- 1 This supplement contains the following items:
- 2 1. Original protocol, final protocol, summary of changes.
- 2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

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6	Α	Prospective Randomized Crossover trial of Oral
7		Flecainide for Catecholaminergic Polymorphic
8		Ventricular Tachycardia
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#### 1.0 29 Background

30

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a genetic arrhythmia 31 syndrome characterized by frequent ventricular ectopy and polymorphic, classically 32 bidirectional ventricular tachycardia with physical or emotional stress, which also carries 33 34 a risk of ventricular fibrillation and sudden death, despite no structural heart abnormality.(Liu et al.) The disease is caused by mutations in the cardiac ryanodine 35 receptor gene (RYR2) or cardiac calsequestrin gene (CASQ2).(Priori et al.:Postma et 36 al.) Exercise can elicit ectopy or VT in the majority of CPVT patients. Treatment 37 consists of beta-blockers and/or calcium channel blockers, but up to 30% of patients 38 require implantable cardioverter-defibrillators (ICDs) due to recurrent symptoms on 39 medical therapy(Priori et al.). 40 41 2.0 42 **Rationale and Specific Aims** 

43

44 Additional forms of therapy for CPVT are needed, as current medications are not completely effective in all patients. By studying mouse models of CPVT (CASQ null 45 mice), we have observed beneficial effects of flecainide, a class IC sodium channel 46 blocker. In a retrospective clinical study in patients with CPVT we have also shown 47 improvement of ventricular ectopy on exercise tests when flecainide is added to 48 standard therapy. 49

50

51 The Specific Aims of this protocol are:

52 1: to test the hypothesis that the addition of oral flecainide to standard therapy will 53 reduce cardiac events, defined as either VT treated by ICD or cardiac death, compared 54 to placebo plus standard therapy, in patients with CPVT. 55

56

57 2. to test the hypothesis that ventricular ectopy and/or VT on treadmill exercise test in patients with CPVT on standard therapy is reduced by flecainide, but not by placebo. 58

59

3. to test the hypothesis that reduction in ventricular ectopy on exercise test is 60

- associated with reduction in cardiac events. 61
- 62

This will be a single-blind (blinded subjects) randomized cross-over study, in which each 63 patient will receive treatment A (flecainide or placebo) for 18 months and, after a 1 week 64 wash-out, treatment B (placebo or flecainide). The event rate and time to event will be 65 assessed during each treatment period. Any events that occur during treatment A will 66 result in early crossover to treatment B after 1 week of wash-out. Any events during 67 68 treatment B will result in the end of the study for that subject.

69

#### **Animal Studies and Previous Human Studies** 3.0 70

72 Since the causal association between stress and arrhythmic symptoms of CPVT was

recognized, beta--blockers have been the mainstay of therapy. Moreover, since

- 74 polymorphic VT is reproducibly induced with exercise in the majority of patients with
- CPVT, it is common practice to use repeated exercise testing to evaluate the efficacy of
   β-blocker therapy. While beta-blockers are very effective for preventing exercise-
- induced sustained polymorphic VT, the majority of patients with CPVT continue to have
- different degrees of ventricular ectopy during exercise despite maximally tolerated
- 79 dosages. In addition, studies report high mortality rates and a high incidence of
- 80 recurrent polymorphic VT despite beta-blocker therapy.
- 81 The addition of calcium channel blockers to beta-blockers was reported in 6 children
- 82 with CPVT, with an improvement in exercise-induced ectopy in all, and a marked clinical
- improvement in 1 (reduction in ICD shocks).(Rosso et al.) Left cardiac sympathetic
- 84 denervation has also been reported as an effective alternative in 5 patients when
- symptoms persist despite the maximum tolerable dose of  $\beta$ -blocker. (Wilde et al.,
- 86 Collura et al.)
- 87 Oral flecainide has also been reported to reduce ventricular tachycardia in another
- genetic arrhythmia syndrome, Andersen-Tawil syndrome (ATS). (Bokenkamp et al.)
- 89 Two siblings with ATS who failed therapy with beta-blockers and calcium channel
- blockers had marked improvement with oral flecainide. ATS shares some features with
- 91 CPVT, in that the characteristic bidirectional ventricular tachycardia (only seen in CPVT,
- ATS, and digoxin toxicity) is frequently observed, again with minimal symptoms, yet
- 93 patients are at risk for ventricular fibrillation.
- Recently, we discovered that the class 1C antiarrhythmic agent flecainide directly blocked RyR2 channels, prevented RyR2-mediated premature Ca<sup>2+</sup> release, and suppressed triggered beats in myocytes isolated from mouse hearts lacking

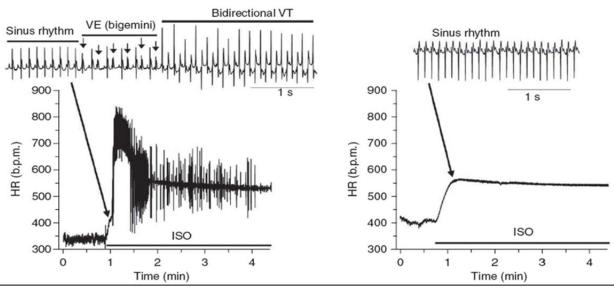


Figure 1. Ventricular arrhythmias during exercise in CASQ null mice (left) are completely abolished with flecainide (right)

calsequestrin, an animal model of CPVT.(Watanabe, et al.) Flecainide treatment completely suppressed ventricular arrhythmias during exercise in this mouse model (Figure 1). Flecainide's mechanism of action can be attributed to an open state block of RyR2 channels, thereby directly targeting the molecular defect responsible for the arrhythmogenic Ca<sup>2+</sup> waves that trigger CPVT *in vivo*. (Hilliard et al.) Flecainide also appeared to be effective during short-term treatment in two highly symptomatic CPVT patients.

104

Based on these animal studies, we have collaborated with international centers to perform am open-label, nonrandomized therapeutic trial of oral flecainide for patients with CPVT and persistent ventricular ectopy on exercise testing on standard therapy. In this trial, 86% of patients had improvement of ventricular ectopy on exercise, and there was no worsening of ectopy with flecainide added to standard therapy.

