Influence of Testosterone Administration On Drug-Induced QT Interval Prolongation and Torsades de Pointes

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1.0 Background

Torsades de pointes (TdP) is a ventricular arrhythmia associated with corrected QT (QT_c) interval prolongation. Acquired TdP is most commonly cause by drugs, and over 50 FDA-approved medications may cause this adverse event. TdP results in catastrophic outcomes, including sudden cardiac death. The risk of drug-induced TdP is lower in men than in women, due largely to the protective effect of testosterone. However, 29-46% of all reported cases of drug-induced TdP have occurred in men. Older age is an independent risk factor for TdP in men, likely as a result of declining testosterone concentrations. Methods to reduce the TdP risk in older men requiring therapy with QT_c interval-prolonging drugs have not been developed. Evidence by our group suggests: 1) Testosterone administration may be protective against TdP, and 2) Oral progesterone attenuates drug-induced QT_c interval lengthening in premenopausal women. The efficacy of exogenous testosterone or progesterone for attenuating drug-induced QT_c interval lengthening in older men has not been studied. Identifying effective means of attenuating drug-induced QT_c interval lengthening will improve medication safety in older men requiring therapy with QT_c prolonging drugs.

The risk of drug-induced QT_c interval prolongation and torsade de points is lower in men than women.[1-7] Ventricular repolarization occurs more rapidly in men, manifested by shorter QT_c intervals.[8] This difference in QT_c intervals becomes apparent only after puberty,[9] suggesting that changes in serum sex hormone concentrations are responsible. Post-pubertal differences in QT_c intervals may be largely due to reduction in QT_c intervals in males as a result of testosterone production. In isolated perfused heart models, including work by our group, DHT shortens ventricular APD and attenuates the QT_c interval prolonging effects of quinidine.[10,11]

However, while female sex is a risk factor for drug-induced TdP, 29-46% of all reported cases have occurred in men. In reports of erythromycin-associated cardiac arrhythmias from 1970-1996, 32% of the cases occurred in men.[3] In an analysis of all published cases of TdP associated with noncardiac drugs, 29% occurred in men.[12] Of 100 cases of cisapride-associated TdP reported to the FDA, for which patient sex was specified, 30% occurred in men.[13] Nearly half (46%) of reported cases of azimilide-induced TdP occurred in men,[14] while 40% of cases of terfenadine-associated TdP occurred in men.[4] Similar percentages have been reported regarding TdP associated with halofantrine (40% of cases in men)[15] and quinidine (34% in men).[1] Therefore, a substantial proportion of drug-induced TdP cases occur in men.

The risk of drug-induced TdP in men 55-65 years of age is > 3x higher than in those 45-55 years, and increases in subsequent decades of age.[14] Our group and others have shown that older age is an independent risk factor for QT_c interval prolongation and TdP in both sexes.[16-20] In men, this may be partly due to declining serum testosterone/DHT concentrations.[21,22] There is an inverse relationship between serum testosterone concentrations and QT intervals.[22] Testosterone is associated with reducing QT intervals[23,24] and protects against QT_c interval prolongation induced by inhibition of potassium (K^+) conductance.[10,11,25] DHT administration attenuates dofetilide-associated ventricular APD lengthening and inhibits early afterdepolarizations.[26] Declining serum testosterone, therefore, may be responsible for the increase in risk of drug-induced TdP

in older men. However, the influence of testosterone/DHT on the incidence of drug-induced TdP has never been studied.

In women, QT_c interval and TdP risk fluctuate throughout the menstrual cycle and during pregnancy.[25,27] The QT_c interval is shorter during the luteal phase than in the follicular phase,[27] and ibutilide-induced QT_c interval response is greatest during menses and ovulation.[25] There was no relationship between serum estradiol concentrations and QT_c interval response, but there were significant inverse correlations between serum progesterone concentrations and QT_c interval[25] and between progesterone:estradiol ratio and ibutilide-induced QT_c interval response, suggesting that progesterone may protect against drug-induced QT_c lengthening.[25] Progesterone is protective effects against QT_c interval prolongation and arrhythmias associated with the long-QT syndrome.[25,28-30] Progesterone's structure is androgenic, and progesterone is a testosterone precursor during testosterone synthesis in testicular Leydig cells.[31] Our data indicates that oral progesterone administration attenuates drug-induced QT_c interval lengthening in healthy premenopausal female volunteers with low endogenous serum estradiol and progesterone concentrations.

In view of the above data indicating that older men are at greater risk of drug-induced TdP than younger men, that this may be due to declining serum testosterone concentrations, and that testosterone exerts protective effects against QT_c interval lengthening and TdP, we hypothesize that exogenous administration of testosterone attenuates drug-induced QT_c interval lengthening in older men and reduces the risk of TdP. Further, in view of our preliminary data suggesting that progesterone attenuates drug-induced QT interval lengthening in premenopausal women and may reduce TdP risk, we hypothesize that these findings may extend to older men, and that oral progesterone administration attenuates drug-induced QT_c interval lengthening in older men.

