The HARMONY Trial: Combined Ranolazine and Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism

Running title: Reiffel et al., The HARMONY Trial

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Abstract:

**Background** - Atrial fibrillation (AF) requires arrhythmogenic changes in atrial ion channels/receptors and usually altered atrial structure. AF is commonly treated with antiarrhythmic drugs (AADs); the most effective block many ion channels/receptors. Modest efficacy, intolerance, and safety concerns limit current AADs. We hypothesized that combining agents with multiple anti-AF mechanisms at reduced individual drug doses might produce synergistic efficacy plus better tolerance/safety.

**Methods and Results** - HARMONY tested mid-range ranolazine (750 mg BID) combined with two reduced dronedarone doses (150 mg BID and 225 mg BID) [chosen to reduce dronedarone’s negative inotropic effect – see text below] over 12 weeks in 134 patients with paroxysmal AF and implanted pacemakers where AF burden (AFB) could be continuously assessed. Patients were randomized double-blind to placebo, ranolazine alone (750 mg BID), dronedarone alone (225 mg BID), or one of the combinations. Neither placebo nor either drug alone significantly reduced AFB. Conversely, ranolazine 750 mg BID/dronedarone 225 mg BID reduced AFB by 59% vs placebo (p=0.008), while ranolazine 750 mg BID/dronedarone 150 mg BID reduced AFB by 43% (p=0.072). Both combinations were well tolerated.

**Conclusions** - HARMONY showed synergistic AFB reduction by moderate dose ranolazine plus reduced dose dronedarone, with good tolerance/safety, in the population enrolled.

**Clinical Trial Registration** - ClinicalTrials.gov; Unique Identifier: NCT01522651

**Key words:** atrial fibrillation, clinical trial, antiarrhythmic drug, drug trials, drug therapy, ranolazine, dronedarone, HARMONY
Introduction

Atrial fibrillation (AF) is increasing; thus, so are its consequences.\textsuperscript{1-5} Overall, AF patients have increased risk of mortality and thromboembolic events and are usually symptomatic with a reduced quality of life (QoL).\textsuperscript{2-9} Although AF ablation is growing, antiarrhythmic drugs (AAD) are typically utilized as first-line treatment for rhythm management in most patients.\textsuperscript{4-9}

Inhibition of ion currents involved in AF initiation/maintenance as well as mechanisms by which AF can “beget” AF\textsuperscript{10-12} represent plausible mechanism-based approaches to treatment.\textsuperscript{4,9,13,14}

Many AADs used for AF inhibit multiple ion channels/receptors so as to both reduce diverse contributors to AF initiation and progression and diminish repolarization reserve. Unfortunately, current AAD have limited efficacy and/or poor safety/tolerability.\textsuperscript{4,9} Many adverse effects (AEs) are dose-related. An alternative to single, multichannel-blocking drugs could be combining two drugs with complementary electrophysiologic properties. Each might be effective at lower doses than when used alone, potentially increasing the safety and tolerability of therapy. This concept is not new\textsuperscript{15,18} but using a fixed dose combination as reported herein is.

Dronedarone (available only as 400 mg) has modestly reduced AF in several multicenter trials.\textsuperscript{19-22} However, dronedarone’s contraindicated with advanced heart failure (HF) due at least in part to negative inotropism from block of L-type Ca\textsuperscript{2+} channels\textsuperscript{19,20,23,24} [which is concentration-dependent (Gilead Sciences, data on file)]. Lower doses should be less cardiodepressant. Similarly ranolazine (at doses of 500 - 1000 mg BID) also appears modestly effective for AF.\textsuperscript{25-28}

We hypothesized that moderate dose ranolazine combined with reduced dose dronedarone would be superior to individual drug therapy in suppressing AF – which we tested in our PHase 2, Proof of Concept, Randomized, Placebo-Controlled, PArallel Study to Evaluate
the Effect of Ranolazine and Dronedarone When Given Alone and in Combination On Atrial Fibrillation Burden in Subjects with Paroxysmal Atrial Fibrillation study, HARMONY, as described below.

Methods

HARMONY was a randomized, double-blind, placebo-controlled, parallel-group study conducted in accordance with the Declaration of Helsinki at 47 U.S., Poland, Germany, Israel, Italy, and the Netherlands centers. Institutional Review Boards or Research Ethics Boards approved the study at each. Patients gave written informed consent. The sponsor, Gilead Sciences, and the Scientific Committee (this manuscript’s authors) designed the study. Data collection, management, and statistical analysis were performed by the sponsor. The data were reviewed and the manuscript was written by the Scientific Committee, who vouch for the accuracy/completeness of the data.

