Venice Arrhythmias
16th October, 2015 - Venice
Drug Propylaxis of AF: 2015 Update

Ranolazine Alone or in Combination with Other Antiarrhythmic Drugs for Atrial Fibrillation

John Camm
St. George’s University of London, UK
Declaration of Interests


Steering Committees: multiple trials including novel anticoagulants

DSMBs: multiple trials including BEAUTIFUL, SHIFT, SIGNIGY, AVERROES, CASTLE-AF, ASTAR II, INOVATE, and others

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects

Editorial Role: Editor-in-Chief, EP-Europace and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incardia, Johnson and Johnson, Mitsubishi, Novartis, Takeda
Antiarrhythmic Effects of Ranolazine

**Late** $I_{\text{Na}}$

**Peak** $I_{\text{Na}}$

Not approved anywhere for AF

**Peak:** IC$_{50} = 428$ µM

**Late:** IC$_{50} = 6.9$ µM

- ↑ late Na$^+$ during AF
- ↑ intracellular Na$^+$
- Reversal Na$^+$/Ca$^{2+}$ Ex
- ↑ intracellular Ca$^{2+}$
- ↑ EADs
- ↑ DADs
- ↑ spontaneous PV automaticity


DAD=delayed afterdepolarization; EAD=early afterdepolarization; PV=pulmonary vein
Synergistic Effect on Atrial Excitability of Combination of Ranolazine and Dronedarone

The shortest CL with 1:1 activation, ms

Diastolic threshold of excitation, mA

* p < 0.05 vs control / washout
† p < 0.05 vs ventricular values

Antzelevitch C, et al. JACC 2010;56:1216-24
**Atrial-Selective Sodium Channel Block With Ranolazine**

- **Ranolazine**: Cor-perfused, dog
- **Amiodarone**: Cor-perfused, dog
- **AZD7009**: In vivo, dog
- **Quinidine**: Tissue, rabbit
- **Lidocaine**: Cor-perfused, dog
- **Lidocaine**: Myocytes, human
- **Ajmaline**: Tissue, rabbit
- **Propafenone**: Cor-perfused, dog
- **Disopyramide**: Tissue, guinea pig
- **Tedisamil**: Tissue, human
- **Mexiletine**: Tissue, guinea pig
- **Moricizine**: Myocytes, guinea pig

**Semi-quantitative assessment of atrial selectivity of sodium channel blockers**


Effect of Ranolazine on SVTs and AF
Merlin-TIMI 36 Trial

Supraventricular tachycardia

Placebo: n=3,281
Ranolazine: n=3,279

New-onset atrial fibrillation

Δ=339, RR 0.81, p<0.001

Δ=20, RR 0.74, p=0.08

Conversion of Paroxysmal or New Onset AF With Oral Ranolazine: "Pill-in-the-Pocket"

- N = 32 with AF 3-48 h
- 18 (56%) PAF, 14 (44%) new onset AF
- Age 71 ± 9 years, 63% men
- EF 49 ± 12%, ≤ 45% in 11 (33%)
- LAE 69%, CAD 41%, HTN 56%, LVH 25%, CHF 6%
- Ranolazine 2 g p.o.
- 1st dose given in-hospital (69%), office (16%), home (16%)
- Well-tolerated, no hemodynamic or electrophysiologic adverse effects

Murdock D, et al. ACC 2010
Oral Ranolazine Facilitates Cardioversion in Cardioversion Resistant Patients

- N = 18 with failed DCC
- Age 65 ± 11 years, 67% men
- EF 62 ± 11%, ≤ 45% in 7 (39%), LAD 44 ± 7 mm
- LAE 67%, CAD 39%, HTN 39%, CHF 22%, DM 22%
- Ranolazine 2 g p.o., no AADs
- DCC repeated 3.5-4 h under the same conditions (pad position, sedation, cardioverter)

Murdock D, et al. ACC 2010
Ranolazine versus Amiodarone
AF Prophylaxis After CABG

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10–14 days) - N=211 (53.7%)
- Ranolazine (1,500 mg preoperative followed by 1,000 mg twice daily for 10–14 days) - N=182 (46.3%)
- Mean age 65 ± 10 years, 72% male

