Atrial fibrillation (AF) is increasing; so are its consequences. Overall, AF patients have increased risk of mortality and thromboembolic events and are usually symptomatic with a reduced quality of life. Although AF ablation is growing, antiarrhythmic drugs (AAD) are typically used as first-line treatment for rhythm management in most patients. Inhibition of ion currents involved in AF initiation and progression and diminished repolarization channels/receptors so as to both reduce diverse contributors to AF initiation and progression and diminish repolarization reserve. Unfortunately, current AAD have limited efficacy or poor safety/tolerability. Many adverse effects (AEs) are dose related. An alternative to single, multichannel-blocking drugs could be combining 2 drugs with complementary electrophysiological 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, but using a fixed dose combination as reported herein is.

Dronedarone (available only as 400 mg) has modestly reduced AF in several multicenter trials. However, dronedarones contraindicated with advanced heart failure (HF) due at least in part to negative inotropism from block of L-type Ca^{2+} channels, 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 seems modestly effective for AF.

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 later.
WHAT IS KNOWN

• Antiarrhythmic therapies for atrial fibrillation (AF), including antiarrhythmic drugs (AAD), are limited by only modest efficacy and frequently by adverse effects (which are usually dose-related if not idiosyncratic).

• Fixed dose AAD combinations have never been studied for human AF; however, preclinical studies suggest that ranolazine combined with dronedarone can enhance efficacy for AF synergistically—that is, beyond the effect of either agent alone.

WHAT THE STUDY ADDS

• The HARMONY trial studied the efficacy and safety/tolerance of ranolazine plus dronedarone on AF burden (AFB) using fixed dose combinations where each dose selected was lower than the standard maximal doses typically used for each drug alone, in patients with paroxysmal AF where atrial fibrillation burden was determined from implanted devices capable of continuous rhythm monitoring and verification.

• In HARMONY, the combination of ranolazine and dronedarone, particularly in doses of 750 mg plus 225 mg respectively, given bid, showed substantial and synergistic efficacy in reducing AFB—compared to placebo, ranolazine alone, or dronedarone alone—with good tolerance and no adverse safety signals.

• If these observations are confirmed in a larger more diverse AF population, the pharmacological management of AF could be substantially enhanced.

Methods

HARMONY was a randomized, double-blind, placebo-controlled, parallel-group study conducted in accordance with the Declaration of Helsinki at 47 US, 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 article’s authors) designed the study. Data collection, management, and statistical analysis were performed by the sponsor. The data were reviewed, and the article 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 before screening. The implanted device had to have atrial arrhythmia detection algorithms and the capacity to store intracardiac electrograms. Only devices with comparable atrial arrhythmia diagnostic algorithms were allowed. Arrhythmia detection parameters and established sensitivity levels could not be altered during the study. PACD had to be electrocardiographically documented within 12 months before enrollment. Recognizing that cardioversion may be performed 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 end point. Only patients with AFB of ≥21% 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 ≥22% and ≤70% during the run-in period were randomized. Major exclusion criteria included (1) persistent/permanent AF; (2) New York Heart Association class III or IV HF, lesser HF with recent (≤1 month) decompensation, and left ventricular ejection fraction <40%; (3) unstable angina, myocardial infarction, or coronary surgery within 3 or coronary angioplasty within 1 month of screening; (4) any prior serious ventricular arrhythmias or a family/personal history of QT prolongation; (5) ablation procedures within 4 months of screening or currently planned; (6) cardioversion within 1 month of screening; (7) concomitant digoxin or dabigatran (based on concerns from the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy [PALLAS]) or any concomitant AAD (AAD washout before the run-in period was allowed); and (8) 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 electrograms) 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 quality of life score). A safety follow-up visit occurred 14 days after dosing completion.