2.0 Rationale and Specific Aims

Establishing the influence of exogenous testosterone or progesterone administration as preventive methods to reduce the risk of TdP may lead to important advances in proarrhythmia risk reduction. Patients at high risk of drug-induced TdP who require therapy with a QT_c interval-prolonging drug could be pre- or concomitantly treated with transdermal testosterone or oral progesterone. Treatment with these exogenous hormones could provide additional protection against potentially fatal arrhythmias; this hypothesis requires testing in subsequent studies.

Our *long-term goal* is to determine mechanisms by which drugs cause arrhythmias, to identify risk factors for drug-induced arrhythmias, and to determine safe and effective methods of prevention and management of drug-induced arrhythmias. The *objectives in this application* are to evaluate and compare the efficacy of novel therapeutic approaches to reduce the risk of drug-induced QT_c interval prolongation and TdP. Our *central hypothesis* is that acquired QT_c interval prolongation and the risk of TdP are attenuated by exogenous testosterone or progesterone administration. To test this hypothesis, we propose the following *specific aims*:

Specific Aim: **Determine the efficacy of exogenous testosterone and progesterone administration as preventive methods by which to diminish the degree of drug-induced QT interval lengthening in older men.**
Working hypothesis: Transdermal testosterone administration and oral progesterone administration are both effective strategies for attenuation of drug-induced QT_c interval response in older men. To test this hypothesis, transdermal testosterone, oral progesterone or placebo will be administered in a three-way crossover study in men ≥ 65 years of age. QT interval response to ibutilide will be assessed.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria:
- Men ≥ 65 years of age

Exclusion Criteria:
- Prostate cancer; history of prostate cancer;
- History of breast cancer; benign prostatic hypertrophy;
- Weight < 60 kg
- Weight > 135 kg
- Serum k^+ < 3.6 mEq/L;
- Serum mg^{2+} < 1.8 mg/dL;
- Hemoglobin < 9.0 mg/dL;
- Hematocrit < 26%;
- Hepatic transaminases > 3x upper limit of normal;
- Baseline Bazett's-corrected QT interval > 450 ms
- Heart failure due to reduced ejection fraction (left ventricular ejection fraction < 40%)
- Family or personal history of long-QT syndrome, arrhythmias or sudden cardiac death;
- Concomitant use of any QT interval-prolonging drug.
- Permanently paced ventricular rhythm

4.0 Enrollment/Randomization

Subject Recruitment:

Fifteen volunteer subjects will be recruited through 2 methods:

- Potential subjects will be recruited through the use of a recruitment database maintained through the CTSI InResearch Volunteer research database. Potential volunteers who meet inclusion criteria will be contacted via email and will be offered the opportunity to participate in this study.

- Advertisements will be placed in public locations throughout the IUPUI campus and on the IU Health website asking for volunteers. Potential subjects will call the PI or research coordinator at 317-880-5410 if interested in participating in the study.

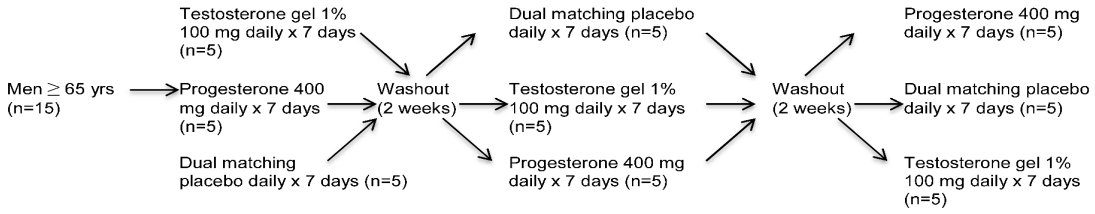
During the initial phone call with the potential subject, the investigator will explain the purpose of the study, study procedures and risks associated with the study. If the potential subject is interested in participating, the investigator will then ask the potential subject specifically about inclusion and exclusion criteria. If the subject meets all inclusion criteria and had no exclusion criteria, the baseline visit will be scheduled.

5.0 Study Procedures

This study will be performed using a crossover design. Each subject will act as his own control. Subjects will be randomized to the order that they receive either the study medication or the placebo. A random number generator will be used to determine the order of randomization. Subjects will be randomized during their first visit to the Indiana Clinical Research Center (ICRC) after informed consent has been obtained.

This study will be conducted at the ICRC. All subjects will undergo a screening physical examination and bloodwork. Using a three-way crossover design (Figure 1), each subject will be studied **three times**, serving as his own control. During each phase, subjects will receive a single IV dose of ibutilide 0.003 mg/kg, diluted in normal saline 20 mL and infused over 10 minutes.[25] Each subject will apply testosterone gel 1% (Androgel**®)** 100 mg once daily in the morning applied to the intact skin of the upper shoulders or arms, **take oral progesterone 400 mg orally once daily**, or use **dual-matching** placebo for 7 days. The crossover order will be randomized.