Study Population

HARMONY enrolled patients with both (1) paroxysmal AF (PAF) and (2) dual-chamber programmable pacemakers implanted for standard clinical indications within 3 months prior to screening. The implanted device had to have atrial arrhythmia detection algorithms and the capacity to store intracardiac electrograms (EGMs). Only devices with comparable atrial arrhythmia diagnostic algorithms were allowed. Arrhythmia detection parameters and established sensitivity levels could not be altered during the study. PAF had to be electrocardiographically documented within 12 months pre-enrollment. Recognizing that cardioversion for symptoms earlier than after 7 days of continuous AF (a definition used for persistent AF), prior cardioversion was allowed so long as it was at least 4 weeks before Screening and the current diagnosis remained PAF.
HARMONY was divided into an initial 4-week Run-in period followed by a 12-week Treatment period. AF burden (AFB) (the total time a patient is in AF expressed as a percentage of total recording time) from the Run-in period qualified a patient for randomization and served as baseline. AFB from the Treatment period provided the primary endpoint. Only patients with AFB of ≥1% and ≤70% between the most recent clinic evaluation and the Screening visit (minimum of 1 month observation) could enter the Run-in period. Patients with an AFB of ≥2% and ≤70% during the Run-in period were randomized.

Major exclusion criteria included: (a) persistent/permanent AF; (b) New York Heart Association class III or IV HF, lesser HF with recent (≤1 month) decompensation, left ventricular ejection fraction <40%; (c) unstable angina, myocardial infarction, or coronary surgery within 3 or coronary angioplasty within 1 month of screening; (d) any prior serious ventricular arrhythmias or a family/personal history of QT prolongation; (e) ablation procedures within 4 months of screening or currently planned; (f) cardioversion within 1 month of screening; (g) concomitant digoxin or dabigatran (based on concerns from PALLAS 24) or any concomitant AAD (AAD washout prior to the Run-in period was allowed); and (h) prior use of ranolazine or dronedarone ≤2 months before Screening.

**Study Design and Procedures**

Qualifying AFB from the Run-in period allowed randomization 1:1:1:1:1 to one of 5 parallel treatment arms: Group 1 (ranolazine placebo plus dronedarone placebo); Group 2 (ranolazine 750 mg plus dronedarone placebo); Group 3 (ranolazine placebo plus dronedarone 225 mg); Group 4 (ranolazine 750 mg plus dronedarone 150 mg); and Group 5 (ranolazine 750 mg plus dronedarone 225 mg) -- each given BID for 12 weeks. Randomization was stratified by the Run-in period AFB (<15% and ≥15%).
Pacemakers were interrogated monthly. Reports of AF (including EGMs) were downloaded/adjudicated at the University of Rochester EP Core laboratory. Monthly visits also included vital signs; 12-lead ECG; clinical laboratory tests; AEs; concomitant medications; and a symptom diary (date and time of onset only, but not type or duration or effect on any QoL score). A safety Follow-up Visit occurred 14 days after dosing completion.

Endpoints

The primary endpoint was AFB over 12 treatment weeks (both absolute and percent change from baseline) analyzed by modified intention-to-treat (mITT) using log-transformed values (which estimate the effect of treatment as a percent change in AFB). Secondary endpoints included change from baseline in AFB for each visit period; percentage of patients with ≥30% and ≥50% reduction from baseline in AFB (≥70% reduction in AFB was added post hoc); and ventricular rate during AF recurrences.

Statistical Analyses

Baseline demographic characteristics, cardiovascular (CV) history, and medications were summarized by treatment regimen for all dosed patients (N=131). Efficacies of the 5 treatment regimens on AFB over the 12-week treatment period were compared by log-transforming baseline (Run-in) AFB and AFB over 12 weeks (after setting values < 1% to 1%) and fitting an equal-slopes analysis of covariance model (with transformed baseline AFB as the covariate) using SAS procedure MIXED (SAS Institute Inc. 2008. SAS/STAT® 9.2 User’s Guide. Cary, NC: SAS Institute Inc.). The overall F-test of equality across the 5 regimens was followed by all pairwise comparisons (with no further adjustment for multiple comparisons, and log-scale point estimates, SEs, and 95% confidence intervals for treatment differences were back-transformed to yield treatment percent difference point estimates, delta-method SEs, and confidence intervals.
AFB was summarized for the full analysis set, defined as all dosed patients with at least 14 days of AFB data obtained for both the baseline period and post-baseline (N=120); the primary analysis of AFB over 12 weeks was further restricted to patients with at least 10 weeks of post-baseline data (N=101). Also, AFB and secondary endpoints were summarized for the per-protocol analysis set, defined as all full analysis set patients with ≥80% adherence for both BID ranolazine/placebo tablets and BID dronedarone/placebo capsules (N=96).

