 2

You will be provided with generic drug A or B, depending on which Study Group you are in, at the end of the first overnight study visit. The dose of the generic medication will be the same as the dose of [redacted] you were taking at the end of period 1. You will take the generic study drug for 7 days. You will need to take your study medication each morning at 9AM.

You will use the same home blood pressure monitor. You will take your blood pressure each morning when you wake up and each evening when you go to bed. If your systolic blood pressure (top number) is above 170 or below 100, diastolic blood pressure (bottom number) is above 110, or heart rate (pulse) is less than 50 for 2 measurements in a row taken about 5 minutes apart, you should contact the study nurse for a BP check visit as soon as possible. You should bring your home blood pressure monitor and study medication pill bottle with any leftover pills with you for your next overnight stay.

After 7 days on the generic blood pressure medication, you will again return to the CRC or to UF Health Shands Hospital for an overnight stay and repeat all of the tests described above during the overnight study visit. At the end of the overnight study visit, you will be provided with up to a 2-week supply of [redacted] at the same dose as the generic product in Period 2 to begin at 9 AM the next day.

You will again wear the data recorder until you notice the "[redacted]" capsule has passed in your stool or for 5 days. You will be able to resume most of your usual activities while wearing the recorder, but should avoid excessive exercise. The recorder should be worn at all times except during bathing and sleeping. The recorder should be kept within 2 feet of you when you are not wearing it. Remove recorder before bathing and place it somewhere nearby where it will not get wet. You may place it under your pillow or on your nightstand while sleeping. You will be asked to return the recorder at your next scheduled study visit.

Period 3

You will again take the brand name blood pressure medication [redacted] at the same dose as the generic product in period 2. You will need to take your study medication each morning at 9AM. You will take this study medication for 7-28 days. The length of time is flexible to help you schedule the final overnight visit after period 4. There is no overnight study visit in period 3. If the blood pressure monitor and/or the heart rate monitor malfunctions during Visit 1, you may be asked to wear the blood pressure monitor and/or the heart rate monitor for a 24 hour period at your home during Period 3. You may choose not to take part in the Period 3 monitoring if you are asked to do

so, and not taking part in this additional monitoring during Period 3 will have no effect on your treatment or ability to complete Period 4 as scheduled. You will need to come to in for an outpatient visit each week during Period 3 for a blood pressure check and to pick up another 7 day supply of medication until you are ready to begin Period 4.

You will use the same home blood pressure monitor. You will take your blood pressure each morning when you wake up and each evening when you go to bed. If your systolic blood pressure (top number) is above 170 or below 100, diastolic blood pressure (bottom number) is above 110, or heart rate (pulse) is less than 50 for 2 measurements in a row taken about 5 minutes apart, you should contact the study nurse for a BP check visit as soon as possible. You should bring your home blood pressure monitor with you and study medication pill bottle with any leftover pills each time you come to the clinic. Your study nurse will provide you with the dates and times you will need to come to clinic.

Period 4

After completing 7-28 days with the brand name [redacted], you will be provided with the second generic blood pressure medication at the same dose as [redacted] you took at the end of Period 3. You will take the second generic study medication for 7 days. You will need to take your study medication each morning at 9AM.

You will use the same home blood pressure monitor. You will take your blood pressure each morning when you wake up and each evening when you go to bed. If your systolic blood pressure (top number) is above 170 or below 100, diastolic blood pressure (bottom number) is above 110, or heart rate (pulse) is less than 50 for 2 measurements in a row taken about 5 minutes apart, you should contact the study nurse for a BP check visit as soon as possible. You should bring your home blood pressure monitor and study medication bottle with any leftover pills with you for your final overnight stay. Your study nurse will provide you with the date for your overnight stay.

After 7 days of taking the second generic blood pressure medicine, you will again return to the CRC or UF Health Shands Hospital for an overnight stay and repeat all of the tests described above during the overnight study visit. You will be discharged from the research unit after the treadmill test is over. If you were taking metoprolol or another β-blocker before the study, you will be placed back on your pre-study medication after the overnight visit. You should start taking your pre-study medication the following day or as instructed by Dr. Cavallari or Dr. Schmidt. If you were not on a β-blocker before the study, you will be given a lower dose of the study medication to take for one week. You should continue to check your blood pressure with your home monitor each morning and evening. If your systolic blood pressure (top number) is above 170 or below 100, diastolic blood pressure (bottom number) is above 110, or heart rate (pulse) is less than 50 for 2 measurements in a row taken about 5 minutes apart, you should contact the study nurse for a BP check visit as soon as possible.

