

Statistical Analysis Plan

SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study

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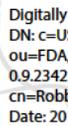
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Contents

Sponsor Signatures Page.....	2
Contents	3
1 Study Objectives.....	6
1.1 Primary Objective 1 (Part 1)	6
1.2 Primary Objective 2 (Part 2)	6
2 Sample Size	6
2.1 Resampling analysis methodology.....	7
2.2 Part 1	8
2.3 Part 2	9
2.4 Replacement Algorithm for Parts 1 and 2.....	10
2.4.1 Crossover part (Part 2):.....	11
2.4.2 Parallel part (Part 1):.....	12
3 Analysis Populations	15
4 General Statistical Considerations, Subject Disposition and Demographics and Baseline Characteristics.....	15
5 Electrocardiogram Analyses.....	16
5.1 Analysis and removal of heart rate dependency for QT and J-T _{peak}	16
5.2 Primary Analyses	17
5.2.1 Parts 1 and 2.....	17
5.2.2 Part 1	18
5.2.3 Part 2	19
5.3 Exploratory Analyses	20
5.3.1 Exposure-response analysis of secondary ECG biomarkers.....	20
5.3.2 $\Delta\Delta$ ECG measurements by time point	20
5.3.3 Analyses using population-based heart rate corrected QT and J-T _{peak}	21
5.3.4 Use of placebo from parallel part in crossover part.....	21
6 Pharmacokinetic Analyses.....	22
7 Safety Analyses	22
8 Missing Data.....	23

9	Data Quality Assurance	23
10	References	24
A	Randomization schedule	25
A.1	Abstract	25
A.2	Study design (pre-specified balanced design within period/cohort)	26
A.3	Treatment codes and subjects IDs from 3 blocks by Part and Cohort	26
A.4	Randomization	31
A.4.1	Seed random number generator	31
A.4.2	Randomization schedule code.....	31
A.5	For clinical site unblinded pharmacist	32
A.5.1	The random generator seed was: 123456.....	32
A.5.2	Randomized treatment codes	32
A.5.3	Randomization schedule table	33
A.5.4	Randomized summary table.....	35
A.6	Appendix: technical information.....	36
B	Step by step example of replacement algorithm	37
B.1	Replacement in crossover part	37
B.1.1	Move RANDIDs from completers to the next period.....	37
B.1.2	Replace dropouts.....	38
B.2	Replacement in parallel part.....	40
B.2.1	Step 1: (replace subject 1014 from placebo).....	41
B.2.2	Step 2: (replace subject 1002 from ranolazine)	41
B.2.3	Step 3: (replace subject 1004 from verapamil).....	42
B.2.4	Step 4: (replace subject 1011 from chloroquine).....	42
B.2.5	Step 5: (replace subject 1007 from lopinavir+ritonavir)	43
B.2.6	Step 6: (replace subject 1028 from placebo).....	43
B.2.7	Step 7: (replace subject 1018 from ranolazine)	43
B.2.8	Step 8: (replace subject 1019 from verapamil).....	44
B.2.9	Step 9: (replace subject 1025 from chloroquine).....	44
B.2.10	Step 10: (replace subject 1024 from lopinavir+ritonavir)	45

B.2.11 Step 11: End (maximum number of 14 replacements reached)..... 45

1 Study Objectives

The primary objectives of this study are:

1. To confirm that exposure-response analysis of the electrocardiographic QTc and J-T_{peakC} intervals in Phase 1 clinical pharmacology studies can be used to confirm that “balanced ion channel” drugs do not cause J-T_{peakC} prolongation and “predominant hERG” drugs cause QTc prolongation.
2. To test the hypothesis that calcium channel block (diltiazem) can reduce the QTc prolongation from hERG block (dofetilide) by shortening J-T_{peakC}.

1.1 Primary Objective 1 (Part 1)

Part 1 of the study will assess primary objective 1. Part 1 will include 4 oral drugs with well-characterized ion channel effects, QTc effects, and torsade de pointes (TdP) risk. Three (3) drugs will be “balanced ion channel” blockers (approximately equipotent hERG and late sodium and/or calcium block) with low TdP risk (ranolazine, verapamil and lopinavir + ritonavir) and 1 drug will be a “predominant hERG” blocker with TdP risk (chloroquine).

1.2 Primary Objective 2 (Part 2)

Part 2 of the study will assess primary objective 2. Part 2 will include 2 oral drugs (dofetilide and diltiazem) with well-characterized individual ion channel effects and TdP risk. Dofetilide is a “predominant hERG” blocker while diltiazem is a calcium channel blocker.

2 Sample Size

Approximately 60 healthy subjects are planned for enrollment, of which 50 will be assigned to Part 1 and 10 will be assigned to Part 2 at randomization. Up to 14 subjects may be qualified as replacements. Thus, a maximum of 74 subjects will be exposed to study drugs and procedures during the study.

The sample size (10 subjects per arm) was selected based on analysis by the sponsor of ECG biomarkers in Studies SCR-002¹ and SCR-003² and by resampling of data from previously conducted thorough QT (TQT) clinical studies, similar to the methodology of Ferber et al.^{3,4} The data sources^{5,6} used in this analysis are appropriate to determine the sample size because (i) the inclusion and exclusion criteria of this study are similar to inclusion and exclusion criteria in SCR-002, SCR-003 and typical TQT studies; (ii) this study will be conducted at the same clinical site than SCR-002 and SCR-003; (iii) the ECG analysis will be performed at FDA using the same methodology used in SCR-002 and SCR-003; and (iv) we observed consistent drug-induced ECG signatures between SCR-002 and SCR-003 (Figure 1 and Figure 2).⁷

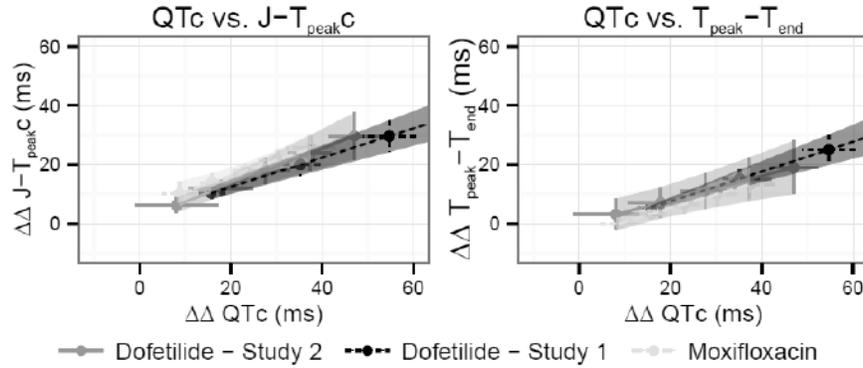


Figure 1. ECG signatures of predominant hERG block with dofetilide in both SCR-002 (Study 1, dark grey) and SCR-003 (Study 2, light grey) and with moxifloxacin in SCR-003 (yellow). Vicente et al. 2016.⁷

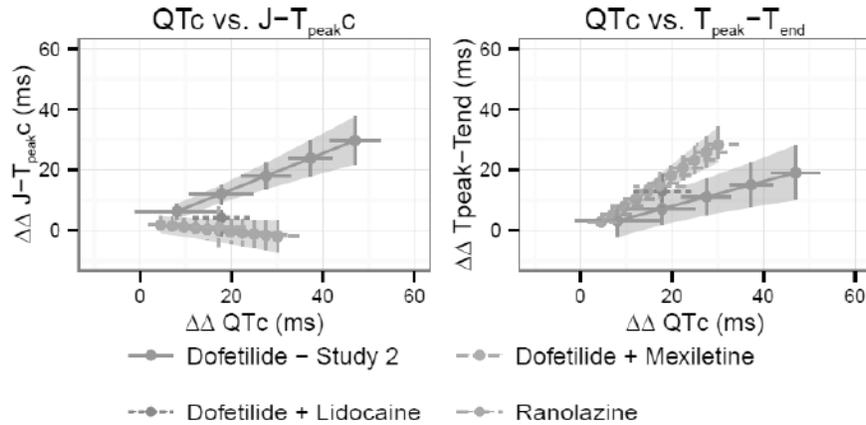


Figure 2. ECG signatures of multichannel block with ranolazine in SCR-002 (Study 1, blue) and dofetilide+lidocaine (green) and dofetilide+mexiletine (orange) vs. predominant hERG block with dofetilide alone (grey) in SCR-003 (Study 2). Vicente et al. 2016.⁷

2.1 Resampling analysis methodology

The overall methodology in this analysis is based on work by Ferber et al.,^{3,4} where data from TQT studies is bootstrapped using sampling without replacement, likely due to the resampling size \ll number of subjects in the study, under different conditions: number of subjects on active drug and number on placebo. In the case of cross-over studies, subjects in either placebo or on active are treated as two different subjects, and the data is modeled using the following model (for QTc):

$$\Delta QTc_{i,j} = Treat_{i,j} + Time_{i,j} + \alpha_i Conc_{i,j} + \beta + \beta_i + \epsilon_{i,j}$$

where subscripts i and j refer to subject i th measurement j th, α is the slope, β is the intercept and there is a random effect on both the intercept and slope, and the random effects and the error term are assumed to be independent and identically distributed (i.i.d) normal. Of note, all time points are included in the analysis.

In our analysis, we bootstrapped the data from SCR-002 and SCR-003 using sampling with replacement because the number of subjects in these studies (22 subjects in each study) was similar to the sample size of the largest sample size of the simulated studies (from 6 to 24 subjects).