Safety data were summarized by treatment regimen for all dosed patients; AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1, and medications (prior and concomitant) were coded using the World Health Organization (WHO) Drug Dictionary (Q2 2013).

Results

Study Population

Of 327 screened patients, 134 were randomized (Figure 1). Screen failures were mostly due to AFB out of the pre-specified range (n=105) or withdrawal of consent (n=41). Baseline characteristics and CV history (Table 1) were relatively well balanced considering the small sized groups. Median durations of study treatment exposure were 85 days in all 5 groups; maximum durations ranged from 90 to 102 days.

Change from Baseline in AFB over 12 Weeks

At baseline, mean AFB was 17.4% (range 2% -72%). Thirty four percent had AFB ≥20%; 11% had ≥40%, and median duration of AF episodes was 2.1 hours across all groups. Over 12 treatment weeks, AFB was reduced by ranolazine 750 mg plus dronedarone 225 mg BID versus placebo (p=0.008), dronedarone 225 mg BID alone (p=0.002), or ranolazine 750 mg BID alone (p=0.049) (Figure 2 and Table 2). A trend towards AFB reduction was also present with
ranolazine 750 mg plus dronedarone 150 mg BID (p=0.072 versus placebo). No significant reduction versus placebo occurred with either drug alone (p ≥ 0.49). On the log scale, the sum of the estimated effects of the individual drugs was numerically less than the estimated effect of ranolazine 750 mg plus dronedarone 225 mg BID, indicating synergy (p=0.11, 2-sided test). Over 12 treatment weeks, 45% (9/20) of patients taking ranolazine 750 mg plus dronedarone 225 mg BID had ≥70% AFB reduction from baseline, versus 11% with placebo (2/18) (Figure 3A). Concordantly, an increase in AFB from baseline occurred in 61% given placebo, versus 20% taking ranolazine 750 mg plus dronedarone 225 mg BID (Figure 3B). One patient in each of these groups had no change in AFB during study. In both combination groups, much of the AFB reduction was attained by 4 weeks and then maintained during continued treatment (Table 3).

Over the 12 treatment weeks, maximum ventricular rate during recurrent AF decreased by 12 - 13 bpm in the combination groups and by 9 bpm in the dronedarone 225 mg BID group. Small increases (8 and 6 bpm) were observed with placebo and ranolazine 750 mg BID alone respectively (F-test p=0.003) (Table 4). A decrease in frequency and/or duration of AF recurrences was noted in all groups, which contributed to decreased AFB. The numbers were too small to meaningfully assess these components separately across groups. However, the largest numerical effect on these two components was with ranolazine 750 mg plus dronedarone 225 mg BID.

No group differences occurred in development of persistent AF; cardioversions; percentage of subjects with total duration of AF ≥ 5.5 hours per day at any point during treatment (small in all groups); or percentage of atrial or ventricular pacing. Of 106 patients in the full analysis set for whom symptom diary data were obtained for the Run-in period (baseline), 76 reported having symptoms on at least 1 day, and mean (median) proportion of days was 23%
(13%). Neither symptom incidence nor mean proportion of diary-reported days with symptoms were different across treatment groups; however, we could not correlate symptoms with the actual AF episodes due to only partial data available on timing of symptoms and/or AF episodes.

**Safety**

**Adverse Events**

The incidence of treatment-emergent (TE) AEs, serious (S) AEs, and AEs leading to discontinuation reported for ranolazine 750 mg BID plus dronedarone 225 mg BID was comparable with each drug’s alone (Table 5). These events were generally mild/moderate and resolved without sequelae. No patient died. Out of FDA custom, episodes of AF recurrence were included among AEs. The most frequently reported TEAE across all treatment groups (>5% patients total) were AF recurrence, dizziness, constipation, INR increase, and nausea. The most frequent reported TEAE for each treatment group (≥3 patients/group) are presented in Table 5.