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111 4.0 Inclusion/Exclusion Criteria

- 112113 Inclusion criteria:
- Clinical diagnosis of CPVT, based on: 114 • reproducible polymorphic or bidirectional ventricular tachycardia with 115 0 exercise 116 117 OR Ventricular ectopy on exercise test with *RYR2* or *CASQ2* mutation 118 0 • Functioning ICD in place 119 On stable dose of standard therapy defined as the maximal tolerated dose of 120 • 121 beta-blocker and may include a calcium channel blocker Patients on flecainide are also eligible for enrollment after a 1 week 122 "washout" period during which flecainide is discontinued, and standard 123 therapy alone is used. 124 125
- 126 Exclusion criteria:
- Pregnant females
- Children < 5 years of age
- Patients unable to perform treadmill exercise
- Patients with significant structural heart disease
- Patients with features consistent with Andersen-Tawil syndrome
  - o Periodic paralysis or unexplained weakness
  - Dysmorphic facies
    - Known KCNJ2 mutation
- Known hypersensitivity to flecainide
- Inability to comply with follow-up
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# 138 **5.0** Enrollment/Randomization

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Patient Enrollment: The treating physicians at each center will identify potential
 subjects and present a brief overview of the study; if the subject (or his/her parent/legal
 guardian for patients < 18 years) is interested, an investigator will be contacted and will</li>

approach them. Informed consent will be obtained by the investigator after discussing 143 144 the study in detail, including the voluntary nature of participation and notification the subject can withdraw at any time. Ample time for questions and answers will be allowed. 145 The investigator will give the subject and his/her legal guardian the opportunity to take 146 the consent home to think about it more, with the option to call or meet with the 147 investigator to ask additional questions. If the subject and his/her parent/legal guardian 148 agree to participate, the investigator will ask them to sign a written, informed consent 149 and assent. A copy of the assent and consent will be given to the subject and his/her 150 parent/legal guardian. Subjects who are < 18 years of age at the time of enrollment 151 who turn 18 years of age during the study period will be re-consented after their 18<sup>th</sup> 152 birthday. Subjects who wish to participate in the clinical trial without providing a DNA 153 sample will be allowed to do so. 154

155

Patients already on flecainide will have a serum level drawn. If the level is > 0.5
mcg/ml, his/her previous dose will be the final study dose (no up titration). If the level is
< 0.5, the previous dose will be the starting dose and up titration will occur as below. All</li>
subjects on flecainide will discontinue it for 1 week prior to the baseline assessment,
continuing on standard therapy alone.

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*Randomization Procedure:* This will be a single-blind placebo-controlled
 randomized crossover study with 2 treatments: oral flecainide or oral placebo. Each
 enrolled patient will receive both treatments for 18 months, with a 1 week washout
 period between. The order of treatments will be randomized 1:1 across all centers.

### 167 6.0 Study Procedures

All patients enrolled in the study will undergo the following baseline assessment anddata collection:

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- Demographics (age, gender, race)
- Review of data confirming clinical diagnosis of CPVT (recordings of polymorphic
  - VT, exercise tests, genetic tests). Required components include:
  - Normal imaging study (echocardiogram or cardiac MRI)
  - No evidence of coronary ischemia on ECG or exercise testing, unless subsequent stress imaging study was not suggestive of ischemia
- For subjects with no family history of CPVT nor a putative pathogenic
   RYR2 or CASQ2 mutation who were > 35 years of age *at the time of initial presentation* with polymorphic VT, a coronary angiogram demonstrating
   no coronary artery disease must be documented.
- Previous anti-arrhythmic treatments
  - Prior ECG and echocardiogram reports
- 183 184
- 185 Randomization
- 187 There will be a 50:50 randomization across all centers, with half the subjects
- randomized to flecainide then placebo, and half randomized to placebo then flecainide.

190 Patients previously on flecainide with a serum level > 0.5 mcg/ml will receive a study dose equal to their previous dose. Patients previously on flecainide with a serum level < 191 192 0.5 mcg/ml will receive a starting dose equal to their previous dose, with uptitration as below. For all subjects not previously on flecainide, the starting dose will be based on 193 age and weight. Children < 12 years of age will be dosed 3 times per day (every 8 194 hours) and patients > 12 years of age will be dosed 2 times per day (every 12 hours), 195 based on plasma elimination half-life (Perry et al.) For children < 12 years of age an 196 oral suspension will be used, the starting dose will be 2 mg/kg/day and the maximum 197 dose will be 8 mg/kg/day. For patients > 12 years of age the starting dose will be 100 198 mg per day (50 mg every 12 hours) and the maximum dose will be 300 mg/day. Study 199 drugs will be prepared and distributed by a central investigational pharmacy; flecainide 200 and placebo will be similar in appearance. 201

202

After enrollment (and after a 1 week washout for subjects previously on flecainide), 203 patients will undergo a baseline exercise test on standard therapy (Exercise test 0). 204 Subjects with baseline ECG or exercise test evidence of ischemia must be excluded, 205 unless stress imaging studies are performed and are not suggestive of ischemia. 206 Patients will then initiate treatment A (flecainide or placebo) in a blinded fashion. After 1 207 208 week, blood samples for DNA isolation and storage, and determination of a flecainide level will be drawn. Each time a serum sample is obtained for a flecainide level, and 209 ECG will be obtained. For patients on flecainide, the target serum level will be 0.5-0.8 210 mcg/ml. Patients with levels < 0.35 mcg/ml will have the dose doubled, and those with 211 levels between 0.35 and 0.5 will increase the dose by 50%, unless the maximum dose 212 has been achieved. Patients requiring a dose adjustment (and an equal number of 213 214 randomly chosen subjects on placebo) will have a second serum sample drawn at 1 month. Any further dose adjustments and serum samples will be made prior to the 3 215 month visit. Serum levels will be obtained locally and dose adjustments will be done by 216 the central pharmacy, after confirmation with the treating physician that there are no 217 side effects or significant QRS widening. 218

- 219
- 220 The dose escalation will continue until either:
- 221
- 222
- 1. The trough flecainide level is > 0.5 mcg/ml
- 223 2. The QRS width is > 120 ms or prolonged by > 50% of the baseline QRS
- 3. The maximum dose is achieved.
- 225

At 3 months, all subjects undergo a repeat exercise test (exercise test A) and a serum
sample drawn for a flecainide level. After 18 months of treatment A, subjects will
discontinue the study drug, and after 1 week of standard therapy alone, start treatment
B. Determination of flecainide levels will be done as above. After 3 months of
treatment B, another exercise test (exercise test B) will be performed. After 18 months
of treatment B, the subject will be removed from the study.

Patients will be followed every 6 months or as clinically indicated for ICD interrogation.