Figure 1, Experimental Design



This study will be conducted with 4 visits: visit one is a baseline assessment with ECGs; visits 2, 3 and 4 includes 7 days of medication self-administration followed by a 10 hour ICRC visit. There will be a 4-week washout period between visits 2 and 3 and between visits 3 and 4.

Visit 1:
Subjects will be asked to come to the ICRC at IU Health University Hospital (IUHUH). After informed consent is obtained, subjects will undergo a screening history and physical examination performed by a physician co-investigator or his designee and blood work will be obtained at this time to determine serum potassium, magnesium, creatinine, liver enzymes, hemoglobin, hematocrit. Once laboratory results are obtained and the physical

is completed and the subject has met inclusion criteria and has no exclusion criteria, the subject will be enrolled in the study. This process will take approximately 1 hour.

At visit 1, prior to randomization, each subject will undergo 10 hours of continuous ECG recordings using 12-lead (Mason-Likar electrode configuration) digital ECG recorders (SEER MC 2.0; GE Healthcare, Milwaukee, WI) to calculate QTcI.[32] Subjects will perform 4 postural provocative tests: supine (10 min), unsupported motionless sitting (10 min), unsupported motionless standing (15 min) and supine (10 min), to ensure broad heart rate ranges.[32] Repeated (5x) 10-second 12-lead ECG segments will be extracted from recordings obtained during these tests. Also, 10-second 12-lead ECG segments will be selected every 30 minutes over 10 hours. QT and RR intervals will be used to determine each subject's QTcI using the parabolic model[33] $QT = \beta \bullet RR^{\alpha}$ as described. The QT_F will also be calculated and analyzed.[34]

Immediately following the screening history and physical examination, subjects will be randomly assigned to three groups:

Group A: (n= 5 subjects)
Each subject will apply testosterone gel 1% (Androgel®**)** 100 mg once daily in the morning applied to the intact skin of the upper shoulders or arms and will take a placebo capsule once daily in the evening for 7 days.
Group B: (n= 5 subjects)
Each subject will take oral progesterone 400 mg orally once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms for 7 days.
Group C: (n= 5 subjects)
Each subject will take one placebo capsule once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms for 7 days.

Visit 2:
All subjects will receive a single intravenous (IV) dose of ibutilide 0.003 mg/kg, diluted in normal saline 20 mL and infused over 10 minutes.

Continuous ECG recording will be initiated 30 minutes prior to ibutilide and continue for 8 hours after ibutilide administration. Three 12 lead ECGs one minute apart will be selected for QT interval measurement before (time 0) and after ibutilide at: end of infusion, 5, 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 6, and 8 hours. Blood (6 mL) for determination of ibutilide concentrations will be obtained before ibutilide administration, at the end of infusion, and 5, 15, 30 & 45 minutes, and $1, 2, 4, 6, \text{and } 8$ hours following end of infusion. An 8-hour data collection and monitoring period is sufficient, as QT_c intervals return to baseline within 2-6 hours.[25]

In addition, blood will be drawn to determine serum progesterone, testosterone, magnesium and potassium concentrations at the same time as the time 0 ibutilide concentration is drawn. If the subjects is found to have hypokalemia or hypomagnesia as defined in the exclusion criteria, then they will be withdrawn from the study.

At the end of this visit, and after at least a 2-week washout period, subjects will take another of the study drugs as follows:

Group A: (n= 5 subjects)
Each subject will take one placebo capsule once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms
Group B: (n= 5 subjects)
Each subject will apply testosterone gel 1% (Androgel®**)** 100 mg once daily in the morning applied to the intact skin of the upper shoulders or arms and will take a placebo capsule once daily in the evening for 7 days.
Group C: (n= 5 subjects)
Each subject will take oral progesterone 400 mg orally once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms for 7 days.

Visit 3:
All subjects will receive a single intravenous (IV) dose of ibutilide 0.003 mg/kg, diluted in normal saline 20 mL and infused 10 minutes.

Continuous ECG recording will be initiated 30 minutes prior to ibutilide and continue for 8 hours after ibutilide administration. Three 12 lead ECGs one minute apart will be selected for QT interval measurement before (time 0) and after ibutilide at: end of infusion, 5, 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 6, and 8 hours. Blood (6 mL) for determination of ibutilide concentrations will be obtained before ibutilide administration, at the end of infusion, and 5, 15, 30 & 45 minutes, and 1, 2, 4, 6, and 8 hours following end of infusion. An 8-hour data collection and monitoring period is sufficient, as QT_c intervals return to baseline within 2-6 hours.[25]

In addition, blood will be drawn to determine serum progesterone, testosterone, magnesium and potassium concentrations at the same time as the time 0 ibutilide concentration is drawn. If the subjects is found to have hypokalemia or hypomagnesia as defined in the exclusion criteria, then they will be withdrawn from the study.