**Vital Signs, 12-Lead ECGs, and Laboratory Values**

Vital signs remained stable throughout the study in all groups, without significant changes from baseline (Table 6). ECG parameter changes from baseline to Week 12 were assessed for the small numbers of patients not excluded from this analysis due to AF, bundle branch block, or paced rhythm. Both combination therapies appeared to prolong mean PR interval slightly more than the other treatment groups, and slightly decrease mean sinus rate (4 to 5 beats per minute) without affecting QRS, QTcB, and QTcF intervals (Table 6). There were no clinically significant trends or persistent changes for any laboratory parameter except mean blood creatinine levels which increased slightly during treatment by 0.1 mg/dl compared to baseline in all treatment groups and returned to baseline values by the 14 day follow up visit (an expected finding for both ranolazine and dronedarone due to their inhibition of renal tubular secretion of creatinine).
Discussion

AF treatment, aside from anticoagulation, targets rate and/or rhythm control.\textsuperscript{6-9} For the latter, individual AAD efficacy has varied from around 40\% to 70\% (with occasional outliers)\textsuperscript{29-33} depending in large part upon AF characteristics, prior AAD experience, dose(s) tried, type/severity of heart disease, efficacy definitions, endpoints, and more.\textsuperscript{9,34,35} Even when efficacious, intolerance or toxicity has been limiting. Herein lies the appeal of HARMONY’s results.

Dronedarone (400 mg BID) is approved for AF. In its pivotal EURIDIS and ADONIS trials\textsuperscript{21} dronedarone reduced AF modestly but significantly (from about 75\% to about 62\%; hazard ratio reduction about 25\%). In part this may be due to the nature of the population; many patients had failed prior AAD regimens [data published in abstract only: Singh BN et al. Circulation 2006; 114 (suppl 2): II-70]. In ATHENA,\textsuperscript{22} dronedarone reduced CV hospitalizations (mainly AF-related) in an older population with moderate co-morbid disease other than NYHA class IV HF. In contrast, in ANDROMEDA and PALLAS\textsuperscript{23,24} dronedarone increased mortality in patients with recent or prior severe HF. Likely contributing factors included LV depression from its L-type Ca\textsuperscript{2+} channel blocking properties\textsuperscript{19-24} and proarrhythmic dronedarone-digoxin interactions\textsuperscript{20}. As dronedarone’s block of L-type Ca\textsuperscript{2+} channels is concentration-dependent, lower doses, as used in HARMONY, should be less cardiodepressant.

Ranolazine is only approved for chronic stable angina. However, preclinical studies\textsuperscript{26,36-42} indicate it can suppress atrial arrhythmia triggers and AF, even in the settings of HF and atrial stretch\textsuperscript{39,40} Moreover, multiple reports (none large multicenter) indicate ranolazine (500-1000 mg BID) can terminate recent onset AF, reduce PAF recurrence; and possibly reduce late AF recurrences after cardioversion.\textsuperscript{25,27,43} As no trial has directly compared ranolazine against an
active control, the relative potency of ranolazine for such effects versus other AADs is unknown.

In atrial myocytes, ranolazine inhibits late inward sodium currents (I_{Na}), and the rapidly activating delayed rectifier potassium current (I_{Kr}). Late I_{Na} inhibition decreases cellular Na\(^+\) and Ca\(^{2+}\) loading and occurrences of early and delayed afterdepolarizations (i.e., arrhythmia triggers)\(^4^4\). In atrial but not ventricular tissue, and at fast drive rates, ranolazine also reduces peak I_{Na} and V_{max} of the action potential upstroke\(^4^1\). Complementing these effects, dronedarone inhibits the acetylcholine-dependent inward rectifying potassium current (I_{K-ACh}), I_{Kr}, peak I_{Na}, and L-type Ca\(^{2+}\) current\(^4^5\). The atrial-selective reduction of peak I_{Na} combined with the effects of both drugs to reduce I_{Kr} alters atrial conduction, slows atrial repolarization, prolongs atrial effective refractory period, and causes significant post-repolarization refractoriness in atrial myocardium, these should impair reentry.

In preclinical studies, ranolazine plus dronedarone significantly reduced atrial arrhythmias with greater rates of AF termination and lower rates of AF reinduction in sensitive models than the arithmetic sum of the effect caused by the drugs individually\(^4^6-4^7\). Such results indicate ranolazine’s effectiveness to prevent initiation and maintenance of AF is increased by dronedarone, and vice versa\(^4^6-4^8\). Importantly, this synergism occurred with dronedarone plasma concentrations below those reached by its approved 400 mg BID dose (MULTAQ\(^\oplus\)). Lower concentrations of dronedarone (below those causing L-type calcium channel block), as used in HARMONY, did not reduce cardiac contractility in an experimental model (Gilead Sciences, data on file).

