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

Published: 16-08-2016
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The primary objective of this study is to compare the effects of bucindolol and metoprolol onthe recurrence of symptomatic AF/AFL in patients with HFREF who have a *1389 arginine homozygous(*1389Arg/Arg) genotype.The secondary objectives of this...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Cardiac arrhythmias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON43294

**Source**
ToetsingOnline

**Brief title**
GENETIC-AF

### Condition

- Cardiac arrhythmias

**Synonym**
atrial fibrillation, irregular hearth rythm

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** ARCA biopharma, Inc.
**Source(s) of monetary or material Support:** ARCA biopharma;Inc.

## Intervention

**Keyword:** atrial fibrillation, heart failure

## Outcome measures

### Primary outcome

Time to first event of symptomatic AF/AFL or ACM during the 24-week Follow-up

Period after

establishment of stable SR on study drug.

### Secondary outcome

- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic) or ACM

during the 24-week

Follow-up Period.

- Proportion of patients with VT, VF, or symptomatic supraventricular

tachycardia (SVT) during the

24-week Follow-up Period. Includes VF and symptomatic SVT events of any

duration, VT events of * 15 seconds, and VT

events that result in appropriate firing of an ICD.

- Total number of hospitalization days per patient (all-cause) during the Total

Study Period.

- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic), HF

hospitalization (as assessed

by the Investigator), or ACM during the Total Study Period.

- Proportion of patients with adequate ventricular rate control in the setting of AF/AFL.

Safety outcomes:

- Incidence of ACM during the Total Study Period.
- Incidence of ACM, cardiovascular-related hospitalization (as assessed by the Investigator), or withdrawal of study drug due to an adverse event (AE) during the Drug Titration Period.
- Incidence of heart block during the Total Study Period.
- Incidence and severity of treatment-emergent AEs/SAEs over time during the Total Study Period.
- Incidence of neoplasm-related AEs/SAEs during the Total Study Period.
- Change from baseline in clinical laboratory tests over time during the Total Study Period.
- Change from baseline in vital signs and weight over time during the Total Study Period.
- Change from baseline in quantitative ECG parameters (i.e., QTc, QRS, PR and HR).
- Proportion of patients attaining target study drug dose during the Drug Titration Period.

# Study description

### Background summary

Please see protocol p.14-20 for more information.

### Study objective

The primary objective of this study is to compare the effects of bucindolol and metoprolol on
the recurrence of symptomatic AF/AFL in patients with HFREF who have a *1389 arginine homozygous
(*1389Arg/Arg) genotype.

The secondary objectives of this study are to compare the effects of bucindolol and metoprolol on clinical
outcomes and other electrocardiographic parameters, and to assess the effects on rate control in patients
who have developed recurrent AF/AFL. The safety and tolerability of bucindolol and metoprolol will also
be evaluated.

### Study design

GENETIC-AF is a double-blind, two-arm, genotype-directed, active-controlled, adaptivedesigned,
superiority study that compares the effects of bucindolol and metoprolol on the time to first
event of symptomatic AF/AFL in HFREF patients in SR who are at high risk of AF/AFL recurrence.

Two patient populations at high risk of AF/AFL recurrence will be included in this study:
1) patients with
symptomatic paroxysmal or persistent AF who are indicated for ECV to attain SR, and;
2) patients in SR who have experienced a recent episode (i.e., * 180 days) of paroxysmal or persistent AF who are
indicated for ECV to attain SR if AF/AFL recurs.
Patients must have HF, a left ventricle ejection fraction (LVEF) < 0.50 in the past 12 months, and no contraindication for beta-blocker therapy.
Beta-blocker therapy is permitted at screening but is not required to be eligible for the study. Patients must be receiving optimal
anticoagulation therapy for stroke prevention prior to randomization. Patients will be genotyped for beta1-1389 AR at screening and those who are

beta1-1389Arg/Arg (50% of patients) will be randomized to study drug.