Murdock D, et al. ACC Abstracts 2011, New Orleans, LA, USA

Ranolazine associated independently with a reduction of post-op AF

CABG=coronary artery bypass grafting
RAFFAELLO: **Ranolazine in Atrial Fibrillation Following An Electrical cardiov version**

- Phase IIb
- ~ 40 centres in Europe (Germany, Italy, Spain, UK)
- Planned DCC off AADs; SR maintained for 2 h
- Ranolazine: 375, 500, 750 mg bd or Placebo
- Treatment duration: 16 weeks or until documented AF recurrence in need of medical intervention
- Recruitment completed (n = 260)
RAFFAELLO: Patient Flow

Screened
n = 310

Screening Failures
n = 69

Randomised
n = 241

Recurrences
n = 116

Not treated
n = 3

Censored
n = 122

n=238
ITT analysis
RAFFAELLO Primary Endpoint
Time to 1° AF recurrence (ITT, N=238)

- Ranolazine 375 mg
- Ranolazine 500 MG
- Ranolazine 750 mg
- Placebo

500 mg vs placebo: log-rank p = 0.116
750 mg vs placebo: log-rank p = 0.121

Not approved anywhere
### RAFFAELLO - Safety Results

<table>
<thead>
<tr>
<th></th>
<th>RAN 375 n=65</th>
<th>RAN 500 n=60</th>
<th>RAN 750 n=58</th>
<th>Placebo n=55</th>
<th>Overall n=238</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Treatment-emergent Signs and Symptoms</strong> (n, %pat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>51 (78.5%)</td>
<td>46 (76.7%)</td>
<td>42 (72.4%)</td>
<td>41 (74.5%)</td>
<td>180 (75.6%)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3 (4.6%)</td>
<td>5 (8.3%)</td>
<td>4 (6.9%)</td>
<td>4 (7.3%)</td>
<td>16 (6.7%)</td>
</tr>
<tr>
<td>SAE</td>
<td>2 (3.1%)</td>
<td>3 (5.0%)</td>
<td>3 (5.2%)</td>
<td>4 (7.3%)</td>
<td>12 (5.0%)</td>
</tr>
<tr>
<td><strong>Related Treatment-emergent Signs and Symptoms</strong> (n, %pat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12 (18.5%)</td>
<td>10 (16.7%)</td>
<td>20 (34.5%)</td>
<td>8 (14.5%)</td>
<td>50 (21.0%)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1.5%)</td>
<td>1 (1.7%)</td>
<td>1 (1.7%)</td>
<td>1 (1.8%)</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>2 (3.4%)</td>
<td>1 (1.8%)</td>
<td>4 (1.7%)</td>
</tr>
</tbody>
</table>

The most common treatment-related TESS (≥ 5% in any treatment group) were constipation, nausea, dizziness, asthenia, and fatigue. The incidence was highest in the Ranolazine 750 mg group (5.2-8.6%, respectively).
Exploratory Analysis
Freedom from AF at Different Doses

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Freedom from AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>43.6%</td>
</tr>
<tr>
<td>375 mg</td>
<td>43.1%</td>
</tr>
<tr>
<td>500 mg</td>
<td>58.3%</td>
</tr>
<tr>
<td>750 mg</td>
<td>60.3%</td>
</tr>
</tbody>
</table>
Synergistic Effect on Atrial PRR of Combination of Ranolazine and Dronedarone

Antzelevitch C, et al. JACC 2010;56:1216-24
Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 µmol/L
- Dronedarone 10 µmol/L

![Graph showing induction or termination of persistent AF, %](image)

- **Induction or termination of persistent AF, %**
  - ACh: 100/10, 0/10, 17/6, 20/5, 60/10
  - ACh+Dronedarone: 83/6, 5/6, 5/7, 10/10
  - ACh+Ranolazine: 71/7, 1/5, 1/10
  - ACh+R+D: 6/10

**Graph showing V_max (% of control at 5000 ms CL)**

- Control: *
- Ranolazine: *
- Dronedarone: *
- R+D: *†

* p < 0.05 vs control
† p < 0.05 vs R or D alone

Synergistic Effect of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 μmol/L
- Dronedarone 10 μmol/L

- Open-chest Yorkshire pigs
- Proximal LCX occlusion (75%)
- Ranolazine i.v. 0.6 mg/kg+0.035 mg/kg/min
- Dronedarone i.v. 0.5 mg/kg

Not approved anywhere
Pharmacological Cardioversion of AF
Combination of Amiodarone and Ranolazine

- Pilot RCT
- N = 51 with AF < 48 h
- Age 63 ± 8 years, 65% men
- HTN 68–77%, CAD 20–27%
- I.V. amio 5 mg/kg for 1 h followed by infusion of 50 mg/h for 24 h
- I.V. amio + ranolazine 1,500 mg p.o.
- 1st EP: conversion within 24 h


[Graph showing the proportion of patients converted to SR: 22/25 (88%) for Amio + Rano compared to 17/26 (65%) for Amio. Median time to conversion: 18 h (Amio) vs 10 h (Amio+Rano).]