The effect of either ranolazine or dronedarone to reduce peak I_{Na} and thereby slow conduction velocity is normally small. But the effects of both drugs increase as rate increases. Similarly, the reduction of peak I_{Na} with either drug is increased when early sodium channel
availability is reduced by myocyte depolarization. As atrial myocytes are relatively depolarized compared to ventricular myocytes, block of peak $I_{Na}^+$ by both ranolazine and dronedarone is greatest in the atria.

Given our disappointment in current AADs and the preclinical evidence for anti-AF synergism of ranolazine and dronedarone, we performed HARMONY. Importantly, the robustness of the continuous monitoring we used allowed us to perform our evaluation with a relatively small sample size. Continuous monitoring with implanted devices is believed to be the most rigorous, complete approach to assessing AFB. Based on the pre-clinical synergism of ranolazine plus dronedarone on atrial parameters, we hypothesized that ranolazine (750 mg BID) combined with reduced doses of dronedarone could enhance efficacy and tolerance/safety versus dronedarone 400 mg BID alone. Doses of 150 and 225 mg dronedarone were chosen in order to achieve exposures of ~25% and ~50% of the exposure of dronedarone 400 mg, and not significantly inhibit the L-type calcium channel (a component of dronedarone’s risk in HF).

In HARMONY, consistent with preclinical observations, ranolazine 750 mg plus dronedarone 225 mg BID significantly reduced AFB (and modestly slowed ventricular rate). No reduction was observed with dronedarone 225 mg BID alone; only a modest, nonsignificant reduction was observed with ranolazine 750 mg BID alone (Figures 2 and 3). Moreover, the arithmetic sum of the effect of ranolazine 750 mg plus dronedarone 225 mg BID exceeded either drug’s alone (Figures 2, 3). Reduced AFB resulted from both a decrease in frequency and/or duration of recurrent AF, usually both. These results were evident within 4 weeks (Table 3), rather than having a delayed efficacy pattern (such as with amiodarone). Moreover, AFB increased in 61% given placebo, suggesting that the ranolazine-dronedarone combination can not only reduce AFB but may also alter its progression, consistent with “sinus rhythm begetting
sinus rhythm”. Also, the 225 mg BID dose of dronedarone (lower than any studied in dronedarone’s dose-ranging DAFNE trial49) appeared ineffective re: reducing AFB. This is a new dronedarone dose-related observation. Importantly, accompanying the ranolazine/dronedarone synergism, there were no significant adverse signals with respect to safety/tolerance.

Limitations

HARMONY’s important limitations: First, only PAF patients with implanted PPMs were enrolled. Although HARMONY has the important advantage of continuous monitoring, rather than intermittent AF assessment as used in most AAD trials, its population may represent only PAF patients specifically, and only those whose mechanism may be linked to sinus node or cardiac conduction disease. HARMONY cannot assure similar outcomes in patients with more diverse types and mechanisms of AF nor in patients with more advanced myocardial dysfunction. Second, the small number of patients in each arm ruled out exploratory subgroup analysis. Third, HARMONY did not study the effects of full dose dronedarone (400 mg BID) or ranolazine (1000 mg BID). Hence HARMONY cannot provide direct evidence of better efficacy or safety versus peak dose of the individual agents. However, for reasons discussed earlier, we would expect the tolerance/safety profile, and likely the efficacy, of the combination to be superior to that of the individual agents alone, even in a broader group of patients.

Conclusions

HARMONY showed moderate dose ranolazine combined with reduced dose dronedarone can decrease AFB yet maintain good tolerance/safety in the population enrolled. This profile appears to offer promise for AF patients and suggests that the concept of combining two AADs with complementary ion channel blocking properties is worthy of testing in a larger, more patient-
diverse population.

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Appendix:
Investigators who randomized patients (listed by country and in descending order of the number of randomized patients). Contributors particularly important to the trial beyond simply the number of patients enrolled are noted in bold.