End Points

The primary end point was AFB over 12 treatment weeks (both absolute and percent change from baseline) analyzed by modified intention-to-treat using log-transformed values (which estimate the effect of treatment as a percent change in AFB). Secondary end points included change from baseline in AFB for each visit period; percent-age 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 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 percent difference point estimates, δ-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 the post-baseline period (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 end points were summarized for the
per-protocol analysis set, defined as all full analysis set patients with \( \geq 80\% \) 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, Version 16.1, and medications (prior and

| Table 1. Baseline Patient Characteristics (All Dosed Patients) |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                  | PL, N=26          | D225, N=26         | R750, N=26         | RD150, N=26        | RD225, N=27        | All, N=131        |
| **Age, y, mean (SD)** | 72 (8.4)          | 75 (7.8)           | 70 (10.8)          | 73 (9.4)           | 71 (7.1)           | 72 (8.8)          |
| **Male**          | 13 (50)           | 10 (39)            | 10 (39)            | 15 (58)            | 15 (56)            | 63 (48)           |
| **AF prior duration, y, mean (median)** | 4.2 (2.6)         | 7.0 (3.6)          | 5.1 (3.1)          | 4.1 (2.5)          | 4.7 (2.8)          | 5.0 (2.8)         |
| **Sinus node dysfunction** | 12 (46)          | 18 (69)            | 16 (62)            | 19 (73)            | 21 (78)            | 86 (66)           |
| **AV Block (2nd or 3rd degree)** | 11 (42)           | 3 (12)             | 3 (12)             | 7 (27)             | 2 (7)              | 26 (20)           |
| **Hypertension**  | 20 (77)           | 22/25 (88)         | 24 (92)            | 22 (85)            | 22 (82)            | 110/130 (85)      |
| **Heart failure** | 7 (27)            | 3 (11)             | 6 (23)             | 3 (11)             | 5 (18)             | 24 (18)           |
| **LVEF, % mean (SD)** | 56 (6)            | 59 (8)             | 57 (10)            | 57 (8)             | 57 (8)             | 57 (8)            |
| **CAD**           | 8 (31)            | 10/25 (40)         | 7/25 (28)          | 9/24 (38)          | 8/26 (31)          | 42/126 (33)       |
| **Diabetes mellitus** | 7 (27)            | 7 (27)             | 4 (15)             | 5 (19)             | 8 (30)             | 31 (24)           |
| **Syncope**       | 4 (15)            | 9/25 (36)          | 9 (35)             | 9 (35)             | 12/26 (46)         | 43/129 (33)       |
| **Cardioversion** | 3 (12)            | 10 (39)            | 11 (42)            | 7 (27)             | 5 (19)             | 36 (28)           |
| **AF ablation**   | 3 (12)            | 3 (12)             | 6 (23)             | 2 (8)              | 7 (26)             | 21 (16)           |
| **Beta-blockers** | 21 (81)           | 19 (73)            | 19 (73)            | 18 (69)            | 21 (78)            | 98 (75)           |
| **Calcium channel blockers** | 4 (15)           | 6 (23)             | 9 (35)             | 10 (39)            | 8 (30)             | 37 (28)           |
| **Antithrombotic therapy** | 26 (100)         | 26 (100)           | 25 (96)            | 25 (96)            | 25 (93)            | 127 (97)          |
| **Vitamin K antagonists** | 18 (69)          | 20 (77)            | 20 (77)            | 17 (65)            | 19 (70)            | 94 (72)           |
| **NOACs**         | 2 (8)             | 2 (8)              | 2 (8)              | 2 (8)              | 1 (4)              | 9 (7)             |
| **Antiplatelets** | 13 (50)           | 7 (27)             | 14 (54)            | 11 (42)            | 10 (37)            | 55 (42)           |
| **Statin**        | 20 (77)           | 18 (69)            | 17 (65)            | 19 (73)            | 19 (70)            | 93 (71)           |
| **ACE-I**         | 9 (35)            | 15 (58)            | 15 (58)            | 14 (54)            | 14 (52)            | 67 (51)           |
| **Any prior AAD** | 11 (42)           | 16 (62)            | 12 (46)            | 5 (19)             | 13 (48)            | 57 (44)           |

AAD indicates antiarrhythmic drug; ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AV, atrio-ventricular; CAD, coronary artery disease; D225, dronedarone 225 mg BID; LVEF, left ventricular ejection fraction; NOACs, novel oral anticoagulants; PL, placebo; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID; and Ran 750, ranolazine 750 mg BID.
≥ four percent had AFB ≥ 20% and 11% had ≥ 40%, and median AFB was 17.4% (range 2%–72%).

