GENETIC-AF: A Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Toprol-XL for Prevention of Atrial Fibrillation/Atrial Flutter in Patients with Heart Failure

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Background

Most anti-arrhythmic agents currently approved for the treatment of atrial fibrillation (AF) and atrial flutter (AFR) are contraindicated or have low labeling for use in heart failure (HF) due to an increased risk of mortality in this patient population.

Bucindolol hydrochloride (bucindolol) is a nonselective β-adrenergic receptor (βAR) blocking agent with mild vasodilator properties that was previously studied in the BEST Phase 3 trial1 in a large pharmacogenomic substudy of the BEST trial, two unique pharmacologic properties of bucindolol, sympatholysis and inverse agonism, were shown to interact with all polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index2. Metoprolol (Toprol-XL), which is approved for the treatment of HF, has demonstrated maintenance of sinus rhythm and prevention of new-onset AF in a HF patient population and is often used in this setting. In contrast to bucindolol, metoprolol does not appear to add value to clinical benefit in HF with reduced left ventricular ejection fraction (HFrEF) patients that possess the β389Arg allele3,4. In addition, limited data from the BEST-HF DNA substudy did not demonstrate any evidence of a β389Arg allele on bucindolol pharmacogenetic differences for prevention of AF. The goal of the GENETIC-AF trial is to demonstrate the superiority of pharmacogenetically targeted bucindolol compared to metoprolol for the prevention of symptomatic AF/AFI in a genotype-defined β389Gly/Arg patient population at high risk of AF, occurrence.

References


Heart Failure Rationale

β-AR Polymorphisms

• β389Arg allele provides substantially greater adrenergic drive compared to the β389Gly form of the receptor: 
  - Greater insilica adrenergic activity 
  - Higher binding affinity for NE 

Bucindolol side-effect profile

• Bucindolol also has two unique pharmacologic properties: 
  - Symptolysis 
  - Inverse agonism 

Baseline Heart Failure Characteristics

• Best was a double-blind, placebo-controlled, Phase 3 trial of bucindolol in 728 HF patients: 
  - Primary Endpoint: 
    - All cause mortality or p<0.001 
  - Improvements in NYHA class I and II patients: p<0.001 
• The β389Gly allele was not associated with any evidence of a β389Arg allele on bucindolol pharmacogenetic differences for prevention of AF.

Atrial Fibrillation Rationale

• Meta-analysis of new onset AF in 7 large Beta-Blocker HF trials (n=13,105): 
  - β-blockers: Relative Risk = 0.73 (73% risk reduction) 
  - Bucindolol’s benefits are enhanced in β389Arg patients (p<0.001) 
  - But no benefit was observed in β389Gly patients (HR=1.01, p=0.59).

Atrial Fibrillation Endpoints

• In over 3,389 Arg patients in AF at baseline who were receiving bucindolol had: 
  - Greater heart rate reductions compared to β389Gly carriers (1.4-7.8% fewer) 
  - Reduction in AF in ACM/CHF (p=0.01) and DCM/CVA (p=0.08) 
  - Not observed for β389Gly carriers (not shown) in other β blockers below

Study Design

Primary Endpoint

• Time to first event of symptomatic AF/AFI or ACM assessed after 1 year of trial treatment. 

Other Study Endpoints

• Time to first event of ACM/HF (30d or ACM) 
• Proportion of patients with VTE or symptomatic VTE 
• Total number of hospitalization (all-causes) days per patient. 
• Time to first event of ACM/HF (30d) hospitalization for ACM. 
• Proportion of patients who have ACM at the end of study who demonstrate ventricular response rate control. 
• All burden assessed at study end with novel/non-existing Medtronic implanted devices (substudy).

Study Status

• The Phase 2a stage of the trial is currently recruiting 230 patients from approximately 70 centers in the US and Canada.
• Approximately 50 centers in Europe are being opened in Q1-2016.
• Phase 2b enrollment began in June 2014. More than 100 patients enrolled.
• The DBMV decision to proceed to Phase 3 is targeted for 1H 2017.
• ACM/HF patients are currently being enrolled in US, Canada, and Europe for Phase 3 expansion (≥150 total sites).
• Phase 3 follow up will continue until a total of at least 330 primary endpoint events have been observed.