

**A Selective Aldose Reductase Inhibitor for the Treatment of Diabetic Cardiomyopathy:
A Randomized Clinical Trial**

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Committees

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Role	Name	Institution
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Member	Javed Butler	Baylor Scott and White Institute; University of Mississippi
Member	Faiez Zannad	Universite de Lorraine, Inserm CIC and CHRU
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Member	Joseph Massaro	Boston University
Member, Nephrology consultant	David Bushinsky	University of Rochester
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Member	Larry Allen	University of Colorado
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D) Core Laboratories

Role	Name	Institution
CPET Core Lab	Greg Lewis	Massachusetts General Hospital
Echo Core Lab	Scott D. Solomon	Brigham and Women's Hospital

National Leaders and Sites

A) National Leaders

Role	Name	Institution
National coordinator	Yehuda Handelsman	Metabolic Institute of America
National coordinator	Vanita Aroda	Brigham and Women's Hospital
National coordinator	Alice Cheng	St. Michael's Hospital
National coordinator	Paul-Elie Valensi	University of Paris Nord
National coordinator	Kamlesh Khunti	University of Leicester
National coordinator	Martin Haluzik	Charles University
National coordinator	Didac Mauricio	Hospital de la Santa Creu I Sant Pau
National coordinator	Ewa Kryzagorska	Posznan University of Technology
National coordinator	Kilian Rittig	Institute for Diabetes and Angiology

B) Clinical Sites

Site - Name	PI - Country	Site - Location
Southwest Family Medicine Associates	United States	Dallas, TX
Broward Research Center	United States	Pembroke Pines, FL
Holston Medical Group	United States	Kingsport, TN
Tribe Clinical Research	United States	Greenville, SC
New Generation of Medical Research	United States	Hialeah, FL
Remington Davis, Inc.	United States	Columbus, OH
ALL Medical Research, LLC	United States	Cooper City, FL
Velocity Clinical Research - Dallas	United States	Dallas, TX
FMC Science	United States	Lampasas, TX
Juno Research, LLC	United States	Houston, TX
Progressive Medical Research	United States	Port Orange, FL
South Oklahoma Heart Research	United States	Oklahoma City, OK
UnityPoint Health - Methodist Hospital	United States	Peoria, IL
Chear Center LLC	United States	Bronx, NY
Lundquist Institute for Biomedical Innovation at Harbor UCLA Medical Center	United States	Torrance, CA
Brigham and Women's Hospital	United States	Boston, MA
Clinical Trials Research	United States	Lincoln, CA
University of Texas Southwestern	United States	Dallas, TX
Metabolic Institute of America	United States	Tarzana, CA
Cleveland