**Change From Baseline in AFB Over 12 Weeks**

Table 2. *Atrial Fibrillation Burden Over 12 Weeks (Full Analysis Set)*

<table>
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<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>
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<td>GM</td>
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<td>2.7</td>
<td>2.0</td>
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<tr>
<td>Over 12 wk</td>
<td>GM, baseline-adjusted</td>
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<td>12.1</td>
<td>8.9</td>
<td>6.4</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>SE</td>
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<td>2.4</td>
<td>2.0</td>
<td>1.3</td>
<td>1.0</td>
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<tr>
<td></td>
<td>% diff vs PL</td>
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<td>−20</td>
<td>−43</td>
<td>−57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>−40 to 98</td>
<td>−58 to 52</td>
<td>−69 to 5</td>
<td>−77 to −20</td>
<td></td>
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<tr>
<td></td>
<td>Pairwise comparison P value (vs PL)</td>
<td>0.78</td>
<td>0.49</td>
<td>0.072</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

AFB indicates atrial fibrillation burden; CI, confidence interval; D225, dronedarone 225 mg BID; Diff, difference; GM, geometric mean; PL, placebo; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID; Ran 750, ranolazine 750 mg BID; and SE, standard error. 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.

**Results**

**Study Population**

Of 327 screened patients, 134 were randomized (Figure 1). Baseline characteristics and cardiovascular 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% and 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 toward 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 the 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 to 13 beats per minute in the combination groups and by 9 beats per minute in the dronedarone 225 mg BID group. Small increases (8 and 6 beats per minute) were observed with placebo and ranolazine 750 mg BID alone, respectively (F-test P=0.003; Table 4). A decrease in frequency, in duration, or both, 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 numeric effect on these 2 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%).

**Figure 2.** Mean percent change from baseline in atrial fibrillation burden (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. Dron 225 indicates dronedarone 225 mg BID; PL, placebo; Ran 750, ranolazine 750 mg BID; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; and R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID.

**Figure 3.** Change from baseline in atrial fibrillation burden (AFB) over 12 weeks. Pairwise comparison P values (vs PL) 0.78 0.49 0.072 0.008. 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 the study. In both combination groups, much of the AFB reduction was attained by 4 weeks and then maintained during continued treatment (Table 3).

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Neither concomitant) were coded using the World Health Organization Drug Dictionary (Q2 2013).
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 because of only partial data available on timing of
symptoms or AF episodes or both.

Safety
Adverse Events
The incidence of treatment emergent 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 gener-
ally 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 treatment
emergent AEs across all treatment groups (>5% patients
total) were AF recurrence, dizziness, constipation, interna-
tional normalized ratio increase, and nausea. The most fre-
quent reported treatment emergent AEs 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
because of 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 (4–5 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 lev-
els, which increased slightly during treatment by 0.1 mg/dL
compared with those at 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 because
of their inhibition of renal tubular secretion of creatinine).