234 Patients who receive therapy (shock or anti-tachycardia pacing) from the ICD will be

carefully assessed and the ICD data downloaded. Therapies will be categorized as 235 236 "appropriate" if delivered for ventricular tachyarrhythmias, or "inappropriate" if delivered for other reasons. In the event of an appropriate ICD therapy, a serum sample will be 237 238 drawn for a flecainide level. Subjects that have events during treatment A will discontinue treatment A, start the 1 week washout period, and crossover to treatment B. 239 Subjects with events during treatment B will be removed from the study and unblinded. 240 Further treatment will be determined by the treating physician. 241 242 The primary endpoint will be cardiac event defined as appropriate ICD therapy (shock or 243 anti-tachycardia pacing for VT) or death. 244 245 Secondary endpoints include reduction in ventricular ectopy at exercise test compared 246 to baseline during treatment with flecainide but not placebo. 247 248 249 250 Exercise tests will be scored using the following scale: 251 252 Exercise test scoring system: 0= no ventricular ectopy 253 254 1=PVC's, < 1 in 2 beats, and < 10/min 2= PVC's in bigeminal pattern or > 10/minute 255 3= ventricular couplets 256 4= nonsustained VT (3 or more consecutive beats) 257 258 259 260 7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to 261 Participants or Others 262 263 264 Any adverse events (AEs) will be recorded on the adverse event form (see attached) 265 and sent to the Data Coordinating Center within 72 hours of the event. AEs will be 266 reported to the IRB according to the IRB policies and procedures. The data coordinating 267 center will notify the DSMB of any major adverse events. Any unanticipated problems 268 involving risk to the participants or others will be discussed with the PI and DSMB. 269 270 Administration of flecainide is associated with the potential for serious side effects. In 271 our preliminary studies, 8% of CPVT patients were unable to take flecainide due to 272 bradycardia or fatigue and dizziness. Patients who discontinue the study drug 273 (flecainide or placebo) due to side-effects will continue to be followed, with an intent-to-274 treat analysis. Adverse events related to the administration of flecainide will be 275 reported. All unanticipated problems/events such as breach of confidentiality will be 276 reported. 277 278 279 Serious Adverse Events (SAEs) will have to be reported according to the

280 following special procedure:

281 The occurrence of serious adverse events will be reported to the Investigator by

telephone or fax; they must be reported to him/her within 24 hours after becoming

aware of their occurrence. The Investigator will report SAEs to the VanderbiltInstitutional Review Board per policy.

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### 286 8.0 Study Withdrawal/Discontinuation

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288 Subjects may withdraw from the study at any time. Subjects will be unblinded at the 289 time of withdrawal.

290

#### 291 9.0 Statistical Considerations

# 292

#### 293 Sample Size Estimation and Power Analysis

The primary endpoint of this randomized controlled 2x2 cross-over trial will be cardiac 294 event defined as appropriate ICD therapy (shock or anti-tachycardia pacing for VT) or 295 death. The objective is to demonstrate decreased event rate in patients treated with 296 flecainide in addition to standard therapy compared to patients treated with standard 297 therapy plus placebo. Previous studies of CPVT patients with ICD's reveal an event rate 298 ranging from 50% over 20 months (Priori et al) to 25% over 3.9 years (Hayashi et al). 299 This wide range results in an estimated event rate during 18 months of treatment with 300 placebo plus standard therapy between 10 and 45%. In our small series of patients 301 receiving open-label flecainide, we observed 1 event in 23 patients (4%), which was 302 likely due to noncompliance. The event rate of the control group is expected to be 15% 303 based on the above data. The sample size estimation was carried out using the 304 305 Pearson chi-square test for paired proportions. With a sample size of 55, the study will have 80% power to detect a 10% difference in the primary endpoint with a two-sided 306 test at 5% significance level. To compensate for reduced power caused by the 307 308 noncompliance (the anticipated dropout rate over 36 months is 8% based on our pilot data), 60 patients will be enrolled. 309 310

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# 312 Statistical Analysis Plan

Descriptive statistics, including means, standard deviations, and ranges for continuous 313 variables, as well as percentages and frequencies for categorical variables, will be 314 provided to describe the study sample. Pearson chi-square test or Fisher's exact test 315 will be used to assess the categorical variables. Differences between group means for 316 continuous variables will be examined using ANOVA or Kruskal-Wallis Test. The 317 Mainland-Gart's test will be used for univariate analysis of the primary outcome, when 318 the assumption of no carry-over effect holds. For multivariate analysis, the Generalized 319 Linear Mixed Model will be used to assess the treatment effect, period effect, and 320 treatment-by-period interaction effect, and to adjust for other risk factors such as gender 321 or age. The analysis of survival data will be carried out if such data are available, using 322 the Kaplan-Meier method with log-rank test to compare time-to-event between the two 323 arms and the proportional hazard Cox model to investigate potential prognostic factors. 324 The alpha-spending function of O'Brien-Fleming will be applied for the interim analysis 325 to maintain an overall significance level at 0.05. Point estimates along with the 326

- values and the corresponding 95% confidence interval will be reported for multivariate analyses. Statistical analysis will be done with R for Windows, version 2.9.2 and SAS
- 329 analyses. Statistical analysis will be done with R for windows, version 2.9.2 and SAS330 9.2.
- 331
- 332 Secondary analysis will include comparison of the exercise treadmill tests after 3
- months of placebo vs. 3 months of flecainide, and quantified as follows for comparison:
- 334
- 335 Ventricular arrhythmia score:
- 336 0 = no ventricular ectopic beats
- 337 1 = single PVC's
- 338 2 = PVC's in bigeminal pattern
- 339 3 = PVC pairs (couplets)
- 340 4 = nonsustained VT ( $\geq$  3 beats, but < 30 seconds)
- 341 5 = sustained VT (> 30 seconds)
- 342
- 343 Quantification of arrhythmias:
- Total number of ventricular ectopic beats during entire exercise test (rest, exercise, and recovery)
- Number of ectopic beats during worst 10 second period of exercise test (rest,
   exercise, and recovery)
  - 3. Ratio of ectopic to sinus beats during worst 10 second period of exercise test (rest, exercise, and recovery)
- 349 350

Based on pilot human studies, we anticipate a reduction in the number of ectopic beats during worst 10 second period of exercise from  $13 \pm 5$  beats to  $5 \pm 5$  beats. Assuming an  $\alpha$  of 0.05 and 80% power, we would need only 5 subjects to show a statistically significant reduction, as this is a paired analysis.