At the end of this visit, and after at least a 2-week washout period, subjects will take another of the study drugs as follows:

Group A: (n= 5 subjects)
Each subject will take oral progesterone 400 mg orally once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms for 7 days.
Group B: (n= 5 subjects)
Each subject will take one placebo capsule once daily in the evening and apply placebo gel once daily in the morning applied to the intact skin of the upper shoulders or arms for 7 days.
Group C: (n= 5 subjects)

Each subject will apply testosterone gel 1% (Androgel®) 100 mg once daily in the morning applied to the intact skin of the upper shoulders or arms and will take a placebo capsule once daily in the evening for 7 days.

Visit 4:

Continuous ECG recording will be initiated 30 minutes prior to ibutilide and continue for 8 hours after ibutilide administration. Three 12 lead ECGs one minute apart will be selected for QT interval measurement before (time 0) and after ibutilide at: end of infusion, 5, 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 6, and 8 hours. Blood (6 mL) for determination of ibutilide concentrations will be obtained before ibutilide administration, at the end of infusion, and 5, 15, 30 & 45 minutes, and 1, 2, 4, 6, and 8 hours following end of infusion. An 8-hour data collection and monitoring period is sufficient, as QT_c intervals return to baseline within 2-6 hours.[25]

In addition, blood will be drawn to determine serum progesterone, testosterone, magnesium and potassium concentrations at the same time as the time 0 ibutilide concentration is drawn. If the subjects is found to have hypokalemia or hypomagnesia as defined in the exclusion criteria, then they will be withdrawn from the study.

Following visit 4, subjects' participation in the study will be complete.

Serum ibutilide concentrations will be performed in the CPAC Laboratory[35] and serum testosterone and progesterone concentrations will be performed in the IU Health Pathology Laboratory as described.[36] Peak serum ibutilide concentrations and area under the serum ibutilide concentration:time curves from 0-1 hours (AUC_{0-1}) will be compared across the groups to assure no differences that could influence QT intervals. QT intervals will be measured by a research nurse (Heather Jaynes) with vast training and experience in QT interval measurement, and who will be blinded to subjects' assigned treatment groups. $AUEC_{0-1}$, an index of QTcI exposure, will be calculated using the linear trapezoidal rule.

In summary, this study will take a total of 25 days to complete, excluding the washout periods. The total study period will take place over a minimum of 78 days. Each subject will need to complete 4 visits, and take a medication for 6 days prior to the visit. The first visits involves no drug administration, but simply involves a 10 hour stay in the ICRC and includes a screening visit, followed by ECGs taken periodically for 10 hours. Then they will begin self-administration of study medications for 7 days. Visit 2 begins on the 7th day of medication administration. During visit 2, the subjects will undergo a 10 hour stay in the ICRC. After a minimum of a 28 day washout period, subjects will self-administrator study medications for 7 days. Visit 3 begins on the 7th day of medication administration. During visit 3, the subjects will undergo a 10 hour stay in the ICRC. After minimum of a 28 day washout period, subjects will self-administer study medications for 7 days. Visit 4 will begin on the 4th day of medication administration. During visit 4, subjects will undergo a 10 hour stay at the ICRC.

Daily blood draws and ECGs prior to visits 2, 3 and 4

Purpose:
We are trying to learn how long we need to treat patients with progesterone and/or testosterone before we see changes in the ECG that would be considered protective against developing drug induced Torsades de Pointes. This will help us determine how long patients need to be treated with progesterone and/or testosterone if needs a medication that could put them at risk for developing Torsades de Pointes in order to reduce that risk.

Study Procedures
In a subset of people participating in the study (5 subjects total), we are drawing blood to test testosterone and progesterone concentrations and taking 3 ECGs one minute apart once every morning each day for 7 days prior to visit 2,3 and 4. These blood draws will take 1 teaspoon of blood or 5 milliliters of blood each time. The first blood draw will take place on the day that you are supposed to start taking the study medication (progesterone/ testosterone/ placebo) and take place daily until you return to the CRC for your scheduled visit. This means that you will have an additional 6 blood draws. A total of 6 additional teaspoons (30 milliliters) of blood will be taken before each visit for a total of 18 additional teaspoons (90milliliters) of blood over the study period.

Each visit will take approximately 30 minutes/ day for a total of 3 additional hours prior to visit 2, 3, and 4 for a total of 9 additional hours.

Subjects are not required to participate in this part of the study in order to participate in the rest of the study as described above and will sign a separate consent if they are willing to participate in this portion of the study.