2.2 Part 1

To estimate the sample size required to meet the endpoint of Part 1, we used data from a “predominant hERG” blocking drug (moxifloxacin from SCR-003), a “balanced ion channel” drug (ranolazine from SCR-002) and placebo (from both SCR-002 and SCR-003). We simulated 1000 parallel studies for each drug + placebo and scenario ranging from 3 subjects on placebo and 3 subjects on drug to 10 subjects on placebo and 14 subjects on drug (i.e. 160,000 studies). We bootstrapped the data using sampling with replacement because the number of subjects in these studies (22 subjects in each study) was similar to the sample size of the largest sample size of the simulated studies (up to 24 subjects). The results of resampling analysis suggest that 9 subjects on active study drug and 6 subjects on placebo will be sufficient to detect QTc prolongation for the “predominant hERG” drug and exclude J-T_{peakC} prolongation for the “balanced ion channel” drugs (Figure 3). Figure 3 below shows simulation results using data from our previous studies and the following model using the lme4 package in R:

$$\text{CHG} \sim \text{TPT} + \text{TRTA} + \text{CONC} + (1 + \text{CONC} | \text{RANDID})$$

where CHG is change from baseline in the ECG biomarker (e.g. ΔQTc), CONC is the drug concentration (set to 0 for placebo), TPT is time, TRT is the treatment (coded as 0 for placebo, 1 for active drug) and USUBJID is the subject identifier.

Due to the long half-life of some drugs that are included in this study and the desire to more closely mimic SAD/MAD studies, Part 1 of the current clinical study will use an entirely parallel study design with 10 subjects in each arm. Specifically, fifty (50) healthy subjects will be enrolled. Multiple doses of each drug will be given to 40 subjects on 3 consecutive days to achieve low and high exposures on Days 1 and 3, respectively, and 10 subjects will receive placebo.

It is anticipated that this study will be completed in 3 cohorts with approximately equal numbers of subjects per cohort. Cohorts 1 and 2 will have 15 subjects each (3 subjects per arm). Cohort 3 will have 20 subjects (4 subjects per arm). Up to 14 replacement subjects may be added to Cohort 3 if it is estimated that fewer than 8 subjects will complete the study in a study arm

following the replacement algorithm specified under “2.4 Replacement Algorithm for Parts 1 and 2”.

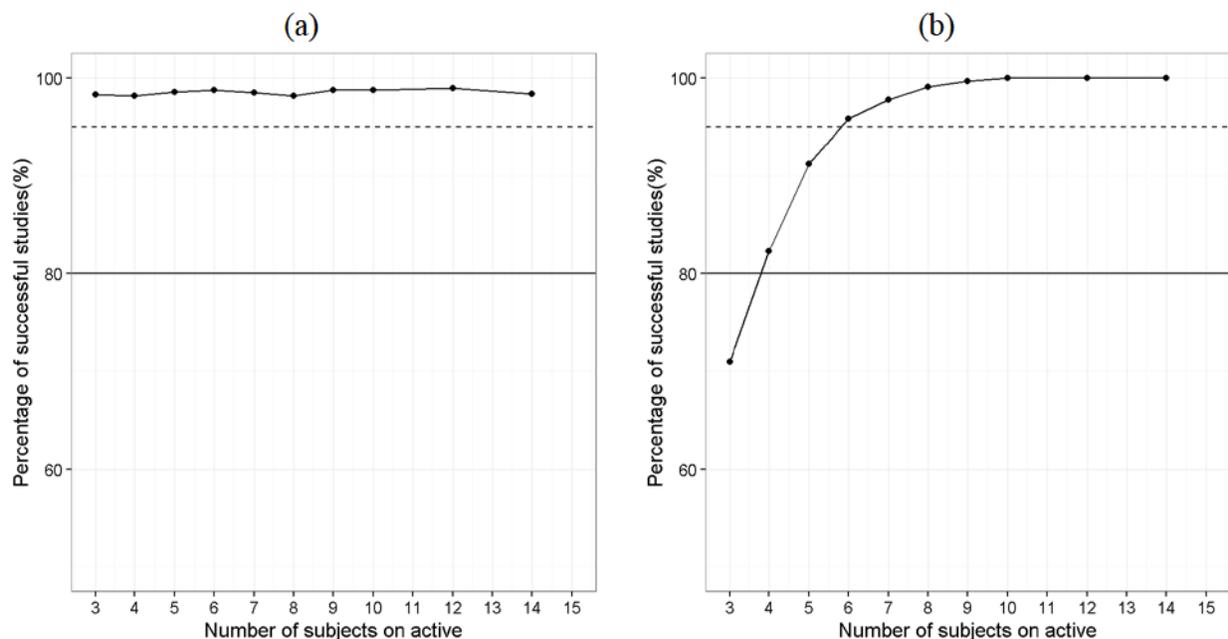


Figure 3. Percentage of studies correctly classified as a function of the number of subjects on active drug with 6 subjects on placebo for (a) a hERG blocker (moxifloxacin) with $QT_c \geq 10$ ms; and (b) a “balanced ion channel” blocker (ranolazine) with $J-T_{peakC} < 10$ ms.

2.3 Part 2

To estimate the sample size required to meet the endpoint of Part 2, we used data from a “predominant hERG” blocking drug alone (dofetilide from SCR-003) and in combination with an inward current blocker (mexiletine from SCR-003). We simulated 1000 crossover studies for each scenario ranging from 3 to 10 subjects completing the study (i.e. 8,000 studies = 8 different sample sizes x 1000 simulations). We bootstrapped the data using sampling with replacement because the number of subjects in study SCR-003 (10 subjects in the each treatment sequence) was equal to the sample size of the largest sample size of the simulated studies (up to 10 subjects). The results of resampling analysis demonstrated that inward current block (mexiletine) effects on the QT_c and $J-T_{peakC}$ slopes could be detected approximately 99% and 99% of the time, respectively, using a crossover design with 8 subjects (i.e., the inward current blocker (mexiletine) significantly reduced prolongation from the hERG blocker (dofetilide)). Figure 4 below shows simulation results using dofetilide and mexiletine data from our previous study SCR-003 and the following model using the lme4 package in R:

$$CHG \sim DOF + MEXI + DOF * MEXI + (1 + DOF | USUBJID) + (1 + MEXI | USUBJID)$$

where CHG is change from baseline in the ECG biomarker (e.g. Δ QTc), DOF is the dofetilide concentration, MEXI is mexiletine concentration and USUBJID is the subject identifier.

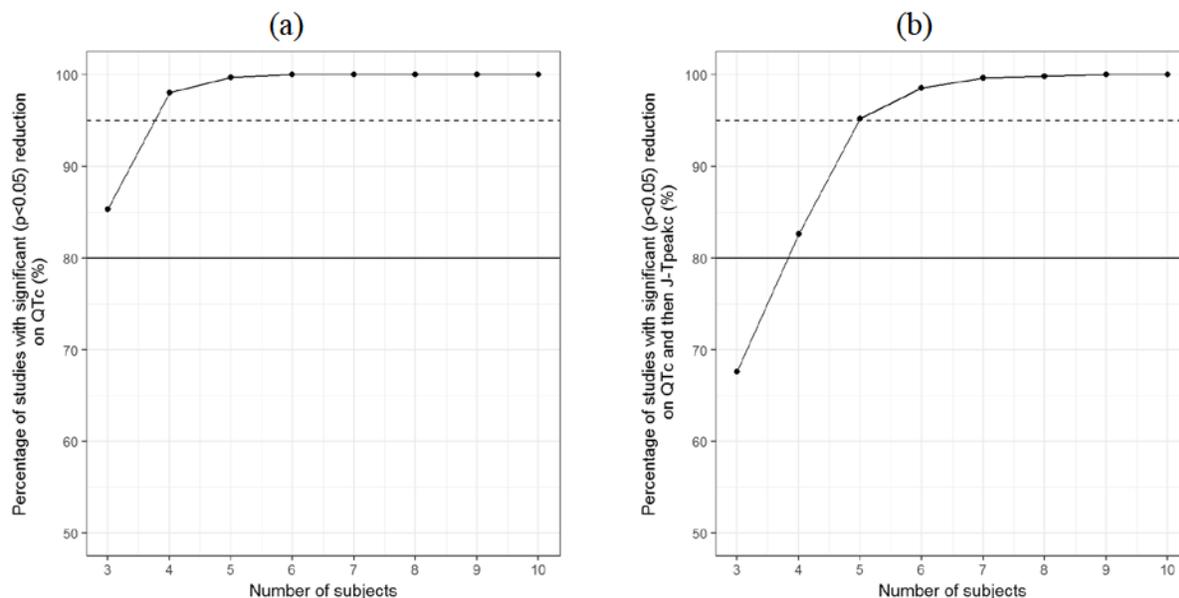


Figure 4: Percentage of studies where late sodium blocker (mexiletine) significantly ($p < 0.05$) reduced prolongation from the hERG blocker (dofetilide) for QTc (left panel) and for QTc first and then J-T_{peakc} (right panel). Each sample size included 1,000 simulated studies using data from SCR-003 Vicente et al. 2016.⁷

Ten (10) healthy subjects will be enrolled for this part. Multiple doses of each drug (dofetilide and diltiazem) will be given either separately or together on 3 consecutive days in the first period and again on 3 consecutive days in the second period, depending on the randomization, to achieve low and high exposures on Days 1 and 3, respectively. There will be no placebo arm.

It is anticipated that Part 2 of this study will be completed in 1 cohort with 10 subjects with a crossover design. Similar to Part 1, subjects may be replaced in a later cohort if it is estimated that fewer than 8 subjects will complete Part 2. A maximum of 14 replacement subjects may be enrolled in the study.