355 356

357 10.0 Privacy/Confidentiality Issues

358 359 Only individuals directly involved with the study will have access to data. Information is for research purposes only and will be used for publication purposes. All participants 360 will have their names concealed. Access to identified patient information will be limited 361 to the investigators listed within this IRB application. De-identified information with 362 HIPPA identifiers removed will be available to other investigators following appropriate 363 IRB approval. Confidentiality and security will be maintained for the database. The 364 database is stored behind a firewall (in addition to the institutional firewall) with the 365 highest level of protection, i.e. the same level of protection as the on-line hospital 366 information system at Vanderbilt. This means that users must logon to a web server 367 that sits between the institutional firewall and the firewall to the database, and only this 368 application server is allowed to query the database. Only users approved through our 369 institutional review board will be allowed access to patient identifiers. Other levels of 370 371 authorization may exist for future approved users following IRB approval, e.g. access to de-identified data. 372

373 374 375 376 377 378 379 380 381 382 383	Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the Case Report Form (CRF). The CRFs will include personal identifiers for participant. However, this data will not be accessible as numbers and initials are assigned for each participant and these will become the identifying information for each study participant. A master list with patient demographics will only be accessible to the principle investigator and his senior co-investigator. This data will not be available to others.
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399	Perry JC, et al. "Flecainide acetate for treatment of tachyarrhythmias in children: review of
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403	polymorphic ventricular tachycardia." <u>Circ.Res.</u> 91.8 (2002): e21-e26.
404	Priori, S. G., et al. "Clinical and molecular characterization of patients with catecholaminergic
405	polymorphic ventricular tachycardia." <u>Circulation</u> 106.1 (2002): 69-74.
406	Priori, S. G., et al. "Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie
407	catecholaminergic polymorphic ventricular tachycardia." Circulation 103.2 (2001): 196-
408	200.
409	Rosso, R., et al. "Calcium channel blockers and beta-blockers versus beta-blockers alone for
410	preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular
411	tachycardia." <u>Heart Rhythm.</u> 4.9 (2007): 1149-54.
412	Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic
413	ventricular tachycardia in mice and humans. Nat Med 2009;15:380-3.
414	Wilde AA, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for
415	catecholaminergic polymorphic ventricular tachycardia. N Engl J Med 2008;358:2024-9
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423	Α	Prospective Randomized Crossover trial of Oral
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#### 447 **1.0 Background**

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a genetic arrhythmia 448 syndrome characterized by frequent ventricular ectopy and polymorphic, classically bidirectional 449 ventricular tachycardia with physical or emotional stress, which also carries a risk of ventricular 450 fibrillation and sudden death, despite no structural heart abnormality.(Liu et al.) The disease is 451 452 caused by mutations in the cardiac ryanodine receptor gene (RYR2) or cardiac calsequestrin gene (CASQ2).(Priori et al.; Postma et al.) Exercise can elicit ectopy or VT in the majority of 453 CPVT patients. Treatment consists of beta-blockers and/or calcium channel blockers, but up to 454 30% of patients require implantable cardioverter-defibrillators (ICDs) due to recurrent symptoms 455 456 on medical therapy(Priori et al.).

457

#### 458 2.0 Rationale and Specific Aim

459

Additional forms of therapy for CPVT are needed, as current medications are not completely
effective in all patients. By studying mouse models of CPVT (CASQ null mice), we have
observed beneficial effects of flecainide, a class IC sodium channel blocker. In a retrospective
clinical study in patients with CPVT we have also shown improvement of ventricular ectopy on
exercise tests when flecainide is added to standard therapy.

The Specific Aim of this protocol is to test the hypothesis that ventricular ectopy and/or VT on treadmill exercise test in patients with CPVT on standard therapy is reduced by flecainide, but not by placebo.

This will be a single-blind (blinded subjects) randomized cross-over study, in which each patient will receive treatment A (flecainide or placebo), undergo an exercise test, crossover to treatment B (placebo or flecainide) and undergo another exercise treadmill test.

472

#### 473 **3.0 Animal Studies and Previous Human Studies**

474

Since the causal association between stress and arrhythmic symptoms of CPVT was
recognized, beta--blockers have been the mainstay of therapy. Moreover, since
polymorphic VT is reproducibly induced with exercise in the majority of patients with
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β-blocker therapy. While beta-blockers are very effective for preventing exerciseinduced sustained polymorphic VT, the majority of patients with CPVT continue to have
different degrees of ventricular ectopy during exercise despite maximally tolerated

dosages. In addition, studies report high mortality rates and a high incidence of
 recurrent polymorphic VT despite beta-blocker therapy.

The addition of calcium channel blockers to beta-blockers was reported in 6 children with CPVT, with an improvement in exercise-induced ectopy in all, and a marked clinical improvement in 1 (reduction in ICD shocks).(Rosso et al.) Left cardiac sympathetic denervation has also been reported as an effective alternative in 5 patients when symptoms persist despite the maximum tolerable dose of  $\beta$ -blocker. (Wilde et al., Collura et al.)

- Oral flecainide has also been reported to reduce ventricular tachycardia in another
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  Two siblings with ATS who failed therapy with beta-blockers and calcium channel
  blockers had marked improvement with oral flecainide. ATS shares some features with
  CPVT, in that the characteristic bidirectional ventricular tachycardia (only seen in CPVT,
  ATS, and digoxin toxicity) is frequently observed, again with minimal symptoms, yet
- 497 patients are at risk for ventricular fibrillation.

Recently, we discovered that the class 1C antiarrhythmic agent flecainide directly 498 blocked *RyR*2 channels, prevented *RyR*2-mediated premature Ca<sup>2+</sup> release, and suppressed 499 500 triggered beats in myocytes isolated from mouse hearts lacking calsequestrin, an animal model of CPVT.(Watanabe, et al.) Flecainide treatment completely suppressed ventricular arrhythmias 501 during exercise in this mouse model (Figure 1). Flecainide's mechanism of action can be 502 attributed to an open state block of RyR2 channels, thereby directly targeting the molecular 503 defect responsible for the arrhythmogenic Ca<sup>2+</sup> waves that trigger CPVT *in vivo*. (Hilliard et al.) 504 Flecainide also appeared to be effective during short-term treatment in two highly symptomatic 505

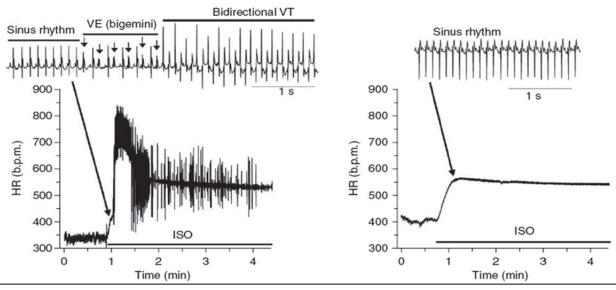


Figure 1. Ventricular arrhythmias during exercise in CASQ null mice (left) are completely abolished with flecainide (right)