You will again wear the data recorder until you notice the "[redacted]" capsule has passed in your stool or for 5 days. You will be able to resume most of your usual activities while wearing the recorder, but should avoid excessive exercise. The

recorder should be worn at all times except during bathing and sleeping. The recorder should be kept within 2 feet of you when you are not wearing it. Remove recorder before bathing and place it somewhere nearby where it will not get wet. You may place the recorder under your pillow or on your nightstand while sleeping. You will be asked to return the recorder at your next study visit.

Follow up study visits after study completion or withdrawal

You will be asked to return for an outpatient visit one week after the final overnight study visit to return the data recorder and get a blood pressure check. You may be asked to return weekly for up to 2 more visits or until you have been safely removed from the study medication and are back on your pre-study medication. You should bring your blood pressure monitor and study medication pill bottle with any leftover pills with you to each visit. The study nurse will call you around 30 days after the final overnight stay for a final follow up to make sure you are back on your pre-study medications and to ask you about your blood pressure readings.

If you have any questions now or at any time during the study, please contact one of the research team members listed in question 3 of this form.

8. How long will you be in this research study?

You will be in this research study for 6-15 weeks.

9. How many people are expected to take part in this research study?

50

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

There is a risk that your blood pressure will become too low which may cause you to feel light headed or dizzy or to feel tightness or pressure in your chest. Your blood pressure may be elevated if it does not respond well to the blood pressure medications you are given, which might cause you to have a headache or feel pressure in your head. This might also cause you to feel pressure in your chest. There is also a risk with elevated blood pressure of heart attack or stroke. If you experience any of these symptoms you should measure your blood pressure with your home monitor and you should call your study nurse or doctor immediately to report your blood pressure and your symptoms.

The study medication is a beta blocker, and may cause you to experience a slow heartbeat, dizziness, light-headedness, drowsiness, fatigue, depression, diarrhea,

nausea or vomiting, shortness of breath and wheezing. If you experience any of these symptoms you should report them immediately to the study nurse listed in section 3. The study medication may also involve risks to the embryo or fetus if you are pregnant or become pregnant while taking the medication.

The risks of placing a catheter in your arm for drawing blood include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and uncommonly, faintness from the procedure. The total amount of blood drawn during the entire study is about 15 tablespoons (about 1/2 pint).

The risks with the "[redacted]" capsule include the capsule staying in the body longer than expected and/or accidentally inhaling the capsule. If you experience any unusual symptoms, you should report them immediately. There is a risk of damage to the stomach or intestines if the "[redacted]" capsule is in the body during an MRI test.

Side effects of the exercise treadmill test can include shortness of breath, light headedness, drop in blood pressure, or abnormal heart rhythm. In rare cases, these side effects can be serious or life-threatening. Medical staff trained in emergency response will be present for the studies. Also possible are direct injuries such as bruises, sprains, and strains and indirect problems such as worsening of pain from arthritis.

The risks of genetic testing include those related to confidentiality surrounding the genetic information, and the chance that the genetic information could in some way expose you to increased risk regarding employment or that future life, health, disability or long term care insurance providers could potentially use this genetic information to deny, limit or raise rates for insurance coverage. To protect you from this risk, your DNA will not be stored with any of your identifying information and the results of your genetic testing will not be given to you and it will not become part of your medical record. If you signed a separate consent form for banking, your left over DNA and study records will be stored for future unknown research in the Center for Pharmacogenomcis Tissue and Data Bank. If you do not sign the consent form for banking, your leftover DNA and study records will be used until the end of this study and then destroyed. None of your personal health information or any identifying information will be stored with your DNA and study records. If your DNA or study recorders are shared with other researchers, none of your personal identifying information will be shared.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Additional information can be obtained at: http://irb.ufl.edu/gina.html or call 1-800-669-3362. If you think this law has been violated, it will be up to you to pursue any compensation from the offending insurance company and/or employer.