Process of obtaining written informed consent:

We will either provide prospective subjects with the informed consent document during recruitment or we will send it via Email or regular mail, and we will establish a time to review the informed consent document with the subject. Written informed consent will be obtained at the beginning of Visit #1, immediately prior to the baseline assessment, in a private room at the CRC by the PI or co-investigator prior to the screening exam and blood work.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others;

Ibutilide is an antiarrhythmic drug used to terminate atrial fibrillation and flutter.[37] Ibutilide prolongs QTc interval dose-dependently, with a rapid onset and return to baseline in 2-6 hours .[25] Serum ibutilide concentrations decline rapidly, and there are no active metabolites. Ibutilide prolongs QT interval via inhibition of I_{Kr} and activation of slow inward sodium current.[38,39] The proposed ibutilide dose (0.003 mg/kg) is approximately 20% of the lowest therapeutic dose (1.0 mg), and approximately 10% of the highest therapeutic dose (2.0 mg). Ibutilide has been administered safely at this dose healthy volunteers (n=58) with no episodes of TdP (Table).[25] Further, we recently completed a study in premenopausal female volunteers during which n=15 subjects

safely received this ibutilide dose, each on two separate occasions.[40] In addition, substantially higher doses of ibutilide (0.7 – 1.0 mg) have been administered to healthy volunteers (n=253), with no episodes of TdP (Table).[41]

The risks associated with this investigation will be minimized by the administration of a subtherapeutic dose of ibutilide (0.003 mg/kg, approximately 20% of the lowest therapeutic dose, approximately 10% of the highest therapeutic dose). In addition, risks will be minimized, in large part, by the exclusion criteria employed, which will allow us to exclude patients that are at risk for experiencing excessive QT interval prolongation associated with a subtherapeutic dose of ibutilide. Subjects with specific risk factors for TdP will be excluded – these risk factors include hypokalemia, hypomagnesemia, pretreatment QTc interval > 450 ms, liver disease, NYHA class IV HF, LVEF < 20%, history of TdP, and taking other QT interval-prolonging drugs. During the day on which ibutilide will be administered, patients will be maintained on continuous ECG telemetry monitors for 6 hours following ibutilide administration. Ibutilide will be administered in the ICRC which is housed within University Hospital and has full medical services if needed in the case of an emergency. A physician investigator (or his MD designee) will be present during ibutilide administration and for 2-3 hours following ibutilide administration. Subjects will not be discharged from the ICRC if they have a QTc interval of > 450ms after treatment. They will be monitored until the QTc interval is below 450ms. This study has a DSMB to periodically monitor the safety and any adverse events which may occur.

In all of the published literature, the overall incidence of TdP associated with ibutilide is 2.0%. TdP has never been reported at the dose that we propose to administer in this study. The lowest dose of ibutilide that has ever been associated with TdP in the published literature is 0.5 mg, and there has only been one reported case at this dose. That is more than double the dose that we propose to administer. In order to achieve this dose in our study, a patient would have to weight 166 kg (based on our dose of 0.003 mg/kg). No subject in this study will receive a dose as high as 0.5 mg, because we have an upper weight exclusion of 135 kg. Therefore, this risk of TdP in our volunteer subjects, at a low dose of 0.003 mg/kg (roughly 20% of the lowest clinical dose), is extremely low, and again, TdP has never been reported at this low dose.

Transdermal testosterone at similar (and higher) doses is associated with minimal (primarily acne or application site skin reactions) or no adverse effects.[42-45] Longer-term administration (> 18 months) of testosterone has been associated in some studies with adverse CV effects, including an increased risk of all-cause mortality, myocardial infarction, and stroke.[46] Conversely, however, other studies have found that men with *lower* serum testosterone are at higher risk of metabolic syndrome and other CV risk factors.[47-49] A recent meta-analysis of randomized controlled trials found no increase in the endpoint of CV death, non-fatal myocardial infarction, and stroke associated with testosterone therapy compared to placebo.[50] The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee concluded that the benefits of testosterone therapy outweigh the risks in appropriate patients.[49]

Oral progesterone 400 mg once daily is the dose that was effective for attenuating drug-associated QTcI interval response in premenopausal women. Oral progesterone 400 mg daily has been administered to men with no reported adverse effects.[51]

Risks related to the blood draws and intravenous catheter placement will be minimized through the use of experienced staff placing the intravenous catheter. Subjects will be evaluated for anemia prior to inclusion in order to minimize the risk of anemia due to blood draws.

Safety Monitoring

Any serious or unexpected adverse event will be reported to the Research and Sponsored Programs Committee on the IUPUI campus within 3 working days of notification of the event. A written report of the adverse event will also be submitted. Any Serious Adverse Event (SAE) that is observed during the study or within 30 days after administration of ibutilide will be recorded and reported to the SAE contact investigator. The SAE contact investigator will serve as the chair for the Data and Safety Monitoring Board (DSMB).