506 CPVT patients.

Based on these animal studies, we have collaborated with international centers to 507 perform am open-label, nonrandomized therapeutic trial of oral flecainide for patients with CPVT 508 and persistent ventricular ectopy on exercise testing on standard therapy. In this trial, 86% of 509 patients had improvement of ventricular ectopy on exercise, and there was no worsening of 510

- 511 ectopy with flecainide added to standard therapy.
- 512

514

519

515 Inclusion criteria:

- Clinical diagnosis of CPVT, based on: 516
- 517 reproducible polymorphic or bidirectional ventricular tachycardia with exercise 0 OR 518
  - Ventricular ectopy on exercise test with RYR2 or CASQ2 mutation 0
- Functioning ICD in place 520 •
- On stable dose of standard therapy defined as the maximal tolerated dose of beta-521 • blocker and may include a calcium channel blocker. On stable doses of CYP2D6 522 inhibitors (quinidine, fluoxetine, paroxetine, bupropion, cimetidine) or inducers (rifampin, 523 carbamazepine, phenytoin, Phenobarbital). If CYP2D6 inhibitor/inducer doses require 524 changes during the course of the subject's treatment with active flecainide, serum 525 526 flecainide levels will be monitored
- Patients on flecainide are also eligible for enrollment after a 1 week "washout" 527 0 528 period during which flecainide is discontinued, and standard therapy alone is used. 529
- 530
- 531 Exclusion criteria:
- **Pregnant females** 532 •
- Children < 5 years of age 533
- Patients unable to perform treadmill exercise 534 •
- Patients with significant structural heart disease 535
- Patients with features consistent with Andersen-Tawil syndrome 536 •
  - Periodic paralysis or unexplained weakness
- Dysmorphic facies 538 539
  - o Known KCNJ2 mutation
- Known hypersensitivity to flecainide 540 •
- Inability to comply with follow-up 541 •
- 542

- 5.0 Enrollment/Randomization 543
- 544

545 Patient Enrollment: The treating physicians at each center will identify potential subjects and present a brief overview of the study; if the subject (or his/her parent/legal guardian for 546 patients < 18 years) is interested, an investigator will be contacted and will approach them. 547 Informed consent will be obtained by the investigator after discussing the study in detail, 548 549 including the voluntary nature of participation and notification the subject can withdraw at any time. Ample time for questions and answers will be allowed. The investigator will give the 550 subject and his/her legal guardian the opportunity to take the consent home to think about it 551 552 more, with the option to call or meet with the investigator to ask additional questions. If the 553 subject and his/her parent/legal guardian agree to participate, the investigator will ask them to sign a written, informed consent and assent. A copy of the assent and consent will be given to 554 555 the subject and his/her parent/legal guardian. Subjects who are < 18 years of age at the time of enrollment who turn 18 years of age during the study period will be re-consented after their 18<sup>th</sup> 556 557 birthday. Subjects who wish to participate in the clinical trial without providing a DNA sample will be allowed to do so. 558

559

Patients already on flecainide will have a serum level drawn. If the level is > 0.5560 mcg/ml, his/her previous dose will be the final study dose (no up titration). If the level is 561 562 < 0.5, the previous dose will be the starting dose and up titration will occur as below. All subjects on flecainide will discontinue it for 1 week prior to the baseline assessment, 563 continuing on standard therapy alone. 564

565

566 Randomization Procedure: This will be a single-blind placebo-controlled randomized crossover study with 2 treatments: oral flecainide or oral placebo. Each enrolled patient will 567 568 receive both treatments for at least 3 months, with a 1 week washout period between. The 569 order of treatments will be randomized 1:1 across all centers.

570

#### 6.0 **Study Procedures** 571

572

573 All patients enrolled in the study will undergo the following baseline assessment and data 574 collection:

575

- Demographics (age, gender, race) 576
- Review of data confirming clinical diagnosis of CPVT (recordings of polymorphic 577 578
  - VT, exercise tests, genetic tests). Required components include:
    - Normal imaging study (echocardiogram or cardiac MRI)
- No evidence of coronary ischemia on ECG or exercise testing, unless 580 subsequent stress imaging study was not suggestive of ischemia 581
- For subjects with no family history of CPVT nor a putative pathogenic 582 *RYR2* or CASQ2 mutation who were > 35 years of age at the time of initial 583

*presentation* with polymorphic VT, a coronary angiogram demonstrating no coronary artery disease must be documented.

- 585 586 •
  - Previous anti-arrhythmic treatments
  - Prior ECG and echocardiogram reports
- 587 588

589 Randomization

- 590
- 591 There will be a 50:50 randomization across all centers, with half the subjects randomized to 592 flecainide then placebo, and half randomized to placebo then flecainide.
- 593

594 Patients previously on flecainide with a serum level > 0.5 mcg/ml will receive a study 595 dose equal to their previous dose. Patients previously on flecainide with a serum level < 0.5 mcg/ml will receive a starting dose equal to their previous dose, with uptitration as 596 below. For all subjects not previously on flecainide, the starting dose will be based on 597 598 age and weight. Children < 12 years of age will be dosed 3 times per day (every 8 hours) and patients > 12 years of age will be dosed 2 times per day (every 12 hours), 599 based on plasma elimination half-life (Perry et al.) For children < 12 years of age an 600 oral suspension will be used, the starting dose will be 2 mg/kg/day and the maximum 601 dose will be 8 mg/kg/day. For patients > 12 years of age the starting dose will be 100 602 mg per day (50 mg every 12 hours) and the maximum dose will be 400 mg/day. Study 603 604 drugs will be prepared and distributed by a central investigational pharmacy; flecainide and placebo will be similar in appearance. 605