2.4 Replacement Algorithm for Parts 1 and 2

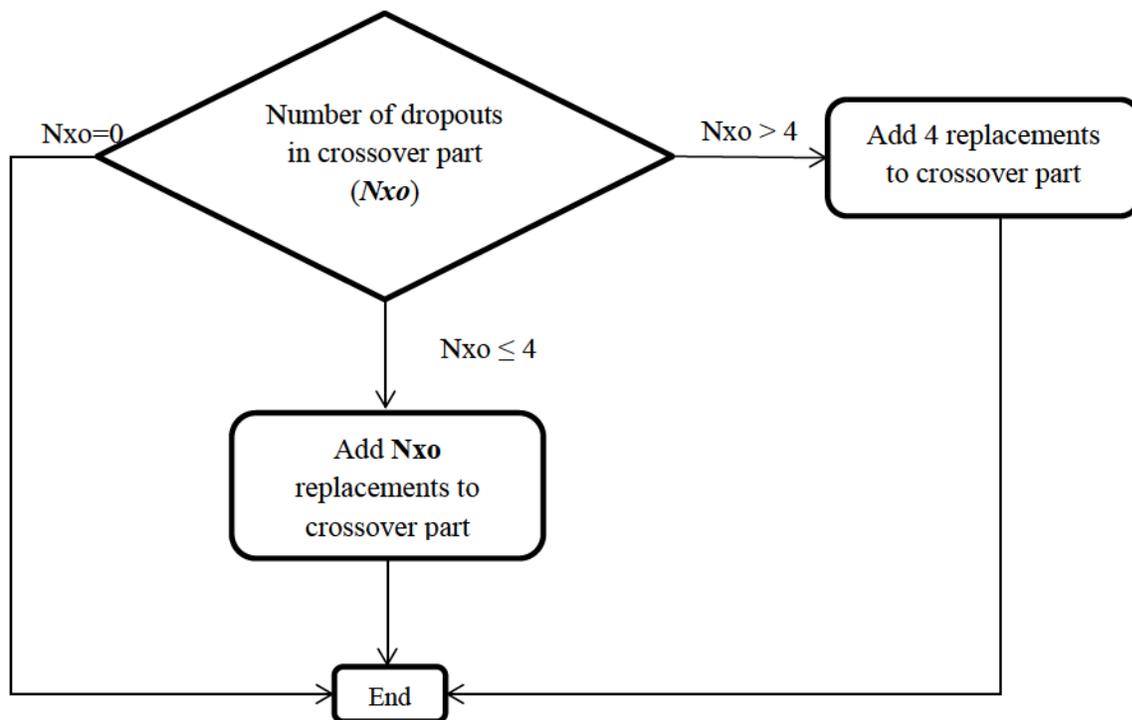
Randomization identifiers for the potential replacements (REPLCMNTID) will be provided in the randomization schedule (see example in appendix A). The replacement algorithm to guide the unblinded Spaulding pharmacist is described below. A step by step example is provided in appendix B.

2.4.1 Crossover part (Part 2):

After Period 1 and before check-in of Period 2:

1. After period 1 assess number of dropouts in the crossover part (Part 2)
2. Allocate 1 replacement for each dropout up to 4 replacements to start on Period 2 together with those already participating.
 - a. If there are more than 4 dropouts, replacements will be done one subject per sequence at a time ordering dropouts by RANDID within sequence and starting with the lowest RANDID (example in appendix A).

Flow-chart of management of replacements for the crossover part. Assessment will be done after Period 1 and before check-in of Period 2



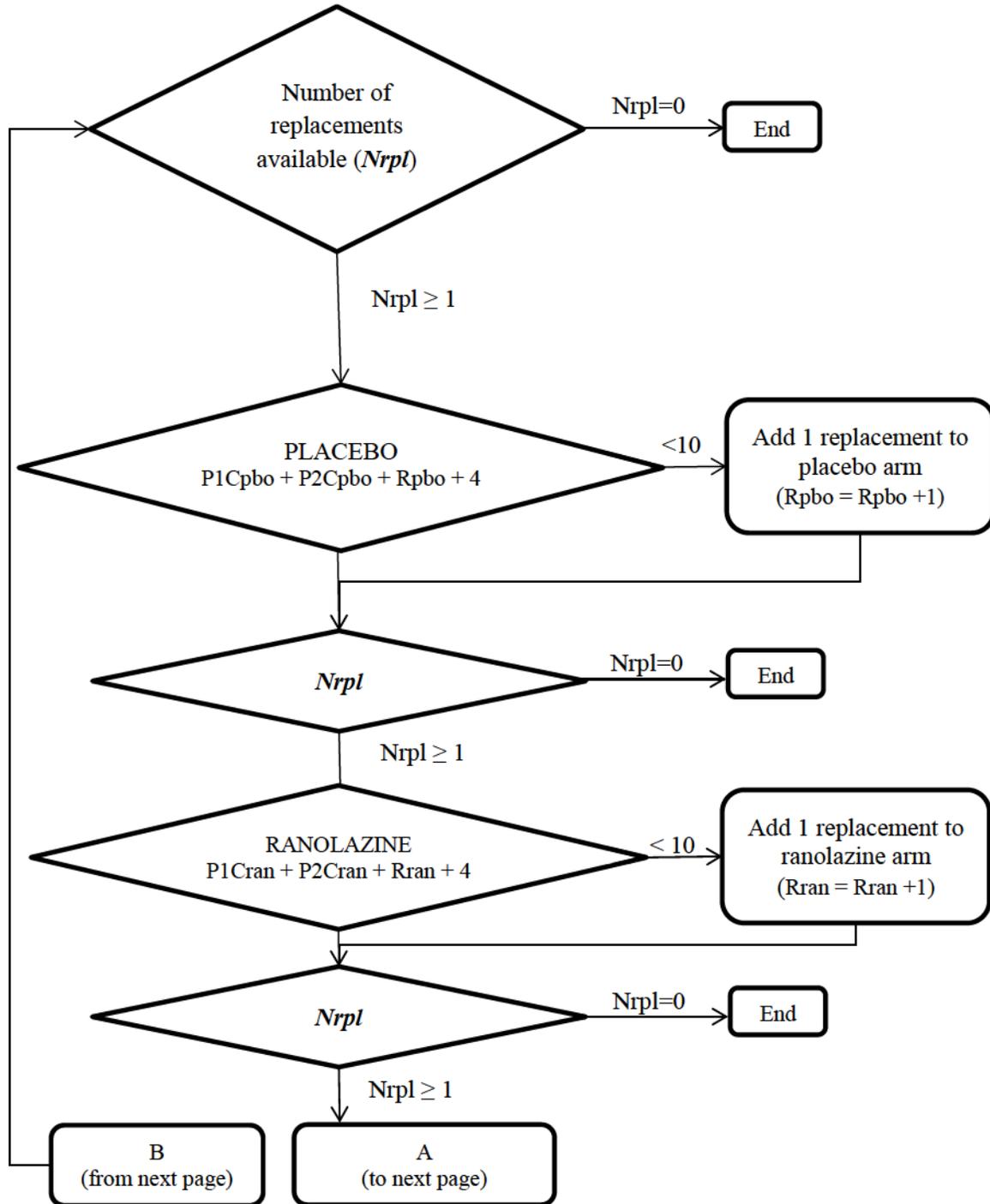
Nxo: Number of dropouts in the crossover part in Period 1 (i.e. before Period 2 check-in).

2.4.2 Parallel part (Part 1):

Parallel part (Part 1) will be assessed after its second cohort (Cohort 3) finishes and before the check-in of its last cohort (Cohort 4):

1. After the second cohort of the parallel part (Cohort 3) finishes assess number of dropouts in the parallel part (Part 1)
2. Replace each dropout up to the maximum number of 14 for the whole study (Parts 1 and 2 together). If the maximum will be reached, prioritize which treatment arms will receive replacements to bring the total number of completers in a treatment arm closer to 10 in the following order: 1) placebo, 2) ranolazine, 3) verapamil, 4) chloroquine, 5) lopinavir/ritonavir. For example, first bring all arms up to having at least 9 subjects per arm, and then if there are 2 remaining potential replacements, allocate them to placebo and ranolazine (see flow chart for parallel part in following pages and example in appendix B).

Flow-chart of management of replacements for the parallel part. Assessment will be done after the second cohort (Cohort 3) finishes and before the check-in of the last cohort (Cohort 4) of the parallel part



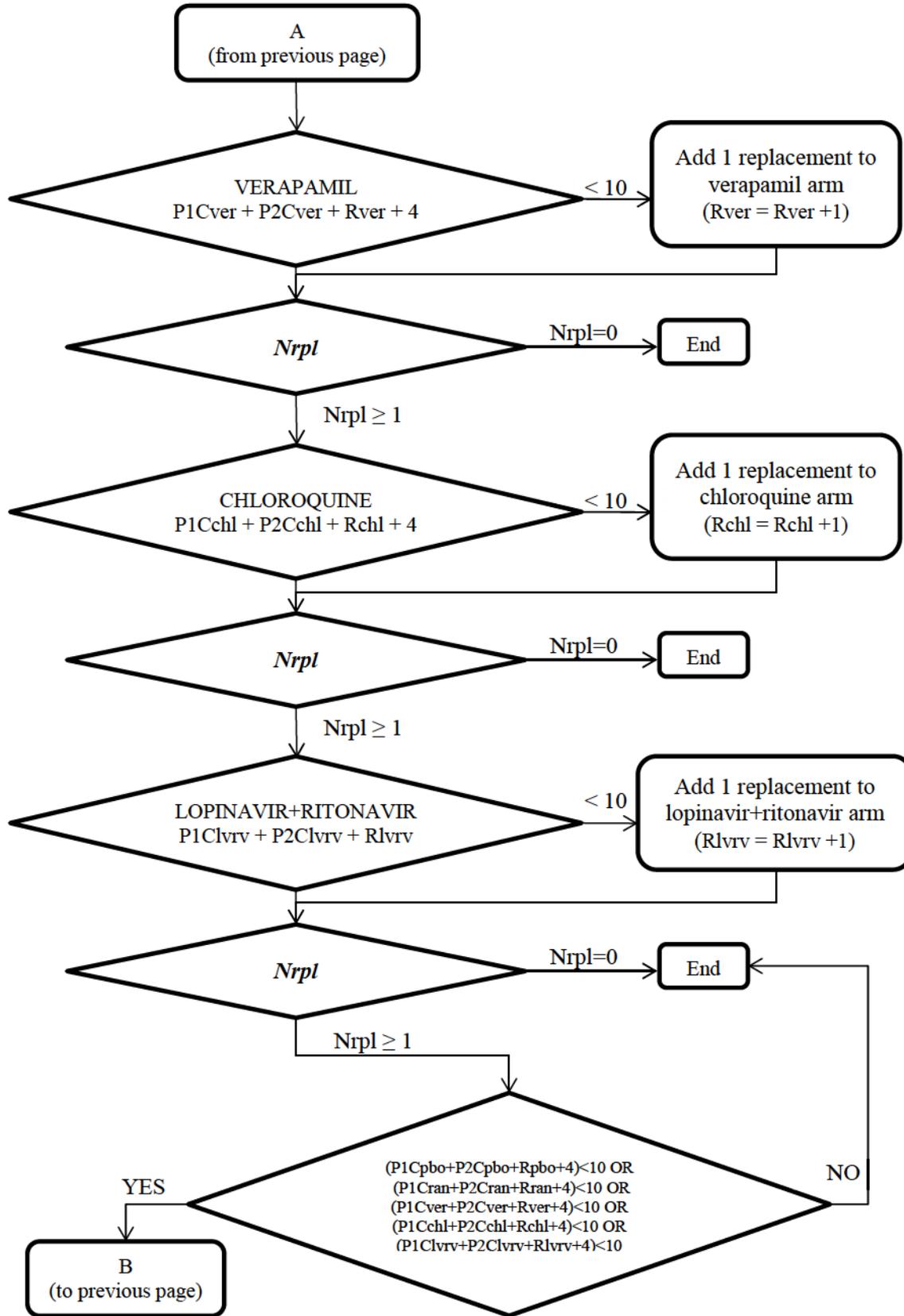


Table of acronyms in the flow chart:

Acronym	Description
Nrpl	Number of replacement that are available (i.e. how many of the 14 potential replacements have not been allocated yet)
C1Cpbo	Number of subjects that completed Cohort 1 of placebo arm
C3Cpbo	Number of subjects that completed Cohort 3 of placebo arm
Rpbo	Number of replacements allocated to the ranolazine arm
C1Cran	Number of subjects that completed Cohort 1 of ranolazine arm
C3Cran	Number of subjects that completed Cohort 3 of ranolazine arm
Rran	Number of replacements allocated to the ranolazine arm
C1Cver	Number of subjects that completed Cohort 1 of verapamil arm
C3Cver	Number of subjects that completed Cohort 3 of verapamil arm
Rver	Number of replacements allocated to the verapamil arm
C1Cchl	Number of subjects that completed Cohort 1 of chloroquine arm
C3Cchl	Number of subjects that completed Cohort 3 of chloroquine arm
Rchl	Number of replacements allocated to the chloroquine arm
C1Clrv	Number of subjects that completed Cohort 1 of lopinavir+ritonavir arm
PC3Clrv	Number of subjects that completed Cohort 3 of lopinavir+ritonavir arm
Rlrv	Number of replacements allocated to the lopinavir+ritonavir arm

3 Analysis Populations

The exposure-response population will include all subjects who receive at least 1 dose of any of the study drugs and have digital ECG (QTc and J-T_{peakC}) data for the treatment period collected before dosing and at 1 or more time points after dosing as well as plasma concentration data (except for the placebo arm) from the same time points after dosing. Subjects in this population will be used for the exposure-response analysis.

The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

4 General Statistical Considerations, Subject Disposition and Demographics and Baseline Characteristics

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of

subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Continuous demographic and baseline characteristic variables (age, height, weight, body mass index) will be summarized overall and by treatment using descriptive statistics (number of subjects, mean, standard deviation [SD], median, and minimum and maximum). The number and percentage of subjects in each class of categorical demographic and baseline characteristic variables will also be summarized.

5 Electrocardiogram Analyses

5.1 Analysis and removal of heart rate dependency for QT and J-T_{peak}

For the primary analysis, the QT interval will be corrected for heart rate using Fridericia's formula ($QT_c = QT/RR^{1/3}$). The J-T_{peak} interval will be corrected for heart rate using the Johannesen et al (2014)⁸ formula ($J-T_{peakC} = J-T_{peakC}/RR^{0.58}$).

If any drug causes an absolute placebo corrected change from baseline in heart rate ($\Delta\Delta HR$) greater than 10 beats per minute (i.e. mean effect >10bpm change in either direction) at any time point, then we will assess goodness of HR correction (visual assessment on plots like the example ones in Figure 5):

1. QT vs RR and QT_c vs RR
2. J-T_{peak} vs RR and J-T_{peakC} vs RR

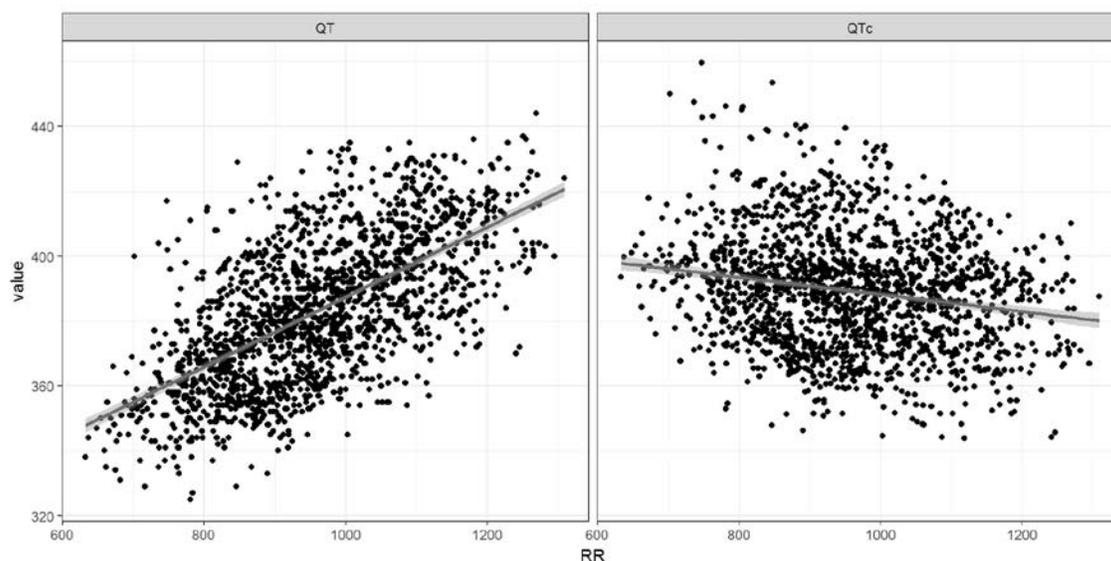
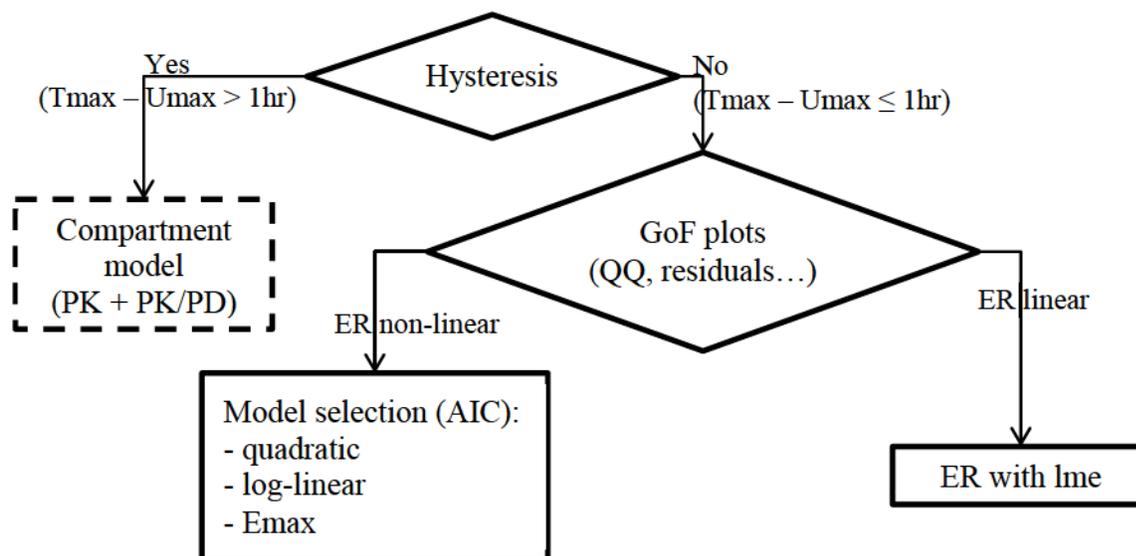


Figure 5: Example of plots for assessing goodness of HR correction. QT and RR data from placebo arm and baseline time points from SCR-003.

If there are HR effects >10 bpm and the relationship does not look appropriate (per visual assessment) then we will perform an analysis using population-based HR correction (described below).

5.2 Primary Analyses

Analysis flow chart (for each endpoint):



5.2.1 Parts 1 and 2

Investigation of hysteresis: Prior to model selection for the exposure-response analysis, the presence of hysteresis will be assessed for QTc and J-T_{peakC}. To detect hysteresis, individual change-from-baseline in J-T_{peakC} ($\Delta J-T_{peakC}$) will be computed. For each day, the time of the largest mean $\Delta J-T_{peakC}$ (U_{max}) will be determined. If the largest mean $\Delta J-T_{peakC}$ exceeds 5 msec at ≥ 3 time points, the time difference between U_{max} and the T_{max} of the drug level exceeds 1 hour, and the 1-sided, 1-sample Wilcoxon test for the difference between $\Delta J-T_{peakC}$ at T_{max} and at U_{max} is formally significant at the 1% level, it will be concluded that hysteresis existed. In such a case, a PK model with an additional effect compartment will replace the model described below. The same steps will be followed for QTc as part of the primary endpoint.

Model selection: To assess the appropriateness of a linear model, normal QQ-plots for the residuals and plots of weighted residuals versus concentration and versus fitted values will be produced. A model with a quadratic term in concentration will be fitted and the quadratic term will be tested on the 2-sided 5% alpha level. If there is a significant quadratic term, nonlinear models, such as a log-linear model and an E_{max} model, will be investigated and the primary

model will be selected based on the Akaike Information Criterion (AIC) and plausibility arguments.

Exposure-response analysis: In the absence of hysteresis and unless the pre-specified test procedure for linearity indicates otherwise, the primary analysis will be based on a linear mixed-effects model implemented in SAS[®] or R software, with $\Delta J-T_{\text{peakC}}$ as the dependent variable, drug plasma concentration as continuous covariate, treatment and time point as categorical factors, and subject-specific random effects for the intercept and slope, depending on whether Part 1 or Part 2 of the study is being considered (details for each part below). All postdose data will be used. The degrees of freedom for the model estimates will be determined by the Kenward-Rogers method. From the model, the slope (i.e., the regression parameter for the concentration) and the treatment effect will be estimated together with 2-sided 90% CIs.