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or

employability. Questions 17-21 in this form discuss what information about you will be collected, used, protected, and shared.

The results of the following tests are being done for research purposes only and might not be evaluated or used to diagnose/ treat the participant's medical problems. The results might not be entered into the participant's medical record. These tests may need to be repeated by the participant's primary care doctor if required for the participant's medical care in the future:

1. All testing performed by CRC

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the research team members listed in question 3 in this form.

11a. What are the potential benefits to you for taking part in this research study?

There may be no direct benefit for you for participating in the study.

11b. How could others possibly benefit from this study?

Others with high blood pressure may benefit from this research if the study results lead to higher quality generic blood pressure medications.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator listed in question 3 of this form may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

If you do not want to participate in this study, you can receive a blood pressure lowering medication via a prescription from your doctor, and you can obtain a blood pressure monitor from your local drug store to monitor your blood pressure at home. You should talk to your doctor about what medications might be most appropriate for you.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

If you decide to withdraw your consent to participate in this study for any reason, please contact one of the research team members listed in question 3 of this form . They will tell you how to stop your participation safely.

If you have any questions regarding your rights as a research subject, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

If you discontinue participation in the study (withdraw), the information about you collected up until the time you withdraw can still be used.

13c. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- At the discretion of the principal investigator or study physician based on what is best for your health and safety.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

Study Drugs and Devices

Toprol XL, [redacted] metoprolol succinate, [redacted] metoprolol succinate, [redacted] and recorder, and home blood pressure monitor will be provided at no cost to you while you are participating in this study.

Study Services

The Sponsor will pay for all medical services required as part of your participation in this study as described above in the question “What Will Be Done Only Because You Are In This Research Study”. If you receive a bill for these services, please contact Dr. Larisa Cavallari at (352) 273-8245.

Items/Services Not Paid for by the Sponsor

Any other medical services provided to you that are not directly required by this study will be billed to you or your insurance company in the usual manner.

15. Will you be paid for taking part in this study?

You will receive [redacted] gift cards depending on how many study visits you attend. A [redacted] gift card will be given to you after your enrollment visit, screening visit, and each outpatient study required to adjust your medication or to repeat monitoring during Period 3. A [redacted] gift card after will be given to you after each overnight study visit that you complete. If you leave the overnight study visit on your own before completing the 24-hour studies (before 9 AM the following day) or are withdrawn by study investigators before completing the 24-hour studies (before 9 AM the following day) study, you will receive [redacted]. If you complete the 24-hour studies but leave the visit on your own or are withdrawn before the exercise treadmill test, you will receive [redacted].

If you are paid more than [redacted] for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. If the payments total [redacted] or more or you are a nonresident alien, payment will be processed through the University of Florida Accounts Payable department and the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

Your payment for participation in this research study is handled through the University of Florida's Human Subject Payment (HSP) Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (HSP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

The study team will provide you with an informational form called the Prepaid Card Facts document. If you have any problems regarding your payment call the HSP Office (352) 392-9057.

16. What if you are injured because of the study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact one of the research team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

17. How will your health information be collected, used and shared?

If you agree to participate in this study, the Principal Investigator will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the Principal Investigator needs your authorization The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Complete past medical history to determine eligibility criteria
- Records of physical exams
- Results of all study related tests and measures
- Name, phone number, address, and email address
- Social Security Number for the purpose of payment

This information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will only include information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, photographs, or other codes that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the

limited data set are required in order to protect your identity and confidentiality and privacy.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, through your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- To determine the effectiveness of the study drugs
- To determine if your genetic makeup affects response study medications

Once this information is collected, it becomes part of the research record for this study.

19. Who will be allowed to collect, use, and share your protected health information?

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- the study Principal Investigator (listed in question 3 of this form) and research staff associated with this project.
- other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures.
- the University of Florida Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research).

20. Once collected or used, who may your protected health information be shared with?

Your PHI may be shared with:

- the study sponsor (listed in Question 4 of this form).
- United States governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections.
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with

authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

21. If you agree to take part in this research study, how long will your protected health information be used and shared with others?

Your PHI will be used and shared with others until the end of the study.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigator.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described in sections 17-21 above. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing	Date