Conflict of Interest Disclosures: James A. Reiffel, A. John Camm; and Peter Kowey have been paid consultants for Sanofi and for Gilead Sciences, Inc in matters directly relating to the development of dronedarone and ranolazine. Wojciech Zareba and Spencer Rosero have received research grants from Gilead Sciences, Inc. Luiz Belardinelli, Dewan Zeng, Ewa Karwatowska-Prokopczuk and Ann Olmsted are employees of Gilead Sciences, Inc.
References:


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Table 1: Baseline Patient Characteristics (all dosed patients)

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<th></th>
<th>PL N=26</th>
<th>D225 N=26</th>
<th>R750 N=26</th>
<th>RD150 N=26</th>
<th>RD225 N=27</th>
<th>All N=131</th>
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<td><strong>Age (yrs) mean (SD)</strong></td>
<td>72 (8.4)</td>
<td>75 (7.8)</td>
<td>70 (10.8)</td>
<td>73 (9.4)</td>
<td>71 (7.1)</td>
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<tr>
<td><strong>Male</strong></td>
<td>13 (50)</td>
<td>10 (39)</td>
<td>10 (39)</td>
<td>15 (58)</td>
<td>15 (56)</td>
<td>63 (48)</td>
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<td><strong>AF prior duration (yrs) mean (median)</strong></td>
<td>4.2 (2.6)</td>
<td>7.0 (3.6)</td>
<td>5.1 (3.1)</td>
<td>4.1 (2.5)</td>
<td>4.7 (2.8)</td>
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<td><strong>Sinus node dysfunction</strong></td>
<td>12 (46)</td>
<td>18 (69)</td>
<td>16 (62)</td>
<td>19 (73)</td>
<td>21 (78)</td>
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<td><strong>AV Block (2nd or 3rd degree)</strong></td>
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<td>3 (12)</td>
<td>3 (12)</td>
<td>7 (27)</td>
<td>2 (7)</td>
<td>26 (20)</td>
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<td><strong>Hypertension</strong></td>
<td>20 (77)</td>
<td>22/25 (88)</td>
<td>24 (92)</td>
<td>22 (85)</td>
<td>22 (82)</td>
<td>110/130 (85)</td>
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<td><strong>Heart failure</strong></td>
<td>7 (27)</td>
<td>3 (11)</td>
<td>6 (23)</td>
<td>3 (11)</td>
<td>5 (18)</td>
<td>24 (18)</td>
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<tr>
<td><strong>LV EF % mean (SD)</strong></td>
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<td>59 (8)</td>
<td>57 (10)</td>
<td>57 (8)</td>
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<td><strong>CAD</strong></td>
<td>8 (31)</td>
<td>10/25 (40)</td>
<td>7/25 (28)</td>
<td>9/24 (38)</td>
<td>8/26 (31)</td>
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<td><strong>Diabetes</strong></td>
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<td>7 (27)</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>8 (30)</td>
<td>31 (24)</td>
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<td>9 (35)</td>
<td>9 (35)</td>
<td>12/26 (46)</td>
<td>43/129 (33)</td>
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<td><strong>Beta-blockers</strong></td>
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<td>9 (35)</td>
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<td>127 (97)</td>
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<td>2 (8)</td>
<td>1 (4)</td>
<td>9 (7)</td>
</tr>
<tr>
<td><strong>Anti-platelets</strong></td>
<td>13 (50)</td>
<td>7 (27)</td>
<td>14 (54)</td>
<td>11 (42)</td>
<td>10 (37)</td>
<td>55 (42)</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>20 (77)</td>
<td>18 (69)</td>
<td>17 (65)</td>
<td>19 (73)</td>
<td>19 (70)</td>
<td>93 (71)</td>
</tr>
<tr>
<td><strong>ACE-I</strong></td>
<td>9 (35)</td>
<td>15 (58)</td>
<td>15 (58)</td>
<td>14 (54)</td>
<td>14 (52)</td>
<td>67 (51)</td>
</tr>
<tr>
<td><strong>Any prior AAD</strong></td>
<td>11 (42)</td>
<td>16 (62)</td>
<td>12 (46)</td>
<td>5 (19)</td>
<td>13 (48)</td>
<td>57 (44)</td>
</tr>
</tbody>
</table>