The predicted mean placebo-adjusted change-from-baseline $J-T_{\text{peakC}}$ ($\Delta\Delta J-T_{\text{peakC}}$) at the observed geometric mean C_{max} (i.e., the product with the slope estimate + treatment effect [$\Delta J-T_{\text{peakCActive}} - \Delta J-T_{\text{peakCplacebo}}$]) and the 2-sided 90% CI of the estimate will be calculated. The same steps will be followed for QTc as part of the primary endpoint.

5.2.2 Part 1

The primary variable for the exposure-response analysis will be the change-from-baseline in QTc (ΔQTc) for the “predominant hERG” drug and change-from-baseline in $J-T_{\text{peakC}}$ ($\Delta J-T_{\text{peakC}}$) for the “balanced ion channel” drugs, where the mean of the 3 predose ECG readings on Day 1 will be used as the Baseline. The concentration of the drug will be used as a covariate. Exposure-response analysis will be done following most recent best practices in concentration-QTc modeling.

Criteria for primary QTc and $J-T_{\text{peakC}}$ assessment:

Criteria for the 3 “balanced ion channel” drugs (ranolazine, verapamil, lopinavir + ritonavir) will be based on the predicted $J-T_{\text{peakC}}$ effect on the third day of dosing. To demonstrate a lack of placebo-adjusted change-from-baseline $J-T_{\text{peakC}}$ ($\Delta\Delta J-T_{\text{peakC}}$) prolongation for each of the 3 drugs:

- The upper bound of the 2-sided 90% CI of the predicted mean $\Delta\Delta J-T_{\text{peakC}}$ must be <10 msec at the observed geometric mean C_{max} on Day 3.
 - $H_0: \Delta\Delta J-T_{\text{peakC}} \geq 10 \text{ ms}$
 - $H_A: \Delta\Delta J-T_{\text{peakC}} < 10 \text{ ms}$

Criteria for the “predominant hERG” drug (chloroquine) will be based on the predicted QTc effect on the first day of dosing. To demonstrate the presence of placebo-adjusted change-from-baseline QTc ($\Delta\Delta\text{QTc}$) prolongation for chloroquine:

- The upper bound of the 2-sided 90% CI of the predicted mean $\Delta\Delta\text{QTc}$ must be ≥ 10 msec at the observed geometric mean C_{max} on Day 1.
 - H_0 : $\Delta\Delta\text{QTc} < 10$ ms
 - H_A : $\Delta\Delta\text{QTc} \geq 10$ ms

We will use the following linear mixed effects model (QTc as example):

$$\Delta\text{QTc} \sim \text{time} + \text{treatment} + \text{concentration} + (1 + \text{concentration} | \text{subjid})$$

where concentration is set to 0 for placebo, treatment is 1 for drug and 0 for placebo, and time is a categorical variable coded as time after first dose (e.g. '1 hr', '1.5 hr', '2 hr', '4 hr', ... '72 hr'). Note that the prediction from the model above is $\Delta\Delta\text{QTc}$ because placebo treatment is coded as 0.

In addition to the tests specified above (e.g. $\Delta\Delta\text{QTc} \geq 10$ ms at C_{max} of Day 1), it will be assessed:

1. whether exploratory plots suggest model misspecification
 - a. Exploratory plot will show the model fit (mean and 95% CIs) plot on top of the observed $\Delta\Delta\text{QTc}$ ($\Delta\text{QTc}_{\text{drug}} - \text{mean } \Delta\text{QTc}_{\text{placebo}}$ by time) and the corresponding deciles of the observed data
 - b. QQ-plots of the model residuals
 - c. Plot of the standardized residuals by time, treatment and concentration (continuous for continuous variables, otherwise boxplot)

If there is an effect (e.g. $\text{abs}(\Delta\Delta\text{QTc}) \geq 10$ ms) and the fit is acceptable then we accept the linear model. If not (i.e. either or both criteria are not met) then further models will be assessed. The same assessment will be performed for J-T_{peakc} in a similar fashion.

5.2.3 Part 2

The primary variable for the exposure-response analysis will be the change-from-baseline in QTc (ΔQTc) for the pooled dofetilide alone, diltiazem alone, and dofetilide + diltiazem, where the mean of the 3 predose ECG readings on Day 1 will be used as the Baseline. The concentration of dofetilide and diltiazem will be used as covariates.

Criteria for primary QTc and J-T_{peakc} assessment:

To demonstrate that calcium channel block (diltiazem) reduces QTc prolongation from hERG block (dofetilide) by shortening J-T_{peakc}:

- It will be assessed whether the projected QTc effect of dofetilide alone is significantly greater (i.e., $p < 0.05$) than the projected QTc effect of the combination of dofetilide +

diltiazem. This will be assessed at the dofetilide peak plasma level on Day 3 (computed from the combination of dofetilide + diltiazem) on the pooled dofetilide alone, diltiazem alone, and dofetilide + diltiazem data using a linear mixed effects model:

$$\Delta QTc \sim DOF + DILT + DOF * DILT + (1 + DOF | USUBJID) + (1 + DILT | USUBJID)$$

where DOF is concentration of dofetilide, and DILT is concentration of diltiazem.

- $H_0: \Delta QTc (Dof\ C_{max}, Dilt=0) \leq \Delta QTc (Dof\ C_{max}, Dilt\ C_{max})$
 - $H_A: \Delta QTc (Dof\ C_{max}, Dilt=0) > \Delta QTc (Dof\ C_{max}, Dilt\ C_{max})$
- If the previous test is statistically significant for QTc, the same test will be performed for J-Tpeakc.
 - $\Delta JTpeakc \sim DOF + DILT + DOF * DILT + (1 + DOF | USUBJID) + (1 + DILT | USUBJID)$
 - $H_0: \Delta JTpeakc (Dof\ C_{max}, Dilt=0) \leq \Delta JTpeakc (Dof\ C_{max}, Dilt\ C_{max})$
 - $H_A: \Delta JTpeakc (Dof\ C_{max}, Dilt=0) > \Delta JTpeakc (Dof\ C_{max}, Dilt\ C_{max})$

In addition to the tests specified above, it will be assessed:

1. whether exploratory plots suggest model misspecification
 - a. Exploratory plot will show the model fit (mean and 95% CIs) plot on top of the observed ΔQTc and the corresponding deciles of the observed data.
 - b. QQ-plots of the model residuals
 - c. Plot of the standardized residuals by time, treatment and concentration (continuous for continuous variables, otherwise boxplot)

If there is a ΔQTc effect and the fit is acceptable then we accept the linear model. If not (i.e. either or both criteria are not met) then further models will be assessed. The same assessment will be performed for J-Tpeakc in a similar fashion.

5.3 Exploratory Analyses

5.3.1 Exposure-response analysis of secondary ECG biomarkers

Exposure-response analysis of secondary ECG biomarkers: For Part 1, exposure-response analysis similar to that described for QTc and J-T_{peakC} will be applied to PR, QRS, QTc, J-T_{peakC}, and T_{peak}-T_{end} for Day 1 and Day 3. This will also include analysis of change from baseline for dofetilide alone, diltiazem alone, and dofetilide + diltiazem combination from Part 2 of the study.

5.3.2 $\Delta \Delta ECG$ measurements by time point

For each time point, an analysis of variance model will be fitted with $\Delta J-T_{peakC}$ as the dependent variable, treatment (active or placebo) as factor, and baseline J-T_{peakC} as a covariate. From this

model, the difference ($\Delta J-T_{\text{peakCactive}} - \Delta J-T_{\text{peakCplacebo}}$) will be estimated with a 2-sided 90% CI. Separate models will be fitted for each treatment, all of them using the same placebo data. The same steps will be followed for QTc. Change from Baseline in heart rate, PR, QRS, and $T_{\text{peak}}-T_{\text{end}}$ will be calculated using descriptive summary statistics.

5.3.3 Analyses using population-based heart rate corrected QT and J-Tpeak

If any drug causes an absolute placebo-corrected change from baseline in heart rate greater than 10 beats per minute, we will perform exposure-response and $\Delta\Delta\text{ECG}$ measurements by time point using population-based heart rate correction factors for QT and J-Tpeak. We will use continuous/Holter 12-lead ECGs recorded at check-in from early afternoon until the subjects go to sleep. During this period, subjects will perform a sequence of postural maneuvers (e.g., 10 minutes supine, 10 minutes sitting, 10 minutes standing, 10 minutes sitting, 10 minutes supine) to characterize ECG biomarkers and heart rate relationship (i.e. QT/RR and J-T_{peak}/RR relationships). From each Holter and postural maneuver window, triplicate 10-second 12-lead ECGs will be extracted at different heart rates. Additional details will be available in the ECG analysis plan. The dependency of the different electrocardiographic intervals on heart rate will be evaluated using the extracted ECGs from the Holvers. We will compute a population-based correction factor using an exponential model. The model will include random effects for the intercept ($\log(\alpha)$) and β (i.e., allowing each individual to have his or her own slope). We will consider that there is heart rate dependency for an ECG biomarker if the ECG biomarker and heart rate relationship is significant and there is at least 10% of change in the ECG biomarker within the heart rate range as described in Johannesen et al 2014.⁸ For heart rate dependent ECG biomarkers, the individual correction factors will be applied using the exponential model. Using QT as an example: $QTcI = QT/RR^{\beta_i}$, where β_i is the slope of the relationship of the i-th subject.

5.3.4 Use of placebo from parallel part in crossover part

The 10-subject placebo group from the parallel part of the study can potentially be used interchangeably with the crossover part. This analysis will test that calcium channel block (diltiazem) reduces QTc prolongation from hERG block (dofetilide) by shortening J-T_{peakC}. The placebo corrected changes from baseline ($\Delta\Delta$) will be computed subtracting the time-matched average placebo changes from baseline (Δ) of the subjects participating in Part 1 of the study from the individual changes from baseline of subjects participating in Part 2.