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

Dronedarone (400 mg BID) is approved for AF. In its piv-
otal EURIDIS (The European Trial in Atrial Fibrillation or
Flutter Patients Receiving Dronedarone for the Maintenance
of Sinus Rhythm) and ADONIS (The American-Australian-
African Trial with Dronedarone in Atrial Fibrillation or
Flutter Patients for the Maintenance of Sinus Rhythm) tri-
als,21 dronedarone reduced AF modestly but significantly
(from ≈75% to ≈62%; hazard ratio reduction ≈25%). In part,
this may be because of the nature of the population: many
patients had failed prior AAD regimens. In ATHENA,22
dronedarone reduced cardiovascular hospitalizations (mainly
AF-related) in an older population with moderate comor-
bid disease other than New York Heart Association class
IV HF. In contrast, in ANDROMEDA (The Antiarrhythmic
Trial With Dronedarone in Moderate to Severe Congestive
Heart Failure Evaluating Morbidity Decrease study) and
PALLAS,23,24 dronedarone increased mortality in patients
with recent or prior severe HF. Likely contributing factors
included LV depression from its L-type Ca2+ channel block-
ing properties19–24 and proarrhythmic dronedarone–digoxin
interactions.20 As dronedarone’s block of L-type Ca2+ chan-
nels is concentration-dependent, lower doses, as used in
HARMONY, should be less cardiodepressant.

Ranolazine is only approved for chronic stable angina.
However, preclinical studies26,36–42 indicate that it can suppress

Figure 3. A, Patients with ≥70% reduction in atrial fibrillation
burden (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). Dron 225 indicates dronedarone 225 mg
BID; PL, placebo; Ran 750, ranolazine 750 mg BID; R750/D150,
ranolazine 750 mg plus dronedarone 150 mg BID; and R750/
D225, ranolazine 750 mg plus dronedarone 225 mg BID.
atrial anhythmia triggers and AF even in the settings of HF and atrial stretch. 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. 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 ($I_{\text{Na}}$) and the rapidly activating delayed rectifier potassium current ($I_{\text{Kr}}$). Late $I_{\text{Na}}$ inhibition decreases cellular Na' and Ca2+ loading and occurrences of early and delayed afterdepolarizations (ie, arrhythmia triggers). In atrial but not ventricular tissue, and at fast drive rates, ranolazine also reduces peak $I_{\text{Na}}$ and $V_{\text{max}}$ of the action potential upstroke. Complementing these effects, dronedarone inhibits the acetylcholine-dependent inward rectifying potassium current ($I_{\text{K-ACh}}$), $I_{\text{Na}}$, and L-type Ca2+ current. The atrial-selective reduction of peak $I_{\text{Na}}$ combined with the effects of both drugs to reduce $I_{\text{Na}}$ alters atrial conduction, slows atrial repolarization, prolongs atrial effective refractory period, and causes significant postrepolarization 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. Such results indicate ranolazine’s effectiveness to prevent initiation, and maintenance of AF is increased by dronedarone, and vice versa. Importantly, this synergism occurred with dronedarone plasma concentrations below those reached by its approved 400 mg BID dose (MULTAQ). 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 $I_{\text{Na}}$ and thereby slow conduction velocity is normally small. But the effects of both drugs increase as rate increases. Similarly, the reduction of peak $I_{\text{Na}}$ with either drug is increased when early sodium channel availability is reduced by myocyte depolarization. As atrial myocytes are relatively depolarized compared with ventricular myocytes, block of peak $I_{\text{Na}}$ 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 preclinical 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 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 that of either drugs alone (Figures 2 and 3). Reduced AFB resulted from both a decrease in frequency and 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 cannot only reduce AFB but may also alter its progression, consistent with sinus rhythm

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<tr>
<td>Baseline</td>
<td>124 (27)</td>
<td>138 (29)</td>
<td>119 (33)</td>
<td>147 (37)</td>
<td>135 (30)</td>
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<tr>
<td>Over 12 wk</td>
<td>132 (34)</td>
<td>128 (30)</td>
<td>125 (27)</td>
<td>133 (29)</td>
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<tr>
<td>Change from baseline at Week 12</td>
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<td>-9 (15)</td>
<td>6 (13)</td>
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</tbody>
</table>

*AF indicates atrial fibrillation; D225, dronedarone 225 mg BID; PL, placebo; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID; and Ran 750, ranolazine 750 mg BID.