PL: placebo, Dron 225: dronedarone 225 mg BID, Ran 750: ranolazine 750 mg BID, R750/D150: ranolazine 750 mg plus dronedarone 150 mg BID, R750/D225: ranolazine 750 mg plus dronedarone 225 mg BID, AF: atrial fibrillation, AV: atrio-ventricular, LVEF: left ventricular ejection fraction, CAD: coronary artery disease, NOACs: novel oral anticoagulants, AAD: antiarrhythmic drug
Table 2: Atrial Fibrillation Burden over 12 Weeks (full analysis set)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Statistic</th>
<th>PL (N=18)</th>
<th>D225 (N=23)</th>
<th>R750 (N=18)</th>
<th>RD150 (N=22)</th>
<th>RD225 (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>GM</td>
<td>12.7</td>
<td>11.6</td>
<td>10.8</td>
<td>11.7</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>2.2</td>
<td>2.5</td>
<td>2.7</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Over 12 Weeks</td>
<td>GM, Baseline-Adjusted</td>
<td>11.1</td>
<td>12.1</td>
<td>8.9</td>
<td>6.4</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>2.5</td>
<td>2.4</td>
<td>2.0</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>% Diff vs PL</td>
<td></td>
<td>9</td>
<td>-20</td>
<td>-43</td>
<td>-57</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td></td>
<td>-40 to 98</td>
<td>-58 to 52</td>
<td>-69 to 5</td>
<td>-77 to -20</td>
</tr>
<tr>
<td></td>
<td>Pairwise Comparison</td>
<td>P-Value (vs PL)</td>
<td></td>
<td>0.78</td>
<td>0.49</td>
<td>0.072</td>
</tr>
</tbody>
</table>

CI: confidence interval; Diff: difference; GM: geometric mean; SE: standard error; vs: versus. Overall AFB GM (SE) at baseline was 11.7% (1.1%). Pairwise comparison p-values obtained by fitting analysis of covariance model (equal slopes model with baseline value as the covariate) to log-transformed AFB. AFB values < 1% (> 99%) were set to 1% (99%) before transformation; GMs and SEs obtained by back-transforming. Overall F-test p-value for testing equality of baseline-adjusted GMs across treatment groups was 0.012.
Table 3: Mean Atrial Fibrillation Burden over Time (full analysis set)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>PL</th>
<th>D225</th>
<th>R750</th>
<th>R750/D150</th>
<th>R750/D225</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline AFB (%)</td>
<td>13.2 (2.1)</td>
<td>12.4 (2.7)</td>
<td>10.4 (2.2)</td>
<td>12.6 (2.1)</td>
<td>12.1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>N=21</td>
<td>N=24</td>
<td>N=24</td>
<td>N=24</td>
<td>N=25</td>
</tr>
<tr>
<td>Week 1-4 AFB (%)</td>
<td>12.7 (2.7)</td>
<td>10.9 (2.1)</td>
<td>8.1 (1.6)</td>
<td>6.9 (1.3)</td>
<td>5.3 (1.0)</td>
</tr>
<tr>
<td></td>
<td>N=21</td>
<td>N=24</td>
<td>N=24</td>
<td>N=24</td>
<td>N=25</td>
</tr>
<tr>
<td>Week 5-8 AFB (%)</td>
<td>9.1 (2.2)</td>
<td>10.8 (2.3)</td>
<td>7.5 (1.7)</td>
<td>6.3 (1.4)</td>
<td>5.2 (1.2)</td>
</tr>
<tr>
<td></td>
<td>N=19</td>
<td>N=24</td>
<td>N=22</td>
<td>N=23</td>
<td>N=20</td>
</tr>
<tr>
<td>Week 9-12 AFB (%)</td>
<td>11.0 (3.1)</td>
<td>11.5 (2.9)</td>
<td>8.2 (2.4)</td>
<td>5.4 (1.4)</td>
<td>4.2 (1.2)</td>
</tr>
<tr>
<td></td>
<td>N=18</td>
<td>N=23</td>
<td>N=18</td>
<td>N=22</td>
<td>N=20</td>
</tr>
</tbody>
</table>
Table 4: Maximum Ventricular Rate During AF Episodes over 12 Weeks