- It will be assessed whether the projected QTc effect of dofetilide alone is significantly greater (i.e., $p < 0.05$) than the projected QTc effect of the combination of dofetilide + diltiazem. This will be assessed at the dofetilide peak plasma level on Day 3 (computed from the combination of dofetilide + diltiazem) on the pooled dofetilide alone, diltiazem alone, and dofetilide + diltiazem data using a linear mixed effects model using the placebo-corrected change from baseline as dependent variable:

$$\circ \Delta\Delta\text{QTc} \sim \text{DOF} + \text{DILT} + \text{DOF} * \text{DILT} + (1 + \text{DOF} | \text{USUBJID}) + (1 + \text{DILT} | \text{USUBJID})$$

where DOF is concentration of dofetilide, and DILT is concentration of diltiazem.

- $H_0: \Delta\Delta QTc (\text{Dof } C_{max}, \text{Dilt}=0) \leq \Delta\Delta QTc (\text{Dof } C_{max}, \text{Dilt } C_{max})$
- $H_A: \Delta\Delta QTc (\text{Dof } C_{max}, \text{Dilt}=0) > \Delta\Delta QTc (\text{Dof } C_{max}, \text{Dilt } C_{max})$
- If the previous test is statistically significant for QTc, the same test will be performed for J-Tpeakc.
 - $\Delta\Delta JT_{peakc} \sim \text{DOF} + \text{DILT} + \text{DOF} * \text{DILT} + (1 + \text{DOF} | \text{USUBJID}) + (1 + \text{DILT} | \text{USUBJID})$
 - $H_0: \Delta\Delta JT_{peakc} (\text{Dof } C_{max}, \text{Dilt}=0) \leq \Delta\Delta JT_{peakc} (\text{Dof } C_{max}, \text{Dilt } C_{max})$
 - $H_A: \Delta\Delta JT_{peakc} (\text{Dof } C_{max}, \text{Dilt}=0) > \Delta\Delta JT_{peakc} (\text{Dof } C_{max}, \text{Dilt } C_{max})$

6 Pharmacokinetic Analyses

PK parameters C_{max} , T_{max} , and AUC will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum) for Day 1 and Day 3 for each active drug and period (i.e., Days 1 and 3 of Part 1 and Days 1, 3, 8 and 10 of Part 2). The PK parameters will be analyzed using non-compartmental methods based on actual sampling times. Mean and individual concentration-time profiles will be presented in graphs.

7 Safety Analyses

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs), organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

Vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and changes from Baseline for these parameters will be summarized by treatment and time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

8 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

9 Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark remote electronic data capture (EDC) system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

10 References

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4. Ferber G, Lorch U, Taubel J. The Power of Phase I Studies to Detect Clinical Relevant QTc Prolongation: A Resampling Simulation Study. *Biomed Res Int.* 2015;2015:293564.
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7. Vicente, J., L. Johannesen, M. Hosseini, J. W. Mason, P. T. Sager, E. Pueyo and D. G. Strauss (2016). "Electrocardiographic Biomarkers for Detection of Drug-Induced Late Sodium Current Block." *PLOS ONE* 11(12): e0163619.
8. Johannesen, L., J. Vicente, R. A. Gray, L. Galeotti, Z. Loring, C. E. Garnett, J. Florian, M. Ugander, N. Stockbridge and D. G. Strauss (2014). "Improving the assessment of heart toxicity for all new drugs through translational regulatory science." *Clin Pharmacol Ther* 95(5): 501-508.

A Randomization schedule

This code does not necessarily reflect any position of the Government or the Food and Drug Administration.

A.1 Abstract

This script generates the randomization schedule for the CiPA ECG clinical study (SCR-004).

After screening, 60 subjects will be randomized to participate in one of the 7 treatment sequences of the study. Example of treatment codes from the study protocol:

- Treatment sequences of Part 1 (parallel part)
 - A: Ranolazine (10 subjects)
 - B: Verapamil (10 subjects)
 - C: Lopinavir+Ritonavir (10 subjects)
 - D: Chloroquine (10 subjects)
 - E: Placebo (10 subjects)
- Treatment sequences of Part 2 (crossover part)
 - F,G: Dofetilide, Diltiazem+Dofetilide (5 subjects)
 - G,F: Diltiazem+Dofetilide, Dofetilide (5 subjects)

This script performs randomization in permuted blocks to achieve balance across treatment groups. The blocks are defined as follows:

- Block 1: First 15 subjects of parallel part (Cohort 1, Period 1) and 10 subjects of crossover part (Cohort 2, Periods 1 and 2)
 - Treatment sequences:
 - Parallel part: A, B, C, D, E
 - Crossover part: F-G, G-F
- Block 2: Second 15 subjects of parallel part (Cohort 3, Period 2)
 - Treatment sequences:
 - Parallel part: A, B, C, D, E
- Block 3: Remaining 20 subjects of parallel part (Cohort 4, Period 3)
 - Treatment sequences:
 - Parallel part: A, B, C, D, E

IDs for the potential replacements (REPLCMNTID) are computed from the randomization IDs (RANDID) as follows.

- In the parallel part (Part 1) $REPLCMNTID = RANDID + 2000$
- In the crossover part (Part 2) there are 2 replacements (one per treatment sequence) for each drop out (up to 4 replacement total). Thus, each subject has two potential replacements IDs:

- For the replacement with same sequence than the dropout REPLCMNTID = $10*(RANDID+2000) + 1$ (e.g. 40011 for subject 2001)
- For the replacement with the alternative sequence than the dropout REPLCMNTID = $10*(RANDID+2000) + 2$ (e.g. 40012 for subject 2001)

A.2 Study design (pre-specified balanced design within period/cohort)

A.3 Treatment codes and subjects IDs from 3 blocks by Part and Cohort

```
##
# List of randomization IDs
##
randids <- c(seq(1001,1050,1),seq(2001,2010,1))

##
# Randomization of treatment codes
##
treatmentcodespart1 <- c('A','B','C','D','E')
treatmentnamespart1 <- c('Ranolazine','Verapamil','Lopinavir+Ritonavir','Chloroquine','Placebo')
treatmentcodespart2 <- c('F','G')
treatmentnamespart2 <- c('Dofetilide','Diltiazem+Dofetilide')

##
# Treatment codes data.frame
##
treatments <- data.frame(CODE=c(treatmentcodespart1,treatmentcodespart2), TREATMENT=c(treatmentnamespart1,treatmentnamespart2),PART=c(1,1,1,1,1,2,2))

##
# Treatment sequences
##
part1seqs <- c('A','B','C','D','E')
part2seqs <- c('F-G','G-F')

##
# Block1
##
block1 <- data.frame(SEQ=c(part1seqs,part2seqs),NSUBJ=c(3,3,3,3,3,5,5),PART=c(1,1,1,1,1,2,2),COHORT=c(1,1,1,1,1,2,2))
block1 <- block1 %>% group_by(PART) %>% mutate(CUMSUBJ=cumsum(NSUBJ)) %>% ungroup()
block1 <- block1 %>% mutate(Group_number=group_indices(block1,.dots=c(SEQ)))
%>% group_by(Group_number) %>% mutate(RANDIDS=paste0(PART*1000+seq(CUMSUBJ-NSUBJ+1,CUMSUBJ,1),collapse=', ')) %>% ungroup() %>% data.frame() %>% mutate(SEQ=as.character(SEQ))
```

```
##
# Block2
##
block2 <- data.frame(SEQ=part1seqs, NSUBJ=3, PART=1, COHORT=3)
block2 <- block2 %>% group_by(PART) %>% mutate(CUMSUBJ=cumsum(NSUBJ)) %>% ungroup()
block2 <- block2 %>% mutate(Group_number=group_indices(block2, .dots=c(SEQ)))
%>% group_by(Group_number) %>% mutate(RANDIDs=paste0(15+PART*1000+seq(CUMSUBJ-NSUBJ+1, CUMSUBJ, 1), collapse=', ')) %>% ungroup() %>% data.frame() %>% mutate(SEQ=as.character(SEQ))

##
# Block3
##
block3 <- data.frame(SEQ=part1seqs, NSUBJ=4, PART=1, COHORT=4)
block3 <- block3 %>% group_by(PART) %>% mutate(CUMSUBJ=cumsum(NSUBJ)) %>% ungroup()
block3 <- block3 %>% mutate(Group_number=group_indices(block3, .dots=c(SEQ)))
%>% group_by(Group_number) %>% mutate(RANDIDs=paste0(30+PART*1000+seq(CUMSUBJ-NSUBJ+1, CUMSUBJ, 1), collapse=', ')) %>% ungroup() %>% data.frame() %>% mutate(SEQ=as.character(SEQ))

##
# Schedule
##
schedule <- bind_rows(block1, block2, block3) %>% select(-c(Group_number, CUMSUBJ, NSUBJ))
# Next statements were used during development to validate wide/long conversion operation
#schedule.summary <- schedule %>% spread(COHORT, RANDIDs)
#schedule.summary[is.na(schedule.summary)] <- ''
#pander(schedule.summary, split.table=Inf)

# Save schedule in long format to facilitate shuffle operations in the randomization process below
schedulelong <- schedule %>% group_by(COHORT, SEQ) %>% mutate(ID1=strsplit(RANDIDs, ',')[[1]][1], ID2=strsplit(RANDIDs, ',')[[1]][2], ID3=strsplit(RANDIDs, ',')[[1]][3], ID4=strsplit(RANDIDs, ',')[[1]][4], ID5=strsplit(RANDIDs, ',')[[1]][5]) %>% ungroup() %>% select(-RANDIDs) %>% gather(ID, RANDID, c(ID1, ID2, ID3, ID4, ID5)) %>% filter(!is.na(RANDID)) %>% select(-ID) %>% distinct() %>% mutate(RANDID=as.numeric(RANDID)) %>% select(RANDID, PART, COHORT, SEQ) %>% arrange(RANDID)

# Schedule printed in section below
# pander(schedulelong, split.table=Inf)
```

```
#Format in summary table
scheduleLong.summary <- scheduleLong %>% group_by(COHORT,SEQ) %>% mutate(RAND
IDS=paste0(RANDID,collapse=', ')) %>% select(-RANDID) %>% ungroup() %>% disti
nct() %>% spread(COHORT,RANDIDS)
scheduleLong.summary[is.na(scheduleLong.summary)] <- ''

# Add potential replacements IDS to the Long format
addpotentialreplacementids<-function(schdf){
  return (schdf %>% mutate(REPLCMNTID=RANDID+2000))
}

scheduleLongwithrplids <- addpotentialreplacementids(scheduleLong)
# Print table
# pander(scheduleLong.summary,split.table=Inf)
```