A Data Safety & Monitoring Board (DSMB) has been established for this study. The DSMB will be chaired by **David Foster, PharmD**, Associate Professor, College of Pharmacy, Purdue University and Adjunct Associate Professor, School of Medicine, Indiana University. Other members of the DSMB will be one cardiologist faculty member of the Krannert Institute of Cardiology, School of Medicine, Indiana University, and one faculty member of the Division of Clinical Pharmacology, School of Medicine, Indiana University – these individuals will be identified prior to the end of **June 2015**. The designated DSMB will be responsible for notifying the Sponsored Programs Committee in the time specific time allotted from above.

Study/Data Monitoring

The following documents will be on file in the primary investigators office before patient enrollment:

Copy of the IU IRB/Ethics Committee approval of the protocol and consent;
Copy of the IRB approved informed consent;

A pre-study start meeting will take place to ensure that investigators and other essential personnel are aware of the protocol requirements for ibutilide administration and data collection.

The DSMB will meet every 6 months during the anticipated duration of the study. The DSMB will monitor subject recruitment, accrual, retention, adverse event data, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects. The DSMB will analyze and interpret data submitted by the principal investigator. In the unlikely event that a subject experiences an ibutilide-associated arrhythmia, the DSMB will determine whether the study should continue or should be suspended.

Data from the study will be monitored continuously throughout the study and will be reviewed at each DSMB meeting.
Definitions (ICH Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and FDA Regulation 21 CFR 312.32, Final Rule October 7,1997)

- **Adverse Event**: Any untoward event, which occurs regardless of its causality, including and side effect, injury, toxicity or sensitivity reaction during testing of protocol treatments (whether or not considered drug-related), will be designated as an adverse clinical event.
- **Serious Adverse Event**: An event that is fatal, life-threatening, or leads to persistent or significant disability; one that requires or prolongs hospitalization; or one that results in a congenital anomaly, or significant medical event.
- **Unexpected Adverse Event**: Any adverse event not identified in nature, severity, or frequency in current package label for ibutilide or product information.
- Adverse events will be defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. (NCI definition). The level of severity of an adverse event will be based on a grading scale which is adopted from the NCI Common Terminology Criteria for Adverse Events: Grade 1, Mild AE; Grade 2, Moderate AE; Grade 3, Severe AE; Grade 4, Life threatening or disabling AE; Grade 5, death related to AE.For prolonged QTc interval Grade 1, QTc>0.45-0.47 seconds; Grade 2, QTc >0.47-0.50 seconds and/or increase in QTc $\geq$0.06 seconds above baseline; Grade 3, QTc >0.50 seconds; Grade 4, QTc >0.50 seconds and/or life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock, syncope) and/or *torsades de pointes*; Grade 5, Death.

Ethical Aspects of the Proposed Research

The minimum possible number of subjects is proposed, based on sample size calculations. Transdermal testosterone at similar (and higher) doses is associated with minimal or no adverse effects.[42-45] Oral progesterone 400 mg daily has been administered to men with no reported adverse effects.[51] While some studies have reported that longer-term testosterone administration has been associated adverse CV effects,[46] recent studies have found that men with *lower* serum testosterone are at higher risk of metabolic syndrome and other CV risks.[47-49] A recent meta-analysis of randomized controlled trials found no increase in adverse CV endpoints associated with testosterone therapy compared to placebo.[52] The EMA's Pharmacovigilance Risk Assessment Committee concluded that the benefits of testosterone therapy outweigh risks in appropriate patients.[49] Thus, evidence suggests that testosterone could be administered safely for long-or short-term reduction of risk of drug-associated QT_c interval prolongation in high-risk patients that require QT_c interval-prolonging agents. We propose to administer transdermal testosterone for 7 days;

adverse effects over such a short time frame are uncommon and mild, mainly acne and application site reactions.

Subjects will be carefully screened and a through physical examination will be performed prior to initiation of the protocol. Extensive exclusion criteria have been included to minimize the risk of adverse effects to subjects enrolled in the study.

Safety measures have been put into place to minimize the potential risks in this study, and the results of this study may provide benefit to society by enhancing patient safety.

DSMB Safety Monitoring

A Data Safety & Monitoring Committee (DSMB) has been established for this study. The DSMB will monitor subject recruitment, accrual, retention, adverse event data, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects. The DSMB will analyze and interpret data submitted by the principal investigator. In the unlikely event that a subject experiences an ibutilide-associated arrhythmia, the DSMB will determine whether the study should continue or should be suspended. The DSMB will meet every 6 months during the anticipated two-year duration of the study.

The IRB will receive information regarding frequency and dates of monitoring, summary of cumulative adverse events, assessment of external factors, including scientific reports, therapeutic developments, & results of related studies that could impact subject safety, summaries of subject privacy and research data confidentiality outcomes, and any changes to the risk: benefit ratio.