606

After enrollment (and after a 1 week washout for subjects previously on flecainide), 607 patients will undergo a baseline exercise test on standard therapy (Exercise test 0). 608 Subjects with baseline ECG or exercise test evidence of ischemia must be excluded, 609 unless stress imaging studies are performed and are not suggestive of ischemia. 610 Patients will then initiate treatment A (flecainide or placebo) in a blinded fashion. After 1 611 week, blood samples for DNA isolation and storage, and determination of a flecainide 612 level will be drawn. Each time a serum sample is obtained for a flecainide level, and 613 ECG will be obtained. For patients on flecainide, the target serum level will be 0.5-0.8 614 mcg/ml. Patients with levels < 0.35 mcg/ml will have the dose doubled, and those with 615 levels between 0.35 and 0.5 will increase the dose by 50%, unless the maximum dose 616 617 has been achieved. Patients requiring a dose adjustment (and an equal number of randomly chosen subjects on placebo) will have a second serum sample drawn at 1 618 month. Any further dose adjustments and serum samples will be made prior to the 3 619 month visit. Serum levels will be obtained locally and dose adjustments will be done by 620 the central pharmacy, after confirmation with the treating physician that there are no 621 side effects or significant QRS widening. 622

623

The dose escalation will continue until either:

625

1. The trough flecainide level is > 0.5 mcg/ml

- 627 2. The QRS width is > 120 ms or prolonged by > 50% of the baseline QRS
- 628 3. The maximum dose is achieved.
- 629

At 3 months, all subjects undergo a repeat exercise test (exercise test A) and a serum sample drawn for a flecainide level. Subjects will then immediately discontinue the Treatment A study drug, and after 1 week of standard therapy alone, start treatment B. Determination of flecainide levels will be done as above. After at least 3 months of treatment B, another exercise test (exercise test B) will be performed. Treatment B study drug will be discontinued at the time of exercise test B, and the subject's participation in the study will be complete. Patients who receive therapy (shock or anti-tachycardia pacing) from their ICD during the course of their participation in the study will be carefully assessed and the ICD data downloaded. Therapies will be categorized as "appropriate" if delivered for ventricular tachyarrhythmias, or "inappropriate" if delivered for other reasons. In the event of an appropriate ICD therapy, a serum sample will be drawn for a flecainide level. Subjects that have events during treatment A will discontinue treatment A, start the 1 week washout period, and crossover to treatment B. Subjects with events during treatment B will be removed from the study and unblinded. Further treatment will be determined by the treating physician.
The primary endpoint will be reduction in ventricular ectopy at exercise test compared to baseline during treatment with flecainide but not placebo.

647	
648	Exercise tests will be scored using the following scale:
649	
650	Exercise test scoring system:
651	0= no ventricular ectopy
652	1=PVC's, < 1 in 2 beats, and < 10/min
653	2= PVC's in bigeminal pattern or > 10/minute
654	3= ventricular couplets
655	4= nonsustained VT (3 or more consecutive beats)
656	
657	
658	7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to
659	Participants or Others

Any adverse events (AEs) will be recorded on the adverse event form (see attached) and sent to the Data Coordinating Center within 72 hours of the event. AEs will be reported to the IRB according to the IRB policies and procedures. The data coordinating center will notify the DSMB of any major adverse events. Any unanticipated problems involving risk to the participants or others will be discussed with the PI and DSMB.

Administration of flecainide is associated with the potential for serious side effects. In our preliminary studies, 8% of CPVT patients were unable to take flecainide due to bradycardia or fatigue and dizziness. Patients who discontinue the study drug (flecainide or placebo) due to side-effects will continue to be followed, with an intent-to-treat analysis. Adverse events related to the administration of flecainide will be reported. All unanticipated problems/events such as breach of confidentiality will be reported.

#### 673 Serious Adverse Events (SAEs) will have to be reported according to the 674 following special procedure:

The occurrence of serious adverse events will be reported to the Investigator by telephone or fax; they must be reported to him/her within 24 hours after becoming aware of their occurrence. The Investigator will report SAEs to the Vanderbilt Institutional Review Board per policy.

679

# 680 8.0 Study Withdrawal/Discontinuation

681

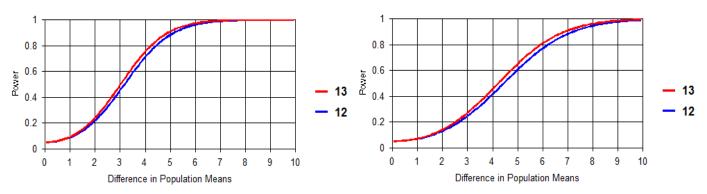
684

682 Subjects may withdraw from the study at any time. Subjects will be unblinded at the 683 time of withdrawal.

## 685 9.0 Statistical Considerations

# 686687 Statistical Analysis Plan

- 688 Our previous open-label comparison of flecainide to standard therapy showed a 7 beat
- reduction in number of ectopic beats in worst 10 seconds of exercise test (from  $12 \pm 5$  beats to
- $5 \pm 5$  beats).<sup>1</sup> A second study in 12 genotype-negative CPVT patients demonstrated a 6 beat
- reduction in number of ectopic beats in worst 10 seconds of exercise test (from  $12 \pm 7$  beats to 692  $6 \pm 7$  beats).<sup>2</sup> A target of 14 enrolled subjects provide adequate statistical power (80% power
- 693 with an alpha of 0.05) to detect the previously observed differences (6-7) in number of PVC's in
- 694 worst 10 second period during exercise testing.<sup>3</sup> Graphs of Power (Y-axis) vs observed
- 695 difference in means (X-axis) are provided below. The 2 panels represent power calculations
- 696 using different values for the within-group standard deviation (SD). These values are informed
- 697 from the 2 previous studies in CPVT patients using the same methodology (left, within group SD
- = 5, observed in reference 1; right within group SD = 7, observed in reference 2). Red lines
- 699 indicate N=13, and blue lines indicate N=12, allowing for potential subject dropout.
- 700 References for statistical analysis plan
- van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W,
   Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J,
   Haïssaguerre M, Knollmann BC, Wilde AA. Flecainide therapy reduces exercise-induced
   ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J
   Am Coll Cardiol. 2011 May 31;57(22):2244-54.
- Watanabe H, van der Werf C, Roses-Noguer F, Adler A, Sumitomo N, Veltmann C, Rosso R, Bhuiyan ZA, Bikker H, Kannankeril PJ, Horie M, Minamino T, Viskin S, Knollmann BC, Till J, Wilde AA. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2013 Apr;10(4):542-7.
- Dupont WD, Plummer WD. Power and Sample Size Calculations: A Review and Computer Program. Controlled Clinical Trials. 1990;11:116-28.





714 Descriptive statistics, including means, standard deviations, and ranges for continuous

variables, as well as percentages and frequencies for categorical variables, will be provided to

716 describe the study sample. Pearson chi-square test or Fisher's exact test will be used to assess

the categorical variables. Differences between group means for continuous variables will be

examined using ANOVA or Kruskal-Wallis Test. Point estimates along with the corresponding p-

values and 95% confidence intervals will be reported. The adjusted p-values and the

corresponding 95% confidence interval will be reported for multivariate analyses. Statistical

analysis will be done with R for Windows, version 2.9.2 and SAS 9.2.