Not approved anywhere
A 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
**AF + I_{Kr} channel block**

- Atrial ERP
- APD - \( I_{Kr} \)
- PRR - \( I_{Na} \) peak

**AF + I_{Kr} + I_{Na} channel block**

- NaCh avail \( \leq 30\% \)
- \( I_{Na} \) block alone: \( \Delta ERP = 20 \) ms

**Combination Therapy: \( I_{Kr} + I_{Na} \) Inhibition**

- S2-induced AF (no drug)

**Rajamani and Belardinelli, Gilead on file, 12/2011**
Ranolazine (Ran): antianginal approved in 2005

Dronedarone (Dron): anti-AF approved in 2009

Ran and Dron are multi-ion channel blockers

- **Ran**: ↓ peak and late $I_{Na}$ ($\downarrow I_{Kr}$ moderate)
- **Dron**: $\downarrow I_{Kr}$, ↓ $I_{KACa}$, ↓ $I_{f}$ ($\downarrow$ peak $I_{Na}$)

Mechanism for synergism

- Inhibitions of peak $I_{Na}$ (Ran $\gg$ Dron) and $I_{Kr}$ (Dron $\gg$ Ran)

Mechanism for safety

- Concentrations of Dron 1.6 - 3 fold below the IC$_{50}$ to inhibit $I_{CaL}$
- Inhibition of late $I_{Na}$ stabilizes ventricular repolarization

*At plasma concentrations achieved by Ran=750 mg bid; Dron=150 or 225 mg bid (HARMONY doses)

References:

Burashnikov, Belardinelli, Antzelevitch et al. JACC 56: 1216-1224, 2010
Wu, Li, Belardinelli. Gilead on file, 04/2011
Ranolazine/Dronedarone Synergy

● Mechanism for synergism
  ▪ Ranolazine and Dronedarone are multi-ion channel blockers
    - Inhibitions of peak $I_{Na}$ (Ran $>>$ Dron) & $I_{Kr}$ (Dron $>>$ Ran)
    - Inhibition of late $I_{Na}$ stabilizes ventricular repolarization and suppresses triggered activity

● Safety
  ▪ Cardio-depressant effects of Dronedarone are concentration-dependent
  ▪ Plasma concentrations achieved by Dronedarone 225 mg in combination with Ranolazine 750 mg (HARMONY dose) were $\geq 50\%$ lower than MULTAQ (Phase 1 DDI study) and were not cardio-depressant (in vitro studies)
  ▪ Inhibition of late $I_{Na}$ prevents VT
Objective

To determine if a combination therapy comprised of a moderate dose of ranolazine and low dose dronedarone is superior to each drug alone, and to placebo, in reducing AF burden in patients with implanted pacemakers who have paroxysmal AF and are off of any antiarrhythmic drug

Note: AF burden = total time a subject was in AF expressed as a percentage of total recording time
A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal AF

- PAF with pacemakers
- N = 150, 45 centres
- Follow-up: 12 weeks
- Ranolazine vs Dronedarone vs Ranolazine + Dronedarone
- Primary endpoint: reduction in AF burden
- $2^0$ endpoints: AF burden at each visit (4, 8, 12 weeks) and # episodes