7.0 Study Withdrawal/Discontinuation

Subjects may withdraw from the study at anytime during the study. If a subject wishes to withdraw from the study, he/she may call the principal investigator and withdraw himself/herself from the study. The subject will receive any compensation for their time up to the period of withdrawal.
The principal investigator may withdraw a subject from the study for the following reasons: a change in the subject' medical condition resulting in an increased risk profile, change in any inclusion or exclusion criteria for the subject, or subject unwilling or unable to complete part of the protocol as stated. If the PI determines that a subject needs to be withdrawn from the study, he will contact the subject by phone and also in writing. The subject will receive compensation for any part of the study that he/she has completed.

8.0 Statistical Considerations

Study Endpoints: Comparison of testosterone, progesterone and placebo phases for: 1) Baseline (pre-ibutilide) maximum QTcI & $QT_{F,}$ 2) Ibutilide effect on maximum QTcI & QT_F, 3) Ibutilide effect on maximum % change in QTcI & QT_F, and 4) $AUEC_{0-1}$. Endpoints will be correlated with testosterone and progesterone concentrations.

Statistical analyses: Will be performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Comparisons of primary endpoints in subjects across the three study phases will be performed using repeated measures analysis of variance (ANOVA). If statistically significant differences are found, *post hoc* testing will be performed using Tukey's Honest Significant Difference (HSD) test to determine between-group differences. For all comparisons, α will be set at 0.05. Correlations between the primary endpoints and serum testosterone and progesterone concentrations will be performed using Pearson's correlation coefficient.

Anticipated Outcomes:
1) Ibutilide-associated maximum QTcI interval and maximum % change in QTcI will be significantly smaller during testosterone and progesterone phases compared to placebo
2) Ibutilide-associated $AUEC_{0-1}$ will be significantly smaller during testosterone and progesterone phases compared to placebo
3) Maximum change in QTcI interval and $AUEC_{0-1}$ will be inversely associated with serum testosterone and progesterone concentrations

Sample Size Calculation: In this 3-way crossover study, at a two-sided α level of 0.05 and a power of 0.80, a sample size of 15 subjects will be sufficient to detect a difference in maximum QTcI of 15 ms, assuming a QTcI interval prolongation of 24±12 ms associated with ibutilide in the absence of testosterone or progesterone.

9.0 Privacy/Confidentiality Issues

All ECGs will be collected using a standard ECG machine, on which the ECG data are collected on paper. This information will not contain the patients' names, just an unique identifier. Blood samples will be collected and maintained in a locked laboratory freezer, they will not contain the patients' names, just an unique identifier. Medical information, such as laboratory and echocardiogram information will be stored on a password protected computer database containing only an unique identifier. All information linking the patient's name and health information to the unique identifier will be stored in a locked cabinet in the study coordinator's office. All this information will not be stored electronically. Information on the password protected computer database will only be accessed by the investigators. All information with unique identifiers will be locked in the study coordinator's office or laboratory, or on a password protected computer. To assure study coordinator's office is physically secure, it is located on the 3th floor of the FTB Faculty Office Building at Eskenazi Medical Center, which requires authorized entry. Furthermore, the study coordinator's office remains locked and any information that can be used to identify patients will be kept in a locked cabinet and not stored electronically. All study documentation will be stored for a minimum of seven years after completion of the study. All paper documentation will be shredded and electronic files deleted.

There will be paper copies of spreadsheet for the purpose of statistical analysis, pharmacokinetic and pharmacodynamic analysis shared with the co-investigators involved in the analysis, however, the unique identifier will be the only information that is available on the spreadsheets. The information linking the unique identifier to the patient will be kelp in a locked cabinet in the study coordinator's office.

Safeguards used to protect the confidentiality and security of health information

Any information that is gathered about these patients will be kept confidential and any information that is generated on a patient will does not ultimately participate in the study will be destroyed immediately.

All ECGs will be collected using digital ECG recordings. Information entered will not contain the patients' names, just a unique identifier. Blood samples will be collected and maintained in a locked laboratory freezer, they will not contain the patients' names, just a unique identifier. Medical information, such as laboratory information will be stored on a password protected computer database containing only a unique identifier. All information linking the patient's name and health information to the unique identifier will be stored in a locked cabinet in Dr. Tisdale's office. All this information will not be stored electronically. Information on the password protected computer database will only be accessed by the investigators. All information with unique identifiers will be locked in the study coordinator's office or laboratory, or on a password protected computer. To assure the study coordinator's office is physically secure, it is located on the 3th floor of the FTB Faculty Office Building at Eskenazi Medical Center, which requires authorized entry. Furthermore, the study coordinator's office remains locked and any information that can be used to identify patients will be kept in a locked cabinet and not stored electronically. All study documentation will be stored for a minimum of seven years after completion of the study. All paper documentation will be shredded and electronic files deleted.

There will be paper copies of spreadsheet for the purpose of statistical analysis and will be shared with the co-investigators involved in the analysis, however, the unique identifier will be the only information that is available on the spreadsheets. The information linking the unique identifier to the patient will be kelp in a locked cabinet in the study coordinator's office.