**P value F-test for testing equality of baseline-adjusted means across treatment groups.
sinus rhythm. Also, the 225 mg BID dose of dronedarone (lower than any studied in dronedarone’s dose-ranging DAFNE trial48) appeared ineffective in 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 were the following: First, only PAF patients with implanted programmable pacemakers 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 or 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.

### Table 5. Summary of Treatment Emergent Adverse Events (TEAE)

<table>
<thead>
<tr>
<th></th>
<th>No (%) of Patients With Any Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>15 (58)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (4)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

Most frequently reported TEAE (≥3 patients in any group)

- Atrial fibrillation: 2 (8), 4 (15), 3 (12), 3 (12), 1 (4)
- Dizziness: 1 (4), 2 (8), 3 (12), 2 (8), 0
- Constipation: 0, 1 (4), 1 (4), 4 (15), 1 (4)
- Nausea: 0, 1 (4), 3 (12), 1 (4), 2 (7)
- Fatigue: 0, 0, 3 (12), 1 (4), 2 (7)
- Urinary tract infection: 3 (12), 2 (8), 1 (4), 0, 0
- Abdominal pain: 0, 3 (12), 0, 0, 2 (7)
- Edema peripheral: 0, 3 (12), 0, 0, 2 (7)
- Vertigo: 0, 0, 3 (12), 1 (4), 1 (4)
- Hypotension: 0, 0, 0, 1 (4), 3 (11)

AE indicates adverse effects; D225, dronedarone 225 mg BID; PL, placebo; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID; Ran 750, ranolazine 750 mg BID; and SAE, serious adverse events.

### Table 6. Changes From Baseline in Vital Signs and 12-Lead ECG Intervals

<table>
<thead>
<tr>
<th></th>
<th>Change From Baseline at Week 12, mean±SE (N*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitals</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>0±2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0±3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−2±2</td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td></td>
</tr>
<tr>
<td>PR ms</td>
<td>9±12 (7)</td>
</tr>
<tr>
<td>QRS ms</td>
<td>−2±1 (7)</td>
</tr>
<tr>
<td>QTc ms (Bazett)</td>
<td>3±14 (7)</td>
</tr>
<tr>
<td>QTc ms (Fridericia)</td>
<td>3±14 (7)</td>
</tr>
<tr>
<td>Ventricular rate, beats per minute</td>
<td>−1±3 (7)</td>
</tr>
</tbody>
</table>

D225 indicates dronedarone 225 mg BID; PL, placebo; R750/D150, ranolazine 750 mg plus dronedarone 150 mg BID; R750/D225, ranolazine 750 mg plus dronedarone 225 mg BID; and Ran 750, ranolazine 750 mg BID.

* N number of patients with ECG parameters measured during spontaneous sinus rhythm.
Conclusions

HARMONY showed that moderate dose ranolazine combined with reduced dose dronedarone can decrease AFB yet maintain good tolerance/safety in the population enrolled. This profile seems to offer promise for AF patients and suggests that the concept of combining 2 AADs with complementary ion channel blocking properties is worthy of testing in a larger, more patient-diverse population.

Appendix

Investigators who randomized patients (listed by country and in descending order of the number of randomized patients).


Acknowledgments

Pacemaker Adjudication Committee: Spencer Rosero, Valentina Kutyifa (Cardiology Division, University of Rochester Medical Center, Rochester, NY); Independent Medical Monitor: Albert Waldo (Case Western University, Cleveland, OH); Gilead Medical Monitors: David Kwon, Saba Sile.

Disclosures

Drs Reiffel, Camm, and Peter Kowey have been paid consultants to Sanofi and for Gilead Sciences, Inc, in matters directly relating to the development of dronedarone and ranolazine. Drs Zareba and Rosero have received research grants from Gilead Sciences, Inc. Drs Belardinelli, Zeng, Karwatowska-Prokopczuk, and Olmsted are employees of Gilead Sciences, Inc.

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

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