The ARISE-HF Study – Development of AT-001 for the Treatment of Diabetic Cardiomyopathy: Rationale and Study Design

James L. Januzzi[1], Riccardo Perfetti[2], Francesca Lawson[2] on behalf of the ARISE-HF Steering Committee, National Coordinators and Investigators New York, NY

Abstract

The ARISE-HF Study – Development of AT-001 for the Treatment of Diabetic Cardiomyopathy: Rationale and Study Design

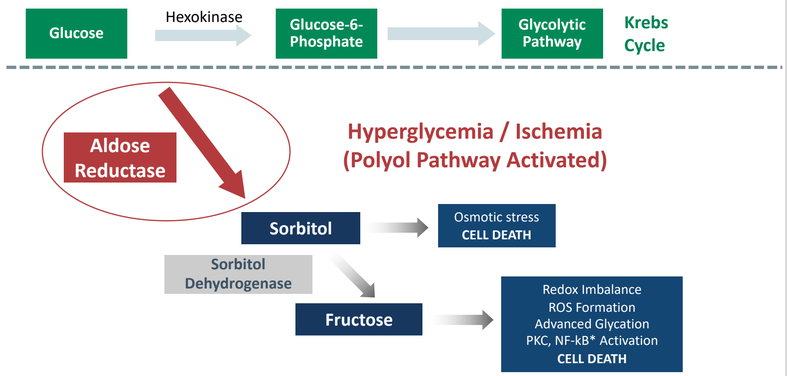
Diabetic Cardiomyopathy (DbCM) is a common sequelae of diabetes, resulting from diabetes-associated metabolic alterations. DbCM is characterized by abnormal cardiac structure and/or performance in the absence of coronary artery disease or hypertensive, valvular or congenital heart disorder. The condition exists in 17-24% of patients with diabetes, with a resulting prevalence of ~77 M patients worldwide (~ 8.0M in North America and ~10.0M in Europe). DbCM is a form of Stage B Heart Failure (SBHF) and is associated with a high risk of progression to overt Stage C Heart Failure (SCHF). Approximately 24% of DbCM patients progress to symptomatic HF or death within 1.5 years and 37% within 5 years. No therapies currently exist to target the metabolic derangement responsible for DbCM or to prevent progression to overt heart failure.

Hyperactivation of the polyol pathway is a pathogenetic mechanism of DbCM. Aldose Reductase (AR), the first and rate-limiting step in the polyol pathway, is activated by hyperglycemia and catalyzes the conversion of glucose into sorbitol. This induces oxidative stress, up-regulates pro-inflammatory signals and ultimately causes cell death. AT-001 is a novel investigational Aldose Reductase Inhibitor (ARI) shown to significantly inhibit the production of sorbitol at well-tolerated doses in a phase 1-2 clinical study. The ARISE-HF pivotal study is a randomized, placebo-controlled, double blind, global clinical study to investigate the safety and efficacy of two doses of AT-001 (1,000 mg BID and 1,500 mg BID) in 675 patients with DbCM/SBHF at high risk of progression to SCHF.

Introduction

Diabetic Cardiomyopathy (DbCM) is a form of Stage B Heart Failure (SBHF) that affects 18-24% of people with type 2 diabetes (T2D)[1,2] and currently lacks any approved therapies, despite being associated with a high risk of progression to overt Stage C Heart Failure (SCHF). Hyperactivation of the polyol pathway is a key underlying mechanism in DbCM and other diabetic complications. In hyperglycemic and ischemic conditions, polyol pathway activation through the action of Aldose Reductase (AR) causes intracellular sorbitol accumulation leading to osmotic stress, cell death and diabetic complications.[3-4] Previous clinical investigations of AR inhibitors for diabetic complications were associated with off-target toxic effects and/or lack of efficacy due to lack of selectivity and specificity.[4] AT-001 is a novel AR inhibitor rationally designed based on the characterization of AR structural changes within the active site following enzymatic activation. AT-001 has demonstrated enhanced specificity, affinity and selectivity compared with previous AR inhibitors that were associated with off-target effects and/or lack of efficacy. The clinical PK and safety of AT-001 has been established in a series of earlier studies. The ARISE-HF study is a global clinical trial designed to evaluate the efficacy and safety of AT-001 in a representative sample of patients with DbCM/SBHF

Background: The Polyol Pathway and Aldol Reductase in DbCM



*Nf-kB is a protein complex that controls transcription of DNA, cytokine production and cell survival

[1]Brownlee M. Diabetes Care. 2005;54(6):1615-1625. [2]Miki T, et al. Heart Fail Rev. 2013;18(2):149-16.
[3]Parim B, et al. Heart Failure Rev 2019:24:279-299 [4]Grewal AS, et al. Min Rev Med Chem 2016; 16:120-62

AT-001: Preclinical and Phase 1/2 clinical data

Pre-Clinical Profile

- 1,000X more potent than old generation best-in-class ARI (zopolrestat), in vitro and in vivo
- Broad tissue exposure: Cardiac and nerve tissue
- Significant reduction of cardiac damage in an animal model of cardiomyopathy

Clinical Profile (Phase 1-2 trial)

- Clinical proof-of-concept observed in T2D patients
  - Dose-dependent inhibition of sorbitol informed dose selection
- Well tolerated: No treatment-related adverse events (AEs), or AEs leading to discontinuation
- Inhibition of NT-proBNP observed in T2D patients with elevated baseline levels (mean=65 pg/ml; range:30-235 pg/ml)

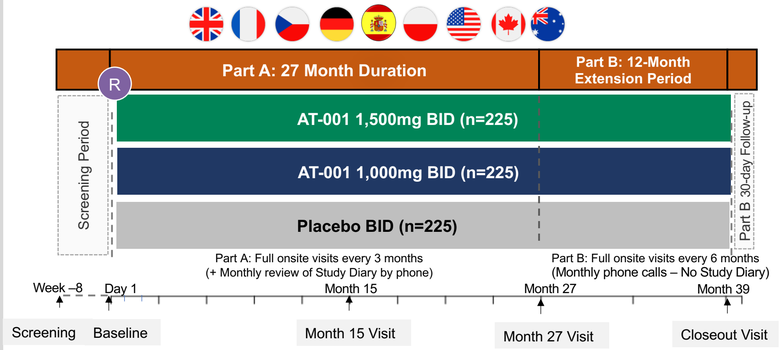
ARISE-HF Primary Objective

Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure (ARISE-HF)
AT-001-2001 - Phase 3 Study

Primary Objective

To demonstrate that AT-001 improves or prevents the decline of functional capacity in patients (N=675) with diabetic cardiomyopathy (DbCM) / Stage B Heart Failure (SBHF) at high risk of progression to overt heart failure (HF)/ Stage C Heart Failure (SCHF)

ARISE-HF Study Scheme



ARISE-HF Inclusion Criteria

1. **T2D**
2. **Age ≥ 60,**

OR

Age ≥ 40 < 60 with 1 additional risk factor: uncontrolled diabetes (HbA1c > 7.5%), long diabetes duration (≥ 10 years), elevated HsTnT (>15.0 pg/mL for men and >10.0 pg/mL for women), obesity (BMI > 30 Kg/m^2), renal impairment (eGFR < 60 ml/min/1.73 m^2), prior diagnosis of diabetic neuropathy, or retinopathy

AND

3. **NT-proBNP > 125 pg/ml (≥ 100 pg/ml if BMI > 30 kg/m^2)**
4. **Echocardiographic demonstration of**
   - LVEF ≥ 45% **AND** at least **2** of the following:
   - Impaired Global Longitudinal Strain (GLS)
   - Left Ventricular Hypertrophy (LVH)
   - Left Atrial Enlargement (LAE)
   - Diastolic Dysfunction (DD)
   - Increased Right Ventricular Systolic Pressure (RSVP)
5. **CPET demonstration of both:**
   - Peak VO2 < 75% of predicted
   - Respiratory Exchange Ratio (RER) ≥ 1.05

ARISE-HF Key Exclusion Criteria

- Prior diagnosis of overt/symptomatic HF (i.e. SCHF)
- History of ACS, PCI, CABG, CAD
- History of severe valve disease, or clinically significant arrhythmia
- History of congenital, infective, toxic (eg chemotherapy), post-partum, infiltrative or hypertrophic CM
- BMI > 40 kg/m^2
- Use of a loop diuretic
- HbA1c >8.5%
- Hb < 10.0 g/dl
- ALT, AST or total bilirubin (except Gilbert's) > 1.5 ULN
- eGFR < 45 mL/min/1.73 m^2
- UACR > 300 mg/g
- SBP >140 mmHg or DBP ≥ 90 mmHg

ARISE-HF Primary Endpoint

Primary Endpoint: Cardio-Pulmonary Exercise test

Timing:
- At Month 15
- Possibly repeated at Month 27

Sample size calculation:
- Difference in **peak VO_2** between active and placebo = **1.2 ml/kg/min**
- Standard deviation = 3
- Power = 90%
- Alpha = 0.0125; 2-sided

ARISE-HF Secondary Endpoints

Progression to SCHF, defined by the occurrence of ≥1 of the following events by Month 27
- CV death
- Hospitalization for HF
- Urgent HF visit
- New diagnosis of HF (requiring initiation of a loop diuretic)

Changes in NT-proBNP
Changes in the modified KCCQ (Kansas City Cardiomyopathy Questionnaire) (mKCCQ) score
Percentage of patients with a clinically significant decrease in peak VO_2 (i.e. >6%)
Changes in GLS, LVH, LAE, E/E' and RVSP by echocardiography from baseline to Month 27
Percentage of patients with worsening of DbCM/SBHF defined by either
- A significant increase (at least 20%) of NT-proBNP, or
- A significant decrease (at least 5 point) in the modified Kansas City Cardiomyopathy Questionnaire (mKCCQ) score

Arise-HF Steering , Operational Committee and National Coordinators

Steering Committee

Chair:
James Januzzi, MGH, Boston, MA, USA

Cardiologists:
Javed Butler, Univ of Mississippi, MS, USA
Justin Ezekowitz, Univ of Alberta, AB, Canada
Nasrien Ibrahim, MGH, Boston, MA, USA
Carolyn Lam, NHC, Singapore, Malaysia
Thomas Marwick, Univ.of Melbourne, Melbourne, Australia
Faiez Zannad, Inserm-CHU, Nancy, France

Endocrinologists:
Stefano Del Prato, University of Pisa, Pisa, Italy
Julio Rosenstock, Diabetes Center of Dallas, Dallas TX, USA

Operational Committee

CPET Core Lab: Greg Lewis, MGH, Boston, MA, USA

Echo Core Imaging Center: Scott Solomon, BWH, Boston, MA, USA

National Coordinators:

Canada: Alice Cheng, Univ. of Toronto, Toronto, ON, Canada

Czech Republic: Martin Haluzik, Inst. for Clinical and Experimental Medicine, Prague, Czech Republic

France: Paul Valensi, Paris-Nord U., Paris, France

Germany: Andreas Fritsche, Univ. of Tubingen, Tubingen, Germany

Poland: Ewa Krzyzagorska, Poznan Univ. of Technology, Poland

Spain: Didac Mauricio, Autonomous Univ. of Barcelona, Barcelona, Spain

UK: Kamlesh Khunti, Univ. of Leicester, Leicester, UK

USA:
Yehuda Handelsman, Metabolic Institute of America, Tarzana, CA, USA
Luigi Meneghini, UT Southwestern, Dallas, TX, USA
Vanita Aroda, BWH, Boston, MA, USA

Data Monitoring Committee

Chair: Chris Cannon, BWH, Boston, MA, USA

Cardiologists:
Antonio Abbate, Virginia Commonwealth Univ., Richmond, VA, USA
Mikhail Kosiborod, Univ. of Missouri, Kansas City, MO, USA

Endocrinologists:
Larry Leiter, Univ. of Toronto, Toronto, ON, Canada

Biostatistician:
Joe Massaro, Boston Univ., Boston, MA, USA

Ad hoc Nephrologist
Orson Moe, UT Southwestern, Dallas, TX, USA

Cardiovascular Event Adjudication Committee

Chair: Kenneth W. Mahaffey, Stanford Univ., Palo Alto, CA, USA

Cardiologists:
Larry Allen, Univ. of Colorado, Denver, CO, USA
Lori Daniels, Univ. of California, San Diego, CA, USA
Mark Petrie, Univ. of Glasgow, Scotland, UK