A subset of patients participating in the trial will have their cardiac rhythm continuously monitored to assess AF burden (AFB). AFB monitoring will be done via the Medtronic Reveal insertable cardiac monitor (ICM) or a Medtronic pacemaker (IPG), implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT) device with a minimum of an atrial and a ventricular lead. Patients participating in the optional AFB substudy must either have a pre-existing Medtronic device that can measure AFB, or agree to have one inserted as clinically indicated. Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.

Eligible patients will be randomized (1:1) to blinded treatment with bucindolol or metoprolol (i.e., study drug) and up-titrated weekly to target doses of 50 mg BID (< 75 kg) or 100 mg BID (* 75 kg) for bucindolol or 200 mg QD for metoprolol. Randomization will be centralized and stratified by: 1) HF etiology (ischemic vs. non-ischemic); 2) LVEF (< 0.35 vs. * 0.35); 3) type of Medtronic device (Reveal vs. Non-Reveal vs. No Device), and; 4) rhythm status at randomization (SR vs. AF/AFL).
Patients in AF at randomization who do not spontaneously convert to stable SR and are in AF/AFL after 3 weeks of treatment with study drug will undergo ECV to establish stable SR. Patients in SR at randomization who are in AF/AFL after 3 weeks of study drug treatment will also undergo ECV to establish stable SR. Patients in SR at randomization who are in stable SR after 3 weeks (± 3 days) of study drug treatment will start the 24-week Follow-up Period at the Week 0 Visit.
ECV may be performed as early as 1 week after randomization if all of the following conditions are met:
1) the patient is receiving the target dose of study drug;
2) the patient is receiving guideline indicated oral anticoagulation therapy for stroke prevention, and;
3) a delay of ECV could be detrimental to patient outcome.
The first ECV attempt may also be performed as late as 8 weeks after randomization if, in the opinion of the Investigator, additional time is needed to attain target doses

of study drug or to achieve
appropriate anticoagulation status prior to ECV.

The primary endpoint, i.e., time to first event of symptomatic AF/AFL or all-cause mortality (ACM), will
be assessed during the 24-week Follow-up Period after establishment of stable SR on study drug. For
patients requiring ECV, establishment of stable SR will be confirmed by electrocardiogram (ECG) at least
1 hour post-ECV. Patients who do not demonstrate stable SR following ECV will undergo a subsequent
ECV to establish a baseline SR unless, in the opinion of the Investigator, it would not be the best course
of treatment for the patient.

The 24-week Follow-up Period will begin on the day of: 1) the ECG that establishes stable SR; 2) the last ECV attempt for patients who fail to convert to stable SR, or; 3) the
Week 0 Visit for patients in AF/AFL who do not undergo ECV for any reason.
During the 24-week Follow-up Period, heart rhythm will be assessed by 12-lead ECG at scheduled clinic
visits. At the time of each ECG assessment, patients will be queried for symptoms potentially related to
AF/AFL. Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22.
Patients will be also be instructed to contact the site immediately if they experience new or worsening symptoms.

Patients will be queried for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts.
If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments.
Patients experiencing recurrence of AF/AFL will be encouraged to remain on blinded study drug and may undergo subsequent
ECV procedures or medical interventions as clinically indicated.

After the Week 24 Visit, patients will enter the Treatment Extension Period and continue to receive
blinded study drug. Phase 3 follow-up will continue until a total of at least 330 primary endpoint events
have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to
the clinic for an end of study visit if already in the Treatment Extension Period. At the end of the study,
patients will discontinue study drug and should transition to

commercially-available *-blocker therapy per
Investigator discretion. Investigators and patients will not be informed of the blinded study drug
assignment at the time of study completion.

**Intervention**

Patients who are not receiving beta-blocker therapy at randomization will initiate treatment with either
6.25 mg twice daily (BID) bucindolol or 25 mg once daily (QD) metoprolol and will be up-titrated in
a blinded manner to the target doses.
Patients receiving *-blocker therapy at baseline will discontinue this treatment at the time of
randomization, initiate blinded *-blocker therapy as described below, and will be up-titrated in a
blinded manner to the target doses.
Study drug should be up-titrated to the target dose for all patients unless clinically contraindicated.
Target doses for study drug are: 1) 200 mg QD metoprolol; 2) 50 mg BID bucindolol for patients who
weigh < 75 kg, and; 3) 100 mg BID bucindolol for patients who weigh * 75 kg.

If needed, the first ECV should be performed 3 weeks after randomization, but it may be performed as
early as 1 week or as late as 8 weeks after randomization, if clinically required.

During the 24-week follow-up period, and the extension phase of treatment, the patients will be treated as mentioned above (target dose).

**Study burden and risks**

Please refer to Subject Information Sheet.

# Contacts

**Public**
ARCA biopharma, Inc.

CirclePoint Road, Suite 140 1180
Westminster, Colorado 80020
US
**Scientific**

ARCA biopharma, Inc.

CirclePoint Road, Suite 140 1180
Westminster, Colorado 80020
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for randomization in this study.;1. Age * 18 years and * 85 years at the Screening Visit.;2. Weight * 40 kg at the Randomization Visit.;3. Possess the *1389Arg/Arg genotype.;4. History of heart failure with reduced left ventricle ejection fraction (HFREF).;a. LVEF < 0.50 assessed at any time during the previous 12 months of the Screening Visit.;5. At least one symptomatic paroxysmal or persistent AF episode * 180 days of the Screening Visit.;a. Qualifying AF episode may be documented by ECG, Holter, TTM, or implanted device. AF documented by implanted device must be a single episode * 60 minutes in duration. Atrial flutter is not considered a qualifying AF episode.;b. Must have experienced AF symptoms * 180 days of the Screening Visit, but these symptoms may overlap with HF symptoms, i.e. may be *arrhythmic* (e.g. palpitations, dizziness) or *heart failure* (e.g. breathlessness, fatigability) in nature.;6. Clinically appropriate for ECV if AF/AFL is present at the Week 0 Visit, including:;a. Patients with AF/AFL at randomization determined by the Investigator to require ECV.;b. Patients in SR at randomization determined by the Investigator to require ECV if AF/AFL recurs.;7. Receiving guideline indicated oral anticoagulation therapy at the Randomization Visit, which is considered optimal for stroke prevention in the opinion of the Investigator.;8. Systolic blood pressure > 90 mmHg and < 150 mmHg at the Randomization Visit.;9. Female of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit.;a. Female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.;10. Female of childbearing potential must agree to use a highly effective contraception for the duration of the trial and for at least 30 days following the last dose of study drug.;a. Female

who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.;11. Must agree not to participate in a clinical study involving another investigational drug or device throughout the duration of this study.;12. Must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved ICF. Must sign the ICF prior to the initiation of any study procedure and not withdraw consent prior to the Randomization Visit.

## Exclusion criteria

1. NYHA Class IV symptoms at the Randomization Visit.
2. Significant fluid overload at the Randomization Visit, in the opinion of the Investigator. Evidence of significant fluid overload may included
a. Mean jugular venous pressure above the clavicle at 90°.
b. Liver congestion.
c. Moist pulmonary rales post-cough.
d. Peripheral edema beyond 1+ pedal not explained by local factors.
3. Permanent AF at the Screening Visit.
a. Permanent AF is defined as an ongoing AF event 1 year or longer in duration in which there is no intervening evidence of SR.
4. More than two ECV procedures within 6 months of the Randomization Visit or if the most recent ECV within 6 months of the Randomization Visit failed to produce SR.
5. Use of any of the following < 7 days of the randomization Visit:
a. Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, propafenone, sotalol, non-dihydropyridine calcium channel blockers, daily NSAIDS (e.g., ibuprofen, celecoxib), thiazolidinediones, or frequent use of short acting nitroglycerin (e.g., > 6 sublingual tablets/week).
b. Note: Amiodarone and dofetilide can be restarted after the start of follow-up if the patient experiences an AF/AFL event or after failure to convert to SR following ECV (see protocol Section 5.8).
6. The presence of a left ventricular assist device (LVAD) or a condition that is likely to require LVAD placement within 6 months of the Randomization Visit.
7. History of a successful atrioventricular node ablation.
8. History of an AF ablation or AFL ablation within 30 days of the Randomization Visit.
9. History of untreated second degree Mobitz II or third degree heart block.
10. History of untreated symptomatic bradycardia or if symptomatic bradycardia is likely on full dose of study drug in the opinion of the Investigator.
11. Heart rate < 60 beats per minute at the Randomization Visit for patients who were not receiving *-blocker therapy during the screening period.
12. Heart rate > 180 beats per minute at the Randomization Visit.
13. Contraindication or previous history of intolerance to *-blocker therapy (e.g., untreated valvular disease) or Toprol-XL (e.g., inability to tolerate at least 25mg QD).
14. Myocardial infarction, unstable angina, acute coronary syndrome, cardiac surgery (including PTCA or stent placement), or evidence of new ischemic changes as assessed by ECG * 90 days of the Randomization Visit.
15. Moderate to severe asthma or other obstructive lung disease requiring chronic use (> 2

days/week) of an inhaled *2-selective adrenergic agonist < 7 days of the Randomization Visit.;16. History of pulmonary hypertension, defined as a systolic pulmonary arterial pressure * 70 mmHg at rest as assessed by echocardiography or right heart catheterization.
17. Known reversible causes of AF such as alcohol intoxication, pulmonary embolism, hyperthyroidism, acute pericarditis, or hypoxemia.
18. Evidence of an appropriate firing of an ICD device for ventricular tachycardia (VT) or ventricular fibrillation (VF) * 90 days of the Randomization Visit.
a. Exception: does not include anti-tachycardia pacing.
19. Untreated thyroid disease, in the opinion of the Investigator, at the Randomization Visit.
20. Serum potassium < 3.5 mmol/L at the Screening Visit.
a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
21. Renal failure requiring dialysis, serum creatinine < 2.5 mg/dL or an estimated creatinine clearance < 30 mL/min (Cockcroft-Gault) at the Screening Visit.
a. Lab values will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.;22. Significant intrinsic liver disease or a total bilirubin > 2.5 mg/dL at the Screening Visit.;
a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
23. Use of strong inhibitors of cytochrome P450 2D6 (e.g., fluoxetine, paroxetine, propafenone, quinidine, or ritonavir) < 7 days prior to the Randomization Visit for patients who are not receiving *-blocker therapy at screening.
24. Participation in a clinical study or treatment with an investigational drug or device within 30 days of the Screening Visit (or 5 half-lives of the investigational agent, whichever is longer).
25. Comorbid condition or illness which, in the opinion of the Investigator, may limit life expectancy to less than 1 year.
26. Serious or active medical or psychiatric condition
27. Treatment for a malignancy * 2 years prior to randomization, the presence of a treated malignancy that has evidence of disease progression
28. History of alcohol, drug or chemical abuse

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |

| | |
|---|---|
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 30-11-2016 |
| Enrollment: | 60 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Generic name: | MedTronic Reveal LINQ Insertable Cardiac Monitor |
| Registration: | Yes - CE intended use |
| Product type: | Medicine |
| Brand name: | bucindolol hydrochloride |
| Generic name: | bucindolol hydrochloride |
| Product type: | Medicine |
| Brand name: | TOPROL-XL |
| Generic name: | metroprolol succinate |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 16-08-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 30-11-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 19-01-2017 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 02-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 16-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 19-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 04-08-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 11-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 24-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 28-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 30-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2016-000302-12-NL |
| ClinicalTrials.gov | NCT01970501 |
| CCMO | NL58618.042.16 |