722

Analysis will consist of a comparison of the exercise treadmill tests after 3 months of

- placebo vs. 3 months of flecainide, and quantified as follows for comparison:
- 725

726 Ventricular arrhythmia score:

- 727 0 = no ventricular ectopic beats
- 728 1 = single PVC's
- 729 2 = PVC's in bigeminal pattern
- 3 = PVC pairs (couplets)
- 4 = nonsustained VT ( $\geq$  3 beats, but < 30 seconds)
- 5 = sustained VT (> 30 seconds)
- 733

734 Quantification of arrhythmias:

- Total number of ventricular ectopic beats during entire exercise test (rest, exercise, and recovery)
- exercise, and recovery)
  Number of ectopic beats during worst 10 second period of exercise test (rest, exercise, and recovery)
- 739
   3. Ratio of ectopic to sinus beats during worst 10 second period of exercise test
   740 (rest, exercise, and recovery)

741 742

### 743 10.0 Privacy/Confidentiality Issues

744

Only individuals directly involved with the study will have access to data. Information is
for research purposes only and will be used for publication purposes. All participants
will have their names concealed. Access to identified patient information will be limited
to the investigators listed within this IRB application. De-identified information with

749 750 751 752 753 754 755 756 757 758 759	HIPPA identifiers removed will be available to other investigators following appropriate IRB approval. Confidentiality and security will be maintained for the database. The database is stored behind a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information system at Vanderbilt. This means that users must logon to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Only users approved through our institutional review board will be allowed access to patient identifiers. Other levels of authorization may exist for future approved users following IRB approval, e.g. access to de-identified data.
760 761 762	Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the Case Report Form (CRF).
763	
764 765 766 767 768	The CRFs will include personal identifiers for participant. However, this data will not be accessible as numbers and initials are assigned for each participant and these will become the identifying information for each study participant. A master list with patient demographics will only be accessible to the principle investigator and his senior co-investigator. This data will not be available to others.
769 770 771	Reference List
772	Bokenkamp, R., et al. "Flecainide for recurrent malignant ventricular arrhythmias in two siblings
773	with Andersen-Tawil syndrome." <u>Heart Rhythm.</u> 4.4 (2007): 508-11.
774	Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of
775	long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-
776	assisted thoracic surgery. Heart Rhythm 2009;6:752-9.
777	Hilliard FA, Steele DS, Laver D, et al. Flecainide inhibits arrhythmogenic Ca(2+) waves by open state block
778	of ryanodine receptor Ca(2+) release channels and reduction of Ca(2+) spark mass. J Mol Cell
779	Cardiol 2009.

780	Knollmann, B. C., et al. "Casq2 deletion causes sarcoplasmic reticulum volume increase,
781	premature Ca2+ release, and catecholaminergic polymorphic ventricular tachycardia."
782	<u>J.Clin.Invest</u> 116.9 (2006): 2510-20.
783	Liu, N., et al. "Catecholaminergic polymorphic ventricular tachycardia." Herz 32.3 (2007): 212-
784	17.
785	Perry JC, et al. "Flecainide acetate for treatment of tachyarrhythmias in children: review of
786 787	world literature on efficacy, safety, and dosing. Am Heart J 1992 Dec; 124(6): 1614-21.
788	Postma, A. V., et al. "Absence of calsequestrin 2 causes severe forms of catecholaminergic
789	polymorphic ventricular tachycardia." <u>Circ.Res.</u> 91.8 (2002): e21-e26.
790	Priori, S. G., et al. "Clinical and molecular characterization of patients with catecholaminergic
791	polymorphic ventricular tachycardia." <u>Circulation</u> 106.1 (2002): 69-74.
792	Priori, S. G., et al. "Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie
793	catecholaminergic polymorphic ventricular tachycardia." Circulation 103.2 (2001): 196-
794	200.
795	Rosso, R., et al. "Calcium channel blockers and beta-blockers versus beta-blockers alone for
796	preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular
797	tachycardia." <u>Heart Rhythm.</u> 4.9 (2007): 1149-54.
798	Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic
799	ventricular tachycardia in mice and humans. Nat Med 2009;15:380-3.
800	Wilde AA, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for
801	catecholaminergic polymorphic ventricular tachycardia. N Engl J Med 2008;358:2024-9.

#### 803 Summary of changes to protocol:

804 The reasons for changes to the protocol are reflected in the manuscript Methods:

805 "The primary endpoint was appropriate ICD therapy, and the secondary endpoint was degree of

ventricular arrhythmias induced on exercise testing. Adequate power for the primary endpoint

required enrolling 60 subjects. In June 2015, after only 14 of the desired 60 subjects were able to

be enrolled, the investigators, with approval from the funding source and the Data and Safety
Monitoring Board (DSMB), modified the study protocol to evaluate only the secondary endpoint

810 (ventricular arrhythmias on exercise test). At that point, subjects who had completed the

811 Treatment A exercise test crossed over, without the 18 month treatment duration. Similarly,

subjects discontinued Treatment B once the three month exercise test was complete."

#### 813 The protocols differ in the following sections:

- 814 **Section 2**: Aims 1 and 3 removed. Aim 2 becomes primary aim.
- 815 **Section 6**: Study procedures: Duration of therapy shortened from 18 months to 3 months.
- 816 Primary endpoint changed from cardiac event to ventricular ectopy at exercise test.

817 **Section 9**: Statistical considerations are significantly revised, with original and final statistical 818 plans copied below.