Available at: http://clinicaltrials.gov/show/NCT01522651
<table>
<thead>
<tr>
<th>Country</th>
<th>Randomized ≥ 5 patients</th>
<th>Randomized ≥ 3&lt;5 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>J. Wilczek; Katowice, PL (10)</td>
<td>A. Katz; Ashkelon, IS (4)</td>
</tr>
<tr>
<td></td>
<td>M. Swissa; Rehovot, IS (8)</td>
<td>E. Nowalany-Kozielska; Zabrze, PL (4)</td>
</tr>
<tr>
<td></td>
<td>K. Wranicz; Lodż, PL (8)</td>
<td>B. Winkelmann; Frankfurt, GE (4)</td>
</tr>
<tr>
<td></td>
<td>D. Czarnecka; Kraków, PL (7)</td>
<td>A. Cohen; Aurora, USA (3)</td>
</tr>
<tr>
<td></td>
<td>S. Kääb; München, GE (7)</td>
<td>G. Jaworska; Toruń, PL (3)</td>
</tr>
<tr>
<td></td>
<td>G. Raczak; Gdańsk, PL (7)</td>
<td>D. Murdock; Wausau, USA (3)</td>
</tr>
<tr>
<td></td>
<td>L. Maier; Göttingen, GE (6)</td>
<td>W. Musial; Białystok, PL (3)</td>
</tr>
<tr>
<td></td>
<td>N. Freedberg; Afula, IS (5)</td>
<td>A. Przybylski; Warszawa, PL (3)</td>
</tr>
<tr>
<td></td>
<td>M. Grabowski; Warszawa, PL (5)</td>
<td>J. Schrickel; Bonn, GE (3)</td>
</tr>
<tr>
<td>Italy</td>
<td>J. Wilczek; Katowice, PL (10)</td>
<td>A. Katz; Ashkelon, IS (4)</td>
</tr>
<tr>
<td></td>
<td>M. Swissa; Rehovot, IS (8)</td>
<td>E. Nowalany-Kozielska; Zabrze, PL (4)</td>
</tr>
<tr>
<td></td>
<td>K. Wranicz; Lodż, PL (8)</td>
<td>B. Winkelmann; Frankfurt, GE (4)</td>
</tr>
<tr>
<td></td>
<td>D. Czarnecka; Kraków, PL (7)</td>
<td>A. Cohen; Aurora, USA (3)</td>
</tr>
<tr>
<td></td>
<td>S. Kääb; München, GE (7)</td>
<td>G. Jaworska; Toruń, PL (3)</td>
</tr>
<tr>
<td></td>
<td>G. Raczak; Gdańsk, PL (7)</td>
<td>D. Murdock; Wausau, USA (3)</td>
</tr>
<tr>
<td></td>
<td>L. Maier; Göttingen, GE (6)</td>
<td>W. Musial; Białystok, PL (3)</td>
</tr>
<tr>
<td></td>
<td>N. Freedberg; Afula, IS (5)</td>
<td>A. Przybylski; Warszawa, PL (3)</td>
</tr>
<tr>
<td></td>
<td>M. Grabowski; Warszawa, PL (5)</td>
<td>J. Schrickel; Bonn, GE (3)</td>
</tr>
</tbody>
</table>

**Scientific Committee**
- J. Camm, Univ of London, UK
- P. Kowey, Main Line Health, PA, USA
- J. Reiffel, Columbia UMC, NY, USA

**EP Core Lab and Adjudication Committee**
- W. Zareba, S. Rosero, M. Brown
  University of Rochester, Rochester, NY

**Independent Medical Reviewer**
- A. Waldo
  Case Western Reserve University
  Cleveland, OH
Entry Criteria

Inclusion Criteria:

• Paroxysmal AF
• Dual chamber pacemaker
  ▪ Implanted at least 3 months prior to screening
  ▪ Atrial arrhythmia algorithm detection
• AF Burden ≥ 2% and ≤ 70% at randomization

Major Exclusion Criteria:

• Persistent / Permanent AF
• History of AFI/AT without successful ablation
• NYHA Class III & IV or Class II with recent decompensation
• Recent history of LVEF<40%
• Stroke, MI, unstable angina, or CABG 3 months prior screening
• LFTs>2xULN, CrCL ≤ 30 mL/min
• CYP3A strong inhibitors or inducers
• AAD Class I/III (within 5-half lives), amiodarone (3 months)
• Use of dabigatran, digitalis, metformin (>1000 mg daily)
Endpoints

• Primary endpoint:
  - Change from baseline in AF burden over 12 weeks

• Key secondary endpoints:
  - Change in AF burden at each study visit
  - Percentage of patients with 50% burden reduction
  - Change in number and duration of AF episodes
  - Change in AF rate

♦ Safety and tolerability of each component and the combination
### Baseline Characteristics & CV History

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=26</th>
<th>Ran750 N=26</th>
<th>Dron225 N=26</th>
<th>RD150 N=26</th>
<th>RD225 N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>72 (8.4)</td>
<td>70 (10.8)</td>
<td>75 (7.8)</td>
<td>73 (9.4)</td>
<td>71 (7.1)</td>
</tr>
<tr>
<td><strong>Male n (%)</strong></td>
<td>13 (50)</td>
<td>10 (39)</td>
<td>10 (39)</td>
<td>15 (58)</td>
<td>15 (56)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>20 (77%)</td>
<td>24 (92%)</td>
<td>22 (85%)</td>
<td>22 (85%)</td>
<td>22 (82%)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>7 (27%)</td>
<td>6 (23%)</td>
<td>3 (11%)</td>
<td>3 (11%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td><strong>LV Ejection Fraction %</strong></td>
<td>56 (6)</td>
<td>57 (10)</td>
<td>59 (8)</td>
<td>57 (8)</td>
<td>57 (8)</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>8 (31%)</td>
<td>7 (27%)</td>
<td>10 (39%)</td>
<td>9 (35%)</td>
<td>8 (30%)</td>
</tr>
<tr>
<td><strong>Prior Cardioversion</strong></td>
<td>3 (11%)</td>
<td>11 (42%)</td>
<td>10 (38%)</td>
<td>7 (27%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td><strong>Ablation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>3 (11%)</td>
<td>6 (23%)</td>
<td>3 (11%)</td>
<td>2 (8%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>AV node</td>
<td>3 (11%)</td>
<td>2 (8%)</td>
<td>3 (11%)</td>
<td>1 (4%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>0</td>
<td>4 (15%)</td>
<td>4 (15%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td><strong>Prior AAD Use (Chronic)</strong></td>
<td>9 (41%)</td>
<td>12 (50%)</td>
<td>16 (64%)</td>
<td>5 (21%)</td>
<td>13 (52%)</td>
</tr>
</tbody>
</table>
Study Objective and Overview

To determine if combination therapy with moderate dose ranolazine and low dose dronedarone is superior to each of the components and to placebo in reducing AF burden in patients with implanted pacemakers who have paroxysmal AF.

Day 1
Randomization# (AFB ≥2 and ≤70%)

Follow-up

Baseline

Treatment

Run-in
(4wks)

Wks 1-4

Wks 5-8

Wks 9-12

Placebo
Ranolazine 750 mg bid
Dronedarone 225 mg bid
Ranolazine 750 mg bid and dronedarone 225 mg bid
Ranolazine 750 mg bid and dronedarone 150 mg bid

# Stratified by AFB<15% and >15%

* PPM Interrogation
Results to Core EP lab (EGMs adjudicated)
Primary Endpoint: % Change from Baseline in AFB over 12 weeks

AFB (% change from baseline)

- PL
- D225
- R750
- R750/D150
- R750/D225

AF Burden, % from Baseline

- D225
- R750
- R750/D225

Synergy

- Σ (D225 + R750)

**p-values**
- PL: p = 0.78
- D225: p = 0.493
- R750: p = 0.072
- R750/D225: p = 0.008
Change in AF Burden by Month

- Placebo (N=17)
  - Months: 1, 2, 3
  - Atrial Fibrillation Burden (% Change from Baseline):
    - 0
    - -20
    - -40
    - -60
    - -80

- R750/D225 (N=20)
  - Months: 1, 2, 3
  - Atrial Fibrillation Burden (% Change from Baseline):
    - 0
    - -20
    - -40
    - -60
    - -80
Changes from Baseline in AFB Over 12 Weeks

**Decrease**

- **Placebo**
- **D225**
- **R750**
- **R750/D150**
- **R750/D225**

**Increase**

- **Placebo**
- **D225**
- **R750**
- **R750/D150**
- **R750/D225**

**AF Burden**

- Decrease
  - > 0 to < 70%
  - ≥ 70%
  - No change

- Increase
  - ≥ 100%
  - ≥ 50 to < 100%
  - > 0 to < 50%
Subjects with ≥70% Reduction in AF burden Over 12 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11%</td>
</tr>
<tr>
<td>D225</td>
<td>9%</td>
</tr>
<tr>
<td>R750</td>
<td>17%</td>
</tr>
<tr>
<td>R750/D150</td>
<td>27%</td>
</tr>
<tr>
<td>R750/225</td>
<td>45%</td>
</tr>
</tbody>
</table>
## Overview of Safety

<table>
<thead>
<tr>
<th>Subjects with any Treatment Emergent:</th>
<th>Placebo N=26</th>
<th>Ran750 N=26</th>
<th>Dron225 N=26</th>
<th>RD150 N=26</th>
<th>RD225 N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>15 (58%)</td>
<td>17 (65%)</td>
<td>18 (69%)</td>
<td>16 (61%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>1 (4%)</td>
<td>7 (27%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>AE leading to premature study drug discontinuation</td>
<td>3 (11%)</td>
<td>5 (19%)</td>
<td>4 (15%)</td>
<td>5 (19%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>
## Overview of Safety

### Subjects with any Treatment Emergent:

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=26</th>
<th>Ran750 N=26</th>
<th>Dron225 N=26</th>
<th>RD150 N=26</th>
<th>RD225 N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event (AE)</strong></td>
<td>15 (58%)</td>
<td>17 (65%)</td>
<td>18 (69%)</td>
<td>16 (61%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td><strong>Serious adverse event (SAE)</strong></td>
<td>1 (4%)</td>
<td>7 (27%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td><strong>AE leading to premature study drug discontinuation</strong></td>
<td>3 (11%)</td>
<td>5 (19%)</td>
<td>4 (15%)</td>
<td>5 (19%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>
## Most Frequent AEs

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=26</th>
<th>Ran750 N=26</th>
<th>Dron225 N=26</th>
<th>RD150 N=26</th>
<th>RD225 N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>INR increased</strong></td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
# QT<sub>CB</sub> Changes from Baseline at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>D225</th>
<th>R750</th>
<th>R750/D150</th>
<th>R750/D225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>428 ± 52</td>
<td>422 ± 32</td>
<td>426 ± 37</td>
<td>430 ± 24</td>
<td>432 ± 28</td>
</tr>
<tr>
<td></td>
<td>(18)</td>
<td>(17)</td>
<td>(16)</td>
<td>(10)</td>
<td>(16)</td>
</tr>
<tr>
<td>Week 12</td>
<td>432 ± 38</td>
<td>430 ± 29</td>
<td>429 ± 34</td>
<td>432 ± 29</td>
<td>425 ± 25</td>
</tr>
<tr>
<td></td>
<td>(7)</td>
<td>(10)</td>
<td>(8)</td>
<td>(10)</td>
<td>(9)</td>
</tr>
</tbody>
</table>

Δ QT<sub>c</sub>  

|        | 3  | 7  | -6 | -13 | 1  |

Values are mean ± SE in msec

(  ) = number of patients

includes only patients with pair QT<sub>c</sub> values (baseline and week 12)
### QT<sub>CB</sub> Changes from Baseline at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>D225</th>
<th>R750</th>
<th>R750/D150</th>
<th>R750/D225</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>428 ± 52 (18)</td>
<td>422 ± 32 (17)</td>
<td>426 ± 37 (16)</td>
<td>430 ± 24 (10)</td>
<td>432 ± 28 (16)</td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td>432 ± 38 (7)</td>
<td>430 ± 29 (10)</td>
<td>429 ± 34 (8)</td>
<td>432 ± 29 (10)</td>
<td>425 ± 25 (9)</td>
</tr>
</tbody>
</table>

Δ QT<sub>c</sub>  

|          | 3       | 7       | -6      | -13       | 1        |

Values are mean ± SE in msec
Summary/Conclusions

• Greater efficacy of the combination RD225 to reduce AF burden when compared to placebo and to either Ran750 or Dron225 alone

• Acceptable safety/tolerability profile: the incidences of AEs, SAEs or AEs leading to discontinuation were similar in the combination RD225 group compared to the sum of R750 + D225
Thank you for your attention
I have been working on a paper exploring the link between physician-patient communication and medication adherence and the implications for health care costs. Medication nonadherence among patients is and has been a “gigantic” problem for the health care industry over the last 20 to 30 years… and not just for pharma. Patients outcomes suffer and health care cost sky rocket as nonadherent patients fill ER and hospitals across the U.S.

“Drugs don’t work in patients who don’t take them.”

C. Everett Koop, former Surgeon General of the US