A.3.1.1 Treatment codes

```
pander(treatments,split.table=Inf)
```

CODE	TREATMENT	PART
A	Ranolazine	1
B	Verapamil	1
C	Lopinavir+Ritonavir	1
D	Chloroquine	1
E	Placebo	1
F	Dofetilide	2
G	Diltiazem+Dofetilide	2

A.3.1.2 Treatment schedule

```
pander(scheduleLongwithrplids ,split.table=Inf)
```

RANDID	PART	COHORT	SEQ	REPLCMNTID
1001	1	1	A	3001
1002	1	1	A	3002
1003	1	1	A	3003
1004	1	1	B	3004
1005	1	1	B	3005
1006	1	1	B	3006
1007	1	1	C	3007
1008	1	1	C	3008
1009	1	1	C	3009

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay
(CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1010	1	1	D	3010
1011	1	1	D	3011
1012	1	1	D	3012
1013	1	1	E	3013
1014	1	1	E	3014
1015	1	1	E	3015
1016	1	3	A	3016
1017	1	3	A	3017
1018	1	3	A	3018
1019	1	3	B	3019
1020	1	3	B	3020
1021	1	3	B	3021
1022	1	3	C	3022
1023	1	3	C	3023
1024	1	3	C	3024
1025	1	3	D	3025
1026	1	3	D	3026
1027	1	3	D	3027
1028	1	3	E	3028
1029	1	3	E	3029
1030	1	3	E	3030
1031	1	4	A	3031
1032	1	4	A	3032
1033	1	4	A	3033
1034	1	4	A	3034
1035	1	4	B	3035
1036	1	4	B	3036
1037	1	4	B	3037
1038	1	4	B	3038
1039	1	4	C	3039
1040	1	4	C	3040
1041	1	4	C	3041
1042	1	4	C	3042
1043	1	4	D	3043

Statistical Analysis Plan

SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study

1044	1	4	D	3044
1045	1	4	D	3045
1046	1	4	D	3046
1047	1	4	E	3047
1048	1	4	E	3048
1049	1	4	E	3049
1050	1	4	E	3050
2001	2	2	F-G	4001
2002	2	2	F-G	4002
2003	2	2	F-G	4003
2004	2	2	F-G	4004
2005	2	2	F-G	4005
2006	2	2	G-F	4006
2007	2	2	G-F	4007
2008	2	2	G-F	4008
2009	2	2	G-F	4009
2010	2	2	G-F	4010

A.3.1.3 Balanced design summary table

Print summary table

```
pander(scheduleLong.summary, split.table=Inf)
```

PART	SEQ	1	2	3	4
1	A	1001, 1002, 1003		1016, 1017, 1018	1031, 1032, 1033, 1034
1	B	1004, 1005, 1006		1019, 1020, 1021	1035, 1036, 1037, 1038
1	C	1007, 1008, 1009		1022, 1023, 1024	1039, 1040, 1041, 1042
1	D	1010, 1011, 1012		1025, 1026, 1027	1043, 1044, 1045, 1046
1	E	1013, 1014, 1015		1028, 1029, 1030	1047, 1048, 1049, 1050
2	F-G		2001, 2002, 2003, 2004, 2005		
2	G-F		2006, 2007, 2008, 2009, 2010		

A.4 Randomization

A.4.1 Seed random number generator

TODO: The unblinded statistician of the sponsor team will be responsible of selecting the seed for the random number generator and update the `set.seed` statement below accordingly.

```
# Seed the random number generator
myseed <- 123456
set.seed(myseed)
```

A.4.2 Randomization schedule code

```
##
# Randomization within blocks by cohort
##
randomizedscheduleLong <- data.frame()
# Randomize treatment codes within each cohort
for(cohort in unique(scheduleLong$COHORT)){
  rsdf <- scheduleLong %>% filter(COHORT==cohort)
  # Randomly permute RANDIDs
  rsdf$RANDID <- levels(fct_shuffle(as.character(rsdf$RANDID)))
  rsdf <- rsdf %>% arrange(RANDID)
  randomizedscheduleLong <- bind_rows(randomizedscheduleLong,rsdf)
}
randomizedscheduleLong$RANDID <- as.numeric(randomizedscheduleLong$RANDID)
randomizedscheduleLongwithrplcids <- addpotentialreplacementids(randomizedsch
cheduleLong)
# Randomization schedule printed in unblinded pharmacist section below
# pander(randomizedscheduleLongwithrplcids,split.table=Inf)
```

A.4.2.1 Randomized summary table

```
#Format in summary table
randomizedscheduleLong.summary <- randomizedscheduleLong %>% group_by(COHORT,
SEQ) %>% mutate(RANDIDs=paste0(RANDID,collapse=', ')) %>% select(-RANDID) %>%
ungroup() %>% distinct() %>% spread(COHORT,RANDIDs)
randomizedscheduleLong.summary[is.na(randomizedscheduleLong.summary)] <- ''
# Randomization summary table printed in unblinded pharmacist section
below
#pander(randomizedscheduleLong.summary,split.table=Inf)
```

A.4.2.2 Randomized treatment codes

A.4.2.3

```

# Randomized treatment codes data.frame
##
randomizetreatmentcodes<-F
randomizedtreatments <- data.frame()
if (randomizetreatmentcodes){
  # Randomize treatment codes within each part
  for(part in unique(treatments$PART)){
    rtrt <- treatments %>% filter(PART==part)
    # Randomly permute the levels of the treatment CODEs
    rtrt$CODE <- Levels(fct_shuffle(as.character(rtrt$CODE)))
    rtrt <- rtrt %>% arrange(CODE)
    randomizedtreatments <- bind_rows(randomizedtreatments,rtrt)
  }
} else {
  randomizedtreatments <- treatments
}
# Randomized treatment codes printed in unblinded pharmacist
section below
#pander(randomizedtreatments,split.table=Inf)

```

A.5 For clinical site unblinded pharmacist

```
pandoc.header(paste0('The random generator seed was: ', myseed),Level=2)
```

A.5.1 The random generator seed was: 123456

A.5.2 Randomized treatment codes

```

if(randomizetreatmentcodes){
  mystr <- 'Treatments code were randomized\n'
}else{
  mystr <- ('Treatments code as per protocol. Treatment codes NOT randomized\n'
n')
}
sprintf(mystr)

## [1] "Treatments code as per protocol. Treatment codes NOT randomize
d\n"

pander(randomizedtreatments,split.table=Inf)

```

CODE	TREATMENT	PART
------	-----------	------

Statistical Analysis Plan

SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study

A	Ranolazine	1
B	Verapamil	1
C	Lopinavir+Ritonavir	1
D	Chloroquine	1
E	Placebo	1
F	Dofetilide	2
G	Diltiazem+Dofetilide	2

```
pdf(file = "SCR-004.treatment.codes.pdf")
grid.table(paste0('The random generator seed was: ', myseed, '\n', mystr, '\n
Table in next page'))
grid::grid.newpage()
grid.table(randomizedtreatments, rows=NULL)
dev.off()

## png
## 2
```

A.5.3 Randomization schedule table

```
pander(randomizedscheduleLongwithrplcids, split.table=Inf)
```

RANDID	PART	COHORT	SEQ	REPLCMNTID
1001	1	1	C	3001
1002	1	1	B	3002
1003	1	1	D	3003
1004	1	1	B	3004
1005	1	1	B	3005
1006	1	1	A	3006
1007	1	1	C	3007
1008	1	1	E	3008
1009	1	1	E	3009
1010	1	1	D	3010
1011	1	1	A	3011
1012	1	1	A	3012
1013	1	1	E	3013
1014	1	1	D	3014
1015	1	1	C	3015
1016	1	3	C	3016
1017	1	3	B	3017

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1018	1	3	A	3018
1019	1	3	D	3019
1020	1	3	B	3020
1021	1	3	E	3021
1022	1	3	E	3022
1023	1	3	C	3023
1024	1	3	B	3024
1025	1	3	C	3025
1026	1	3	E	3026
1027	1	3	D	3027
1028	1	3	A	3028
1029	1	3	A	3029
1030	1	3	D	3030
1031	1	4	E	3031
1032	1	4	B	3032
1033	1	4	A	3033
1034	1	4	D	3034
1035	1	4	A	3035
1036	1	4	E	3036
1037	1	4	C	3037
1038	1	4	D	3038
1039	1	4	C	3039
1040	1	4	D	3040
1041	1	4	A	3041
1042	1	4	B	3042
1043	1	4	D	3043
1044	1	4	B	3044
1045	1	4	E	3045
1046	1	4	B	3046
1047	1	4	A	3047
1048	1	4	E	3048
1049	1	4	C	3049
1050	1	4	C	3050
2001	2	2	G-F	4001

2002	2	2	G-F	4002
2003	2	2	G-F	4003
2004	2	2	F-G	4004
2005	2	2	F-G	4005
2006	2	2	G-F	4006
2007	2	2	F-G	4007
2008	2	2	F-G	4008
2009	2	2	F-G	4009
2010	2	2	G-F	4010

```
pdf(file = "SCR-004.randomization.schedule.pdf")
grid.table(paste0('The random generator seed was: ', myseed, '\n Tables by cohort in next page'))
grid::grid.newpage()
for(cohort in unique(randomizedscheduleLongwithrplcids$COHORT)){
  gridExtra::grid.table(randomizedscheduleLongwithrplcids %>% filter(COHORT==cohort),rows=NULL)
  grid::grid.newpage()
}
dev.off()

## png
## 2
```

A.5.4 Randomized summary table

```
pander(randomizedscheduleLong.summary,split.table=Inf)
```