#### 820 Original Statistical Considerations:

821

#### 822 Sample Size Estimation and Power Analysis

823 The primary endpoint of this randomized controlled 2x2 cross-over trial will be cardiac event defined as appropriate ICD therapy (shock or anti-tachycardia pacing for VT) or 824 death. The objective is to demonstrate decreased event rate in patients treated with 825 flecainide in addition to standard therapy compared to patients treated with standard 826 therapy plus placebo. Previous studies of CPVT patients with ICD's reveal an event rate 827 ranging from 50% over 20 months (Priori et al) to 25% over 3.9 years (Hayashi et al). 828 This wide range results in an estimated event rate during 18 months of treatment with 829 placebo plus standard therapy between 10 and 45%. In our small series of patients 830 receiving open-label flecainide, we observed 1 event in 23 patients (4%), which was 831 likely due to noncompliance. The event rate of the control group is expected to be 15% 832 based on the above data. The sample size estimation was carried out using the 833 Pearson chi-square test for paired proportions. With a sample size of 55, the study will 834 have 80% power to detect a 10% difference in the primary endpoint with a two-sided 835 836 test at 5% significance level. To compensate for reduced power caused by the noncompliance (the anticipated dropout rate over 36 months is 8% based on our pilot 837 data), 60 patients will be enrolled. 838

839

#### 840 Statistical Analysis Plan

841 Descriptive statistics, including means, standard deviations, and ranges for continuous variables, as well as percentages and frequencies for categorical variables, will be provided to 842 describe the study sample. Pearson chi-square test or Fisher's exact test will be used to assess 843 the categorical variables. Differences between group means for continuous variables will be 844 examined using ANOVA or Kruskal-Wallis Test. The Mainland-Gart's test will be used for 845 846 univariate analysis of the primary outcome, when the assumption of no carry-over effect holds. For multivariate analysis, the Generalized Linear Mixed Model will be used to assess the 847 848 treatment effect, period effect, and treatment-by-period interaction effect, and to adjust for other 849 risk factors such as gender or age. The analysis of survival data will be carried out if such data are available, using the Kaplan-Meier method with log-rank test to compare time-to-event 850 851 between the two arms and the proportional hazard Cox model to investigate potential prognostic 852 factors. The alpha-spending function of O'Brien-Fleming will be applied for the interim analysis 853 to maintain an overall significance level at 0.05. Point estimates along with the corresponding pvalues and 95% confidence intervals will be reported. The adjusted p-values and the 854 855 corresponding 95% confidence interval will be reported for multivariate analyses. Statistical analysis will be done with R for Windows, version 2.9.2 and SAS 9.2. 856

857

858 Secondary analysis will include comparison of the exercise treadmill tests after 3 months of

placebo vs. 3 months of flecainide, and quantified as follows for comparison:

860

861 Ventricular arrhythmia score:

- 862 0 = no ventricular ectopic beats
- 863 1 = single PVC's

- 864 2 = PVC's in bigeminal pattern
- 865 3 = PVC pairs (couplets)
- 4 = nonsustained VT ( $\geq$  3 beats, but < 30 seconds)
- 867 5 = sustained VT (> 30 seconds)
- 869 Quantification of arrhythmias:
- Total number of ventricular ectopic beats during entire exercise test (rest, exercise, and recovery)
- 872
   2. Number of ectopic beats during worst 10 second period of exercise test (rest, exercise, and recovery)
- 874
   3. Ratio of ectopic to sinus beats during worst 10 second period of exercise test (rest, exercise, and recovery)
- 876

- 877 Based on pilot human studies, we anticipate a reduction in the number of ectopic beats during
- worst 10 second period of exercise from  $13 \pm 5$  beats to  $5 \pm 5$  beats. Assuming an  $\alpha$  of 0.05
- and 80% power, we would need only 5 subjects to show a statistically significant reduction, as
- this is a paired analysis.

#### 882 Final Statistical Analysis Plan

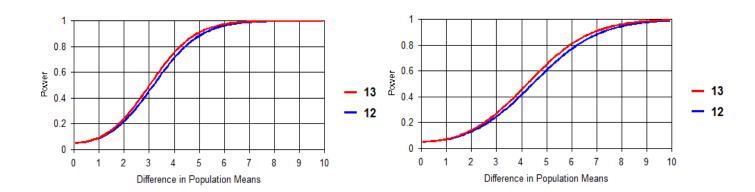
883 Our previous open-label comparison of flecainide to standard therapy showed a 7 beat

- reduction in number of ectopic beats in worst 10 seconds of exercise test (from  $12 \pm 5$  beats to
- $5 \pm 5$  beats).<sup>1</sup> A second study in 12 genotype-negative CPVT patients demonstrated a 6 beat
- reduction in number of ectopic beats in worst 10 seconds of exercise test (from  $12 \pm 7$  beats to 6 ± 7 beats).<sup>2</sup> A target of 14 enrolled subjects provide adequate statistical power (80% power
- with an alpha of 0.05) to detect the previously observed differences (6-7) in number of PVC's in
- 889 worst 10 second period during exercise testing.<sup>3</sup> Graphs of Power (Y-axis) vs observed
- 890 difference in means (X-axis) are provided below. The 2 panels represent power calculations
- using different values for the within-group standard deviation (SD). These values are informed
- 892 from the 2 previous studies in CPVT patients using the same methodology (left, within group SD
- = 5, observed in reference 1; right within group SD = 7, observed in reference 2). Red lines
- 894 indicate N=13, and blue lines indicate N=12, allowing for potential subject dropout.
- 895 References

896

- van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W,
   Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J,
   Haïssaguerre M, Knollmann BC, Wilde AA. Flecainide therapy reduces exercise-induced
   ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J
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- 907
   3. Dupont WD, Plummer WD. Power and Sample Size Calculations: A Review and Computer
   908 Program. Controlled Clinical Trials. 1990;11:116-28.

910



- 912 Descriptive statistics, including means, standard deviations, and ranges for continuous
- variables, as well as percentages and frequencies for categorical variables, will be provided to
- describe the study sample. Pearson chi-square test or Fisher's exact test will be used to assess
- the categorical variables. Differences between group means for continuous variables will be
- 916 examined using ANOVA or Kruskal-Wallis Test. Point estimates along with the corresponding p-
- values and 95% confidence intervals will be reported. The adjusted p-values and the
- corresponding 95% confidence interval will be reported for multivariate analyses. Statistical
- analysis will be done with R for Windows, version 2.9.2 and SAS 9.2.
- 920
- Analysis will consist of a comparison of the exercise treadmill tests after 3 months of placebo vs.
- 3 months of flecainide, and quantified as follows for comparison:
- 923
- 924 Ventricular arrhythmia score:
- 925 0 = no ventricular ectopic beats
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- 928 3 = PVC pairs (couplets)
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932 Quantification of arrhythmias:

- 933 1. Total number of ventricular ectopic beats during entire exercise test (rest, exercise, and 934 recovery)
- 935
   936
   2. Number of ectopic beats during worst 10 second period of exercise test (rest, exercise, and recovery)
- 3. Ratio of ectopic to sinus beats during worst 10 second period of exercise test (rest,
- 938 exercise, and recovery)
- 939

#### 940 Summary of changes to statistical plan:

- The originally proposed secondary analysis becomes the primary analysis, and power
- 942 calculations are presented for the enrolled subjects, with new references added.