Discuss the methods for ensuring participant privacy, and the methods for protecting privacy and confidentiality.

10.0 Follow-up and Record Retention

The estimated time frame for completion of this study is 24 months. All identifiable data (informed consents) will be stored in a locked filing cabinet in the PI or study coordinator's office behind a locked door with limited access. All electronic data will be stored on a password protected computer in the same location. Data will be stored a minimum of 7 years per Indiana State Law. All ECGs, clinical assessment data, laboratory data and blood samples will be de-identified at the time of data collection. List the duration of the study. List the duration of record retention and the method for destruction or the possibility of indefinite archiving of information.

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Appendix. **Incidence of Ibutilide-Associated Torsades de Pointes in Published Literature**

Paper	n	Population	**Ibutilide 0.003 mg/kg** Dose for our study – 0.21 mg in a 70 kg person	Ibutilide 0.25 mg	Ibutilide 0.5 mg	Ibutilide 0.005 mg/kg	Ibutilide 0.7 mg	Ibutilide 1.0 mg x 1	Ibutilide 1.0 mg x 1 then 0.5 mg x 1	Ibutilide 0.025 mg/kg	Ibutilide 1.0 mg x 2	Total
Guo, J Am Coll Cardiol 1996	n=8 ibutilide two x 1 mg n=4 ibutilide 1 x 1.0 mg then 1 x 0.5 mg n=13 ibutilide 1.0 mg n=10 placebo	Spontaneous sustained a.flutter	--	--	--			0/13	0/4		0/8	
Stambler Am J Cardiol 1996	N=18 ibutilide N= 11 placebo	Patients with atrial flutter				0/2	0/1	0/2	0/4	0/3	0/3	
Ellenbogen J Am Coll Cardiol 1996	N=157, dose-ranging N=41 placebo	Patients with AF or atrial flutter	--		1/42 (2.4%) (n=1)¶		2/39 (5.1%)§	1/39 (2.6)%		1/39 (2.6%)		
Stambler Circulation 1996	N=79, ibutilide 1.0 mg then 0.5 mg N=82, ibutilide 1.0 mg then 1.0 mg N=81, placebo	Patients with AF or a. flutter	--	--	--		--	11/161 (6.8%)	2/144 (1.4%)		2/144 (1.3%)	

Vanderlugt Circulation 1999	2.0 mg – 70 1.0 mg – 73 0.5 mg – 75 Placebo - 84	Post-CABG AF conversion	--	0	0			2/70 (2.9%)*			2/70 (2.9%)*	
Stambler Am J Cardiol 1997	Ibutilide 1 mg - 12 Ibutilide 2 mg - 12 Placebo - 12	Patients with or without HF	--	--	--						0/12 – no HF 1/12 (8.5%) – with HF	
Oral NEJM 1999	N = 64, Ibutilide N=36, placebo	Patients with AF undergoing DCC	--	--	--		--	2/64 (3.1%)‡	--		--	
Glatter Circulation 2001	n=70	Elective conversion of AF – also on amio	--	--	--			--			1/70 (1.4%)	
Rodriguez JAMA 2001	n=58	Young healthy volunteers (38 men, 20 women) – received 3 doses in crossover fashion	0/58	--	--			--			--	
Gowda Am J Ther 2003	n=52 – two x 1 mg n =6 – 1 x 1 mg	Patients with new-onset AF or a.flutter	--	--	--			0/6			4/52 (7.7%)	
Giudici, J Cardiovasc Nurs 2008	n=238, retrospective study		--	--	--			4/238 (1.7%)			--	
Kannankeril, Heart Rhythm 2011	N=253 Ibutilide 10 mcg/kg up to total dose of 1 mg	Healthy volunteers aged 18-40	--	--	0		--	0/253			--	

Tisdale, J Clin Pharmacol 2012	N=15	Patients with AF N=6 had decreased LVEF	--	--	--			0/6			--	
Tisdale JE et al, Circulation 2014 (abstract)	N=16, randomized crossover (n=31 doses of ibutilide 0.003 mg/kg)	Healthy premenopausal female volunteers during menses phase	0/31									
Total in all studies			0/89	0/252	1/42	0/2	2/40	20/852 (2.3%)	2/152 (1.3%)	1/42 (2.4%)	10/371 (2.7%)	36/1,842 (1.9%)

*patients with torsades had reduced LVEF
¶This patient had NYHA class II HF with decreased LVEF
§These 2 patients had NYHA class III HF with LVEF 45% and NYHA class II HF with LVEF 30%
‡both patients had LVEF < 20%
Other data:
Gowda, et al - Am J Ther 2002 – 4 cases of ibutilide-induced TdP – two doses of 1.0 mg (n=3), one dose of 1.0 mg (n=1)