PART	SEQ	1	2	3	4
1	A	1006, 1011, 1012		1018, 1028, 1029	1033, 1035, 1041, 1047
1	B	1002, 1004, 1005		1017, 1020, 1024	1032, 1042, 1044, 1046
1	C	1001, 1007, 1015		1016, 1023, 1025	1037, 1039, 1049, 1050
1	D	1003, 1010, 1014		1019, 1027, 1030	1034, 1038, 1040, 1043
1	E	1008, 1009, 1013		1021, 1022, 1026	1031, 1036, 1045, 1048
2	F-G		2004, 2005, 2007, 2008, 2009		
2	G-F		2001, 2002, 2003, 2006,		

2010

A.6 Appendix: technical information`sessionInfo()`

```
## R version 3.3.2 (2016-10-31)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 7 x64 (build 7601) Service Pack 1
##
## locale:
## [1] LC_COLLATE=English_United States.1252
## [2] LC_CTYPE=English_United States.1252
## [3] LC_MONETARY=English_United States.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United States.1252
##
## attached base packages:
## [1] stats      graphics  grDevices  utils      datasets  methods   base
##
## other attached packages:
## [1] gridExtra_2.2.1 forcats_0.1.1  pander_0.6.0  dplyr_0.5.0
## [5] purrr_0.2.2     readr_1.0.0    tidyr_0.6.0   tibble_1.2
## [9] ggplot2_2.2.0   tidyverse_1.0.0
##
## loaded via a namespace (and not attached):
## [1] Rcpp_0.12.7      knitr_1.14      magrittr_1.5    munsell_0.4
## [5] colorspace_1.2-7 R6_2.2.0        stringr_1.2.0   plyr_1.8.4
## [9] tools_3.3.2      grid_3.3.2      gtable_0.2.0    DBI_0.5-1
## [13] htmltools_0.3.5  yaml_2.1.13     lazyeval_0.2.0  assertthat_
## [17] digest_0.6.12    formatR_1.4     evaluate_0.10   rmarkdown_1
## [21] stringi_1.1.2    scales_0.4.1
```

B Step by step example of replacement algorithm

This is just an example of a potential but very unlikely scenario with more than 14 dropouts and with number of dropouts above 20% in at least 2 treatment sequences. In particular, this example shows how replacement will be done with 5 dropouts in the crossover part and 11 dropouts in the parallel part using the randomization schedule example above.

B.1 Replacement in crossover part

Potential snapshot of completers and dropouts after Period 1

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete		
2002	2	2	F-G	4002	Complete		
2003	2	2	F-G	4003	Dropout		
2004	2	2	F-G	4004	Dropout		
2005	2	2	F-G	4005	Complete		
2006	2	2	G-F	4006	Complete		
2007	2	2	G-F	4007	Dropout		
2008	2	2	G-F	4008	Dropout		
2009	2	2	G-F	4009	Dropout		
2010	2	2	G-F	4010	Complete		

B.1.1 Move RANDIDs from completers to the next period

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete	2001	
2002	2	2	F-G	4002	Complete	2002	
2003	2	2	F-G	4003	Dropout		
2004	2	2	F-G	4004	Dropout		
2005	2	2	F-G	4005	Complete	2005	
2006	2	2	G-F	4006	Complete	2006	
2007	2	2	G-F	4007	Dropout		
2008	2	2	G-F	4008	Dropout		
2009	2	2	G-F	4009	Dropout		
2010	2	2	G-F	4010	Complete	2010	

B.1.2 Replace dropouts

Add one (1) replacement (with lowest RANDID) at a time from each sequence until there are no more replacements to be done or we reach 4 replacements (whichever happens first)

B.1.2.1 Step 1: (replace 2003 from F-G with 4003)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete	2001	
2002	2	2	F-G	4002	Complete	2002	
2003	2	2	F-G	4003	Dropout	4003	
2004	2	2	F-G	4004	Dropout		
2005	2	2	F-G	4005	Complete	2005	
2006	2	2	G-F	4006	Complete	2006	
2007	2	2	G-F	4007	Dropout		
2008	2	2	G-F	4008	Dropout		
2009	2	2	G-F	4009	Dropout		
2010	2	2	G-F	4010	Complete	2010	

B.1.2.2 Step 2: (replace 2007 from G-F with 4007)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete	2001	
2002	2	2	F-G	4002	Complete	2002	
2003	2	2	F-G	4003	Dropout	4003	
2004	2	2	F-G	4004	Dropout		
2005	2	2	F-G	4005	Complete	2005	
2006	2	2	G-F	4006	Complete	2006	
2007	2	2	G-F	4007	Dropout	4007	
2008	2	2	G-F	4008	Dropout		
2009	2	2	G-F	4009	Dropout		
2010	2	2	G-F	4010	Complete	2010	

B.1.2.3 Step 3: (replace 2004 from F-G with 4004)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete	2001	
2002	2	2	F-G	4002	Complete	2002	

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

2003	2	2	F-G	4003	Dropout	4003
2004	2	2	F-G	4004	Dropout	4004
2005	2	2	F-G	4005	Complete	2005
2006	2	2	G-F	4006	Complete	2006
2007	2	2	G-F	4007	Dropout	4007
2008	2	2	G-F	4008	Dropout	
2009	2	2	G-F	4009	Dropout	
2010	2	2	G-F	4010	Complete	2010

B.1.2.4 Step 4: (replace 2008 from G-F with 4008)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Period 1	Period 2	Period 3
2001	2	2	F-G	4001	Complete	2001	
2002	2	2	F-G	4002	Complete	2002	
2003	2	2	F-G	4003	Dropout	4003	
2004	2	2	F-G	4004	Dropout	4004	
2005	2	2	F-G	4005	Complete	2005	
2006	2	2	G-F	4006	Complete	2006	
2007	2	2	G-F	4007	Dropout	4007	
2008	2	2	G-F	4008	Dropout	4008	
2009	2	2	G-F	4009	Dropout		
2010	2	2	G-F	4010	Complete	2010	

B.1.2.5 End (maximum number of replacements reached)

We have reached the maximum number of replacements (4) for the crossover part, thus we stop adding replacements (subject 2009 is not replaced)

B.2 Replacement in parallel part

Potential snapshot of completers and dropouts after Cohorts 1 and 3 finished.

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status
1001	1	1	A	3001	Complete
1002	1	1	A	3002	Dropout
1003	1	1	A	3003	Complete
1004	1	1	B	3004	Dropout
1005	1	1	B	3005	Complete
1006	1	1	B	3006	Complete
1007	1	1	C	3007	Dropout
1008	1	1	C	3008	Complete
1009	1	1	C	3009	Complete
1010	1	1	D	3010	Complete
1011	1	1	D	3011	Dropout
1012	1	1	D	3012	Complete
1013	1	1	E	3013	Complete
1014	1	1	E	3014	Dropout
1015	1	1	E	3015	Dropout
1016	1	3	A	3016	Complete
1017	1	3	A	3017	Complete
1018	1	3	A	3018	Dropout
1019	1	3	B	3019	Dropout
1020	1	3	B	3020	Complete
1021	1	3	B	3021	Complete
1022	1	3	C	3022	Complete
1023	1	3	C	3023	Complete
1024	1	3	C	3024	Dropout
1025	1	3	D	3025	Dropout
1026	1	3	D	3026	Complete
1027	1	3	D	3027	Complete
1028	1	3	E	3028	Dropout
1029	1	3	E	3029	Complete
1030	1	3	E	3030	Complete

Table of the 10 dropouts to be replaced:

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status
1002	1	1	A	3002	Dropout
1004	1	1	B	3004	Dropout
1007	1	1	C	3007	Dropout
1011	1	1	D	3011	Dropout
1014	1	1	E	3014	Dropout
1015	1	1	E	3015	Dropout
1018	1	3	A	3018	Dropout
1019	1	3	B	3019	Dropout
1024	1	3	C	3024	Dropout
1025	1	3	D	3025	Dropout
1028	1	3	E	3028	Dropout

B.2.1 Step 1: (replace subject 1014 from placebo)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	
1004	1	1	B	3004	Dropout	
1007	1	1	C	3007	Dropout	
1011	1	1	D	3011	Dropout	
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	

B.2.2 Step 2: (replace subject 1002 from ranolazine)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	
1007	1	1	C	3007	Dropout	
1011	1	1	D	3011	Dropout	

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	

B.2.3 Step 3: (replace subject 1004 from verapamil)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	
1011	1	1	D	3011	Dropout	
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	

B.2.4 Step 4: (replace subject 1011 from chloroquine)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1025	1	3	D	3025	Dropout
1028	1	3	E	3028	Dropout

B.2.5 Step 5: (replace subject 1007 from lopinavir+ritonavir)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	

B.2.6 Step 6: (replace subject 1028 from placebo)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	3028

B.2.7 Step 7: (replace subject 1018 from ranolazine)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
--------	------	--------	-----	------------	--------	-------------

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay
(CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	3018
1019	1	3	B	3019	Dropout	
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	3028

B.2.8 Step 8: (replace subject 1019 from verapamil)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	3018
1019	1	3	B	3019	Dropout	3019
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	
1028	1	3	E	3028	Dropout	3028

B.2.9 Step 9: (replace subject 1025 from chloroquine)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014

Statistical Analysis Plan**SCR-004: Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Clinical Phase 1 ECG Biomarker Validation Study**

1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	3018
1019	1	3	B	3019	Dropout	3019
1024	1	3	C	3024	Dropout	
1025	1	3	D	3025	Dropout	3025
1028	1	3	E	3028	Dropout	3028

B.2.10 Step 10: (replace subject 1024 from lopinavir+ritonavir)

RANDID	PART	COHORT	SEQ	REPLCMNTID	Status	Replacement
1002	1	1	A	3002	Dropout	3002
1004	1	1	B	3004	Dropout	3004
1007	1	1	C	3007	Dropout	3007
1011	1	1	D	3011	Dropout	3011
1014	1	1	E	3014	Dropout	3014
1015	1	1	E	3015	Dropout	
1018	1	3	A	3018	Dropout	3018
1019	1	3	B	3019	Dropout	3019
1024	1	3	C	3024	Dropout	3024
1025	1	3	D	3025	Dropout	3025
1028	1	3	E	3028	Dropout	3028

B.2.11 Step 11: End (maximum number of 14 replacements reached)

We have reached the maximum number of replacements (14) for the study, thus we stop adding replacements (subject 1015 is not replaced in this example)