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bpm Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>124 (27)</td>
<td>138 (29)</td>
<td>119 (33)</td>
<td>147 (37)</td>
<td>135 (30)</td>
<td></td>
</tr>
<tr>
<td>Over 12 weeks</td>
<td>132 (34)</td>
<td>128 (30)</td>
<td>125 (27)</td>
<td>133 (29)</td>
<td>123 (22)</td>
<td></td>
</tr>
<tr>
<td>Change from</td>
<td>8 (13)</td>
<td>-9 (15)</td>
<td>6 (13)</td>
<td>-13 (16)</td>
<td>-12 (23)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline at Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p value F-test for testing equality of baseline adjusted means across treatment groups*
Table 5: Summary of Treatment Emergent Adverse Events (TEAE)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with Any TEAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>15 (58)</td>
<td>18 (69)</td>
<td>17 (65)</td>
<td>16 (62)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>7 (27)</td>
<td>1 (4)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>3 (12)</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>5 (19)</td>
<td>5 (19)</td>
</tr>
<tr>
<td><strong>Most Frequently Reported TEAE (≥3 patients in any group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (8)</td>
<td>4 (15)</td>
<td>3 (12)</td>
<td>3 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>4 (15)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (4)</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>3 (12)</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>0</td>
<td>3 (12)</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>0</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>3 (11)</td>
</tr>
</tbody>
</table>
Table 6: Changes from Baseline in Vital Signs and 12-lead ECG Intervals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>0 ± 2</td>
<td>3 ± 3</td>
<td>0 ± 5</td>
<td>1 ± 4</td>
<td>0± 2</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>0 ± 3</td>
<td>0 ± 3</td>
<td>4 ± 6</td>
<td>3 ± 3</td>
<td>-3 ± 3</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>-2 ± 2</td>
<td>0 ± 2</td>
<td>1 ± 3</td>
<td>0 ± 2</td>
<td>-2 ± 2</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR msec (msec)</td>
<td>9 ± 12</td>
<td>0 ± 8</td>
<td>7 ± 12</td>
<td>26 ± 19</td>
<td>18 ± 12</td>
</tr>
<tr>
<td>QRS msec (msec)</td>
<td>-2 ± 1</td>
<td>6 ± 3</td>
<td>-4 ± 6</td>
<td>-13 ± 10</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>QTc msec (Bazett)</td>
<td>3 ± 14</td>
<td>7 ± 5</td>
<td>-6 ± 12</td>
<td>-13 ± 14</td>
<td>1 ± 10</td>
</tr>
<tr>
<td>QTc msec (Fridericia)</td>
<td>3 ± 14</td>
<td>6 ± 4</td>
<td>-8 ± 11</td>
<td>-8 ± 12</td>
<td>6 ± 8</td>
</tr>
<tr>
<td>Ventricular rate (bpm)</td>
<td>-1 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>-4 ± 4</td>
<td>-5 ± 3</td>
</tr>
</tbody>
</table>

bpm = beats per minute;
*N number of patients with ECG parameters measured during spontaneous sinus rhythm.
Figure Legends:

Figure 1: Disposition of Patients in each treatment group.
*Randomized but not dosed, randomized in error (n=2); withdrew consent (n=1).
†Other: withdrew consent, protocol violation, noncompliance, unblinded in error.
Abbreviations: PL = placebo, Dron 225 = dronedarone 225 mg BID, Ran 750 = ranolazine 750 mg BID, R750/D150 = ranolazine 750 mg plus dronedarone 150 mg BID, R750/D225 = ranolazine 750 mg plus dronedarone 225 mg BID.

Figure 2: Mean % Change from Baseline in AFB over 12 Weeks. Pairwise comparison p-values obtained by fitting analysis of covariance model (equal-slopes model with baseline value as the covariate) to log-transformed AFB. AFB values <1% (>99%) were set to 1% (99%) before transformation. The geometric mean percent changes from baseline (SEs) shown, obtained by back-transforming, are -5.9(18.0), 3.5(15.7), -23.0(21.2), -45.5(10.7), and -59.1(10.5) for the PL, D225, R750, R750/D150, and R750/D225 groups, respectively.
See Figure 1 for Abbreviations.

Figure 3: A. Patients with ≥70% Reduction in AFB over 12 Weeks B. Overall change in AFB over 12 weeks
P=0.044 (Fisher exact test for equality of rates across the 5 treatment groups).
See Figure 1 for Abbreviations.
Patients screened
n=327

Majority did not meet the inclusion criteria for AFB

Patients randomized
n=134

Patients dosed
n=131 *

Placebo (n=26)
n=17 completed study

Dron225 (n=26)
n=22 completed study

Ran 750 (n=26)
n=19 completed study

R750/D150 (n=26)
n=21 completed study

R750/D225 (n=27)
n=20 completed study

Withdrawal reasons

n=3 AE(s)
n=1 cardioversion
n=5 other †

n=4 AE(s)

n=4 AE (s)
n=3 other †

n=4 AE (s)
n=1 other †

n=5 AE (s)
n=2 other †
A. ≥70% Reduction in AF Burden

B. Overall Reduction in AF Burden
The HARMONY Trial: Combined Ranolazine and Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism

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