HEART FAILURE 2018
including the World Congress on Acute Heart Failure

VIENNA
26 - 29 MAY

GENETIC-AF

Phase II Trial of Pharmacogenetic Guided Beta-Blocker Therapy with Bucindolol vs. Metoprolol for the Prevention of Atrial Fibrillation/Flutter in Heart Failure

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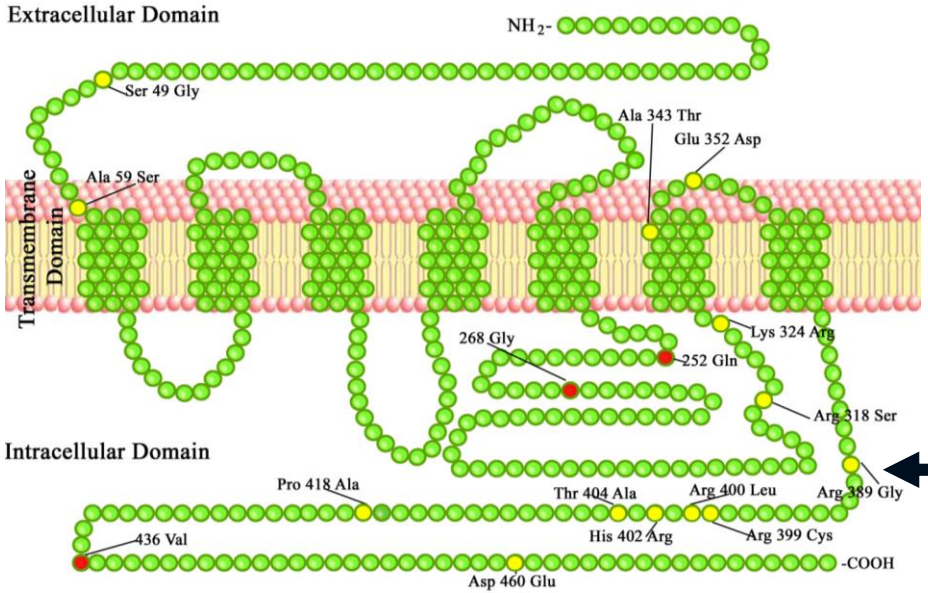
β_1 Adrenergic Receptor Polymorphism-Dependent Differences



C → G nt 1165
Arg → Gly 389
Frequency =
EA 0.52, AA 0.32

$\beta_1$389Arg >>> $\beta_1$389Gly

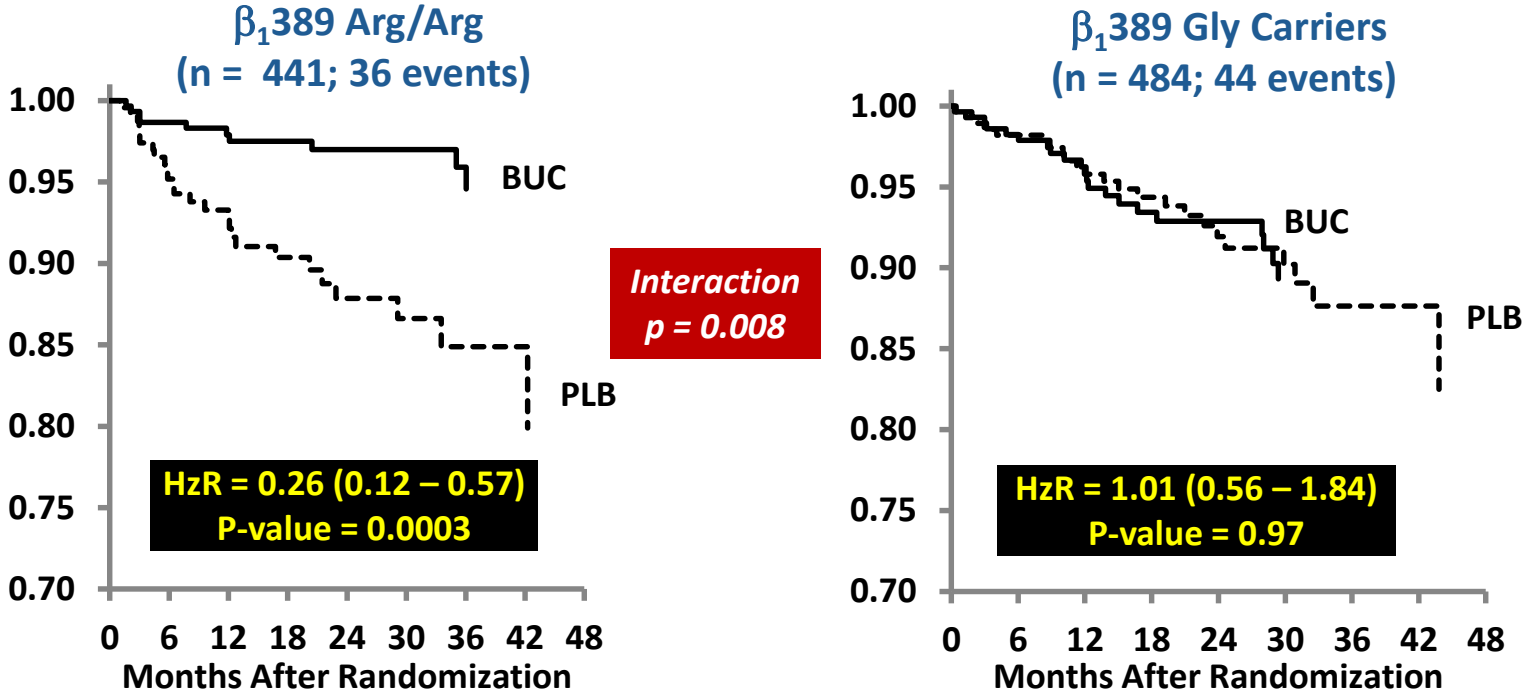
- ✓ Binding affinity for norepinephrine
- ✓ Signal transduction capacity
- ✓ Constitutively active receptors

Bucindolol has two *unique* properties that are specific for 389Arg β_1-ARs:

- Sympatholysis
- Inverse Agonism

Mason DA et al. JBC 1999; Taylor et al. Cong Heart Fail 2004; Liggett et al. PNAS 2006; Walsh et al. J Card Fail 2008; O'Connor et al. PLOS ONE, 2012.

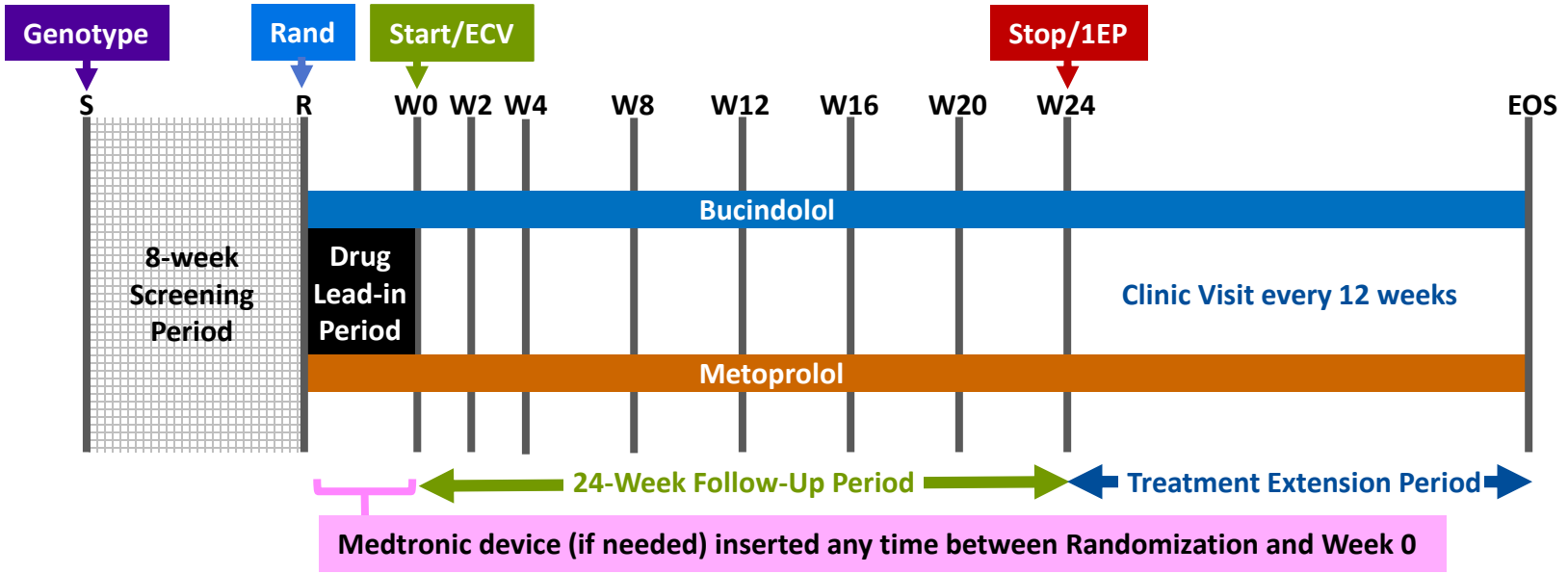
BEST DNA Substudy: Prevention of Atrial Fibrillation by Bucindolol



Aleong et al, JACC Heart Fail; 1:338-44, 2013

GENETIC-AF Study Design

- Phase 2B → 3 Seamless Design
- Phase 2 interim analysis (230 pts)
- Bayesian predicted probability of success (PPoS)
  1. PPoS < 0.10 (Futility, stop study)
  2. 0.10 ≤ PPoS < 0.40 (Complete Phase 2)
  3. PPoS ≥ 0.40 (Seamless transition to Phase 3)



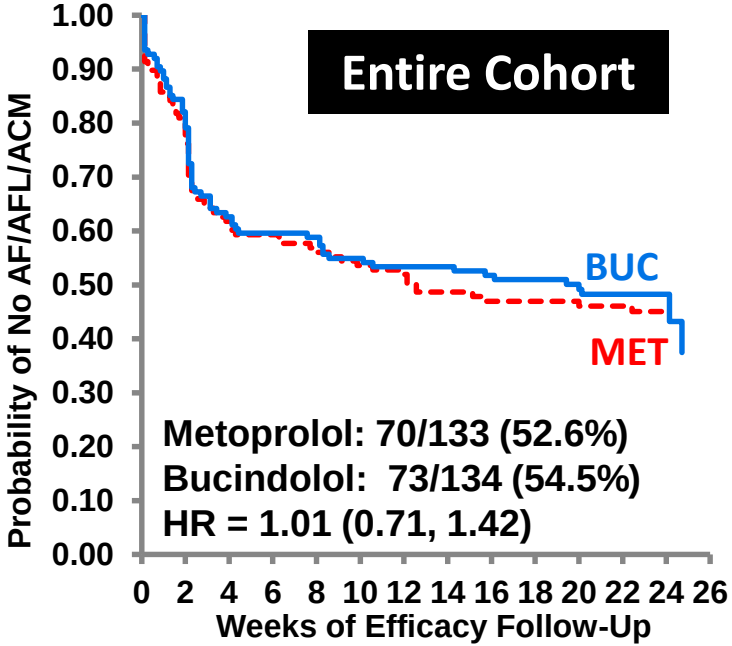
Key Eligibility Criteria

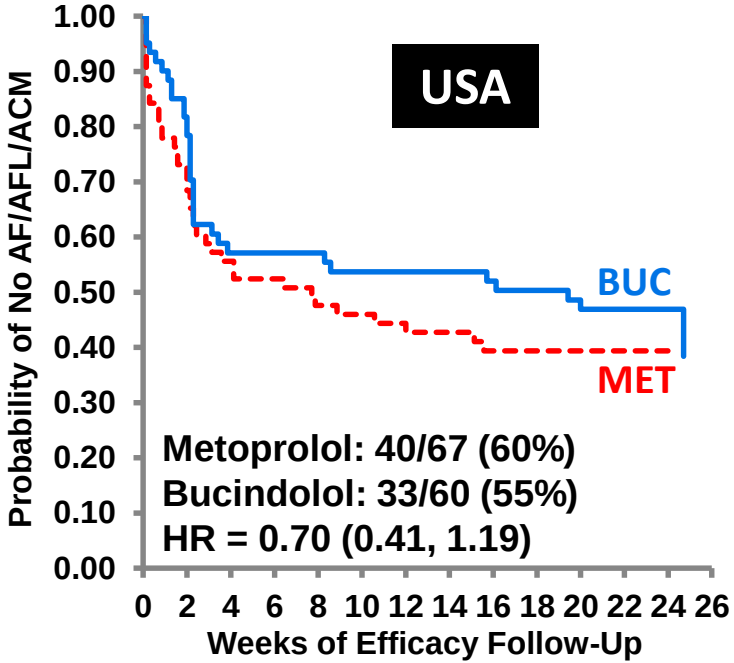
1. History of HF with reduced left ventricle ejection fraction (HFrEF + HFmrEF)
   - LVEF < 0.50 within 12 months of the Screening Visit
   - Excluded: NYHA class IV
   - Excluded: Significant fluid overload at Randomization
2. Symptomatic paroxysmal or persistent AF episode ≤ 180 days of Screening Visit
   - Excluded: Permanent AF > 1 year
3. Possess the $\beta_1$389Arg/Arg (*ADRB1* Arg389Arg) genotype
4. Receiving appropriate anticoagulation therapy prior to randomization for stroke
5. Clinically appropriate for ECV if AF/AFL is present at the Week 0 Visit
   - Excluded: More than 2 ECVs within 6 months of Randomization
   - Excluded: Most recent ECV failed to produce sinus rhythm
6. Systolic BP > 90 mmHg and < 150 mmHg at Randomization
7. Heart rate ≥ 60 bpm (if BB naïve) and < 180 bpm (all) at Randomization

Baseline Characteristics (± SD; *p <0.05 vs. MET)

Parameter	MET n = 133	BUC N = 134
Age	65.5 ± 10.0	65.8 ± 10.3
Gender M/F (%)	81 / 19	83 / 17
LVEF	0.36 ± 0.10	0.36 ± 0.10
NYHA I / II / III (%)	26 / 54 /20	30 / 60 / 10
Hx Ischemic / Non-Ischemic HF (%)	33 / 67	31 / 69
Randomized in AF / Not in AF (%)	52 / 48	49 / 51
Hx Persistent/Paroxysmal AF (%)	51 / 49	51 / 49
AF Dx to Randomization, days	1180 ± 2209	1431 ± 2271
HF Dx to randomization, days	1054 ± 1733	1252 ± 2070
sBP (mm Hg)	122 ± 15.7	125 ± 14.9
Heart Rate, bpm	76.0 ± 17.7	76.5 ± 17.9
Previous ECV / AF ablation / Class III AADs (%)	50 / 20 / 46	49 / 21 / 50
Device Type: ILR / CRT / ICD / PM (%)	15 / 10 / 12 / 10	17 / 6 / 18 / 9
HF Rx: β-bl / ACEI or ARB / Dig / Diuretic / MRA / Scbtl-Val (%)	92 / 78 / 17 / 61 / 32 / 5	94 / 75 / 15 / 57 / 32/ 4
NT-proBNP (pg/ml)	1343 ± 1846	1159 ± 1306
Norepinephrine (NE) (pg/ml)	664 ± 359	682 ± 348
Change in NE at Week 4, median (Q1, Q3)	-10 (198, 121)	-101 (-241, 43)*

Primary Endpoint: Time to First AF/AFL/ACM Event

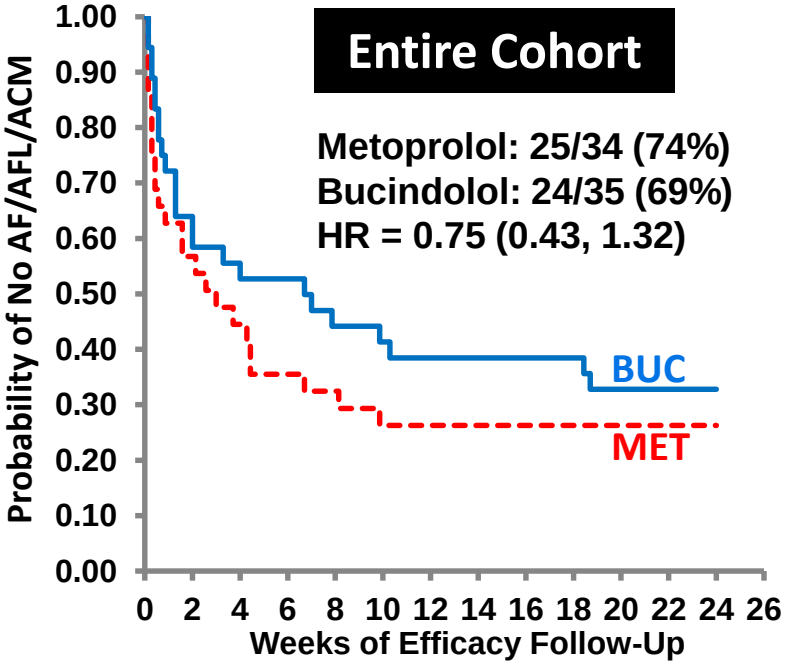


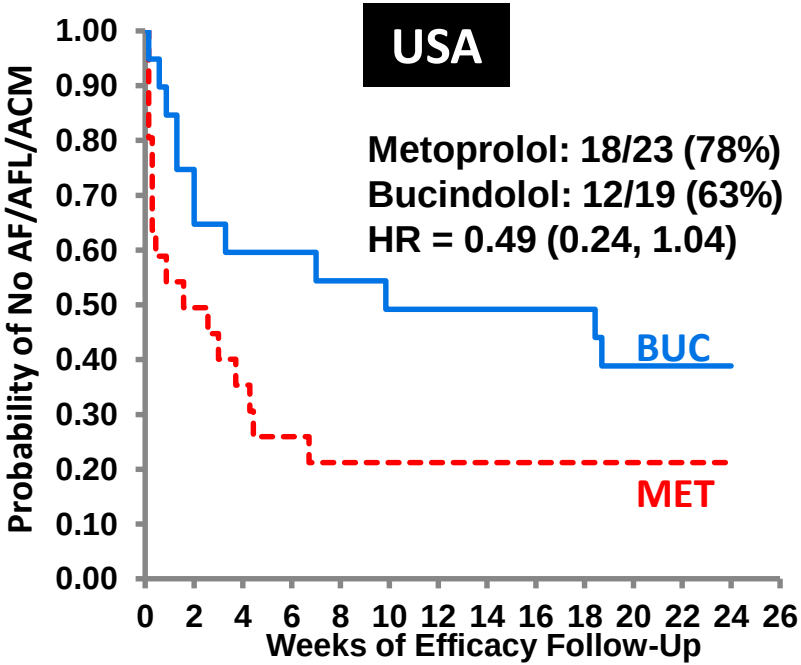


Unadjusted HR: Entire Cohort = 0.96 (95% CI: 0.69, 1.33); U.S. Cohort = 0.77 (95% CI: 0.48, 1.22)

Time to First AF/AFL/ACM Event: AF Burden Substudy

AF Event = AFB ≥ 6 hours/day



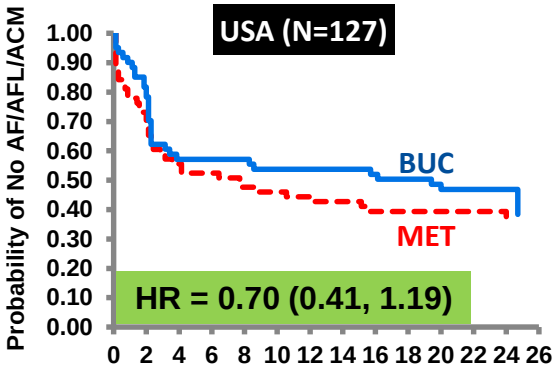


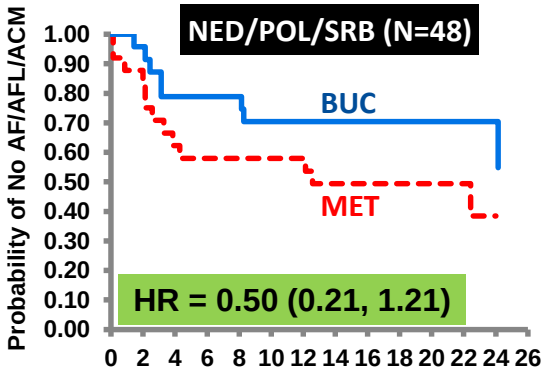
Adjusted HR: Entire Cohort = 0.74 (95% CI: 0.38, 1.45); U.S. Cohort = 0.50 (95% CI: 0.17, 1.42)

AEs, Hospitalization, Stroke or Death

Endpoint	Metoprolol (N=133)	Bucindolol (N=134)
AEs leading to permanent study drug discontinuation	8.3%	8.2%
AEs leading to study withdrawal (excluding death)	1.5%	1.5%
AEs: Bradycardia	12.0%	3.7%
AEs: Stroke (99% on OACs)	0.0%	0.0%
SAEs: Any cardiovascular event	9.8%	9.0%
All-cause hospitalization	15.0%	20.1%
Cardiovascular hospitalization	10.5%	12.7%
Heart failure hospitalization	7.5%	6.7%
All-cause mortality	2.3%	2.3%
Cardiovascular mortality	1.5%	0.7%
Heart failure mortality	0.7%	0.0%

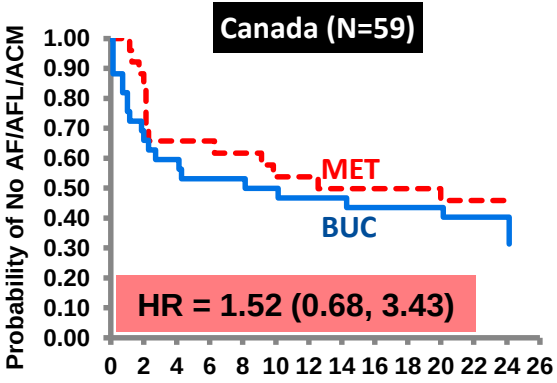
Time to First AF/AFL/ACM Event by Region

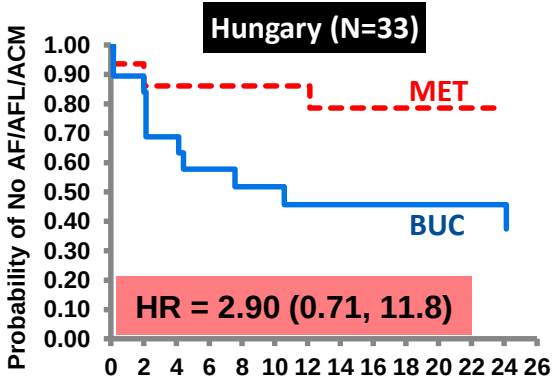




USA/NED/POL/SRB (N=175)

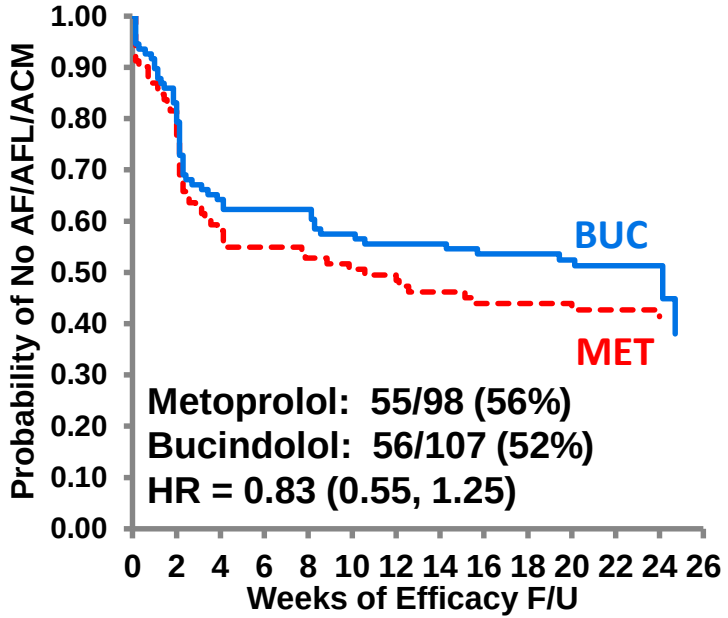
Canada/Hungary (N=92)





Time to First AF/AFL/ACM Event

LVEF < 0.39 (median) or LVEF 0.39-0.49 with HF Dx to Rand – AF Dx to Rand (DTRI) >-30 days



Country	Included (%)
All	77%
USA	85%
Canada	78%
Hungary	39%
Poland	78%
Serbia	81%
Netherlands	75%

Unadjusted HR: Entire Cohort = 0.84 (95% CI: 0.58, 1.22)

GENETIC-AF Conclusions

- Pharmacogenetic guided bucindolol did not reduce AF/AFL/ACM recurrence compared to the active comparator metoprolol in the overall population
- Trends for bucindolol benefit were observed in several large subpopulations
- Bucindolol appears to have a similar safety profile compared to metoprolol
- These Phase 2 results merit further investigation in a redefined population
  - ✓ HFrEF (LVEF < 0.40)
  - ✓ HFmrEF (LVEF ≥0.40 and <0.50) if DTRI > -30 days
  - ✓ Symptomatic paroxysmal/persistent AF ≤ 180 days of randomization
  - ✓ $\beta_1$389Arg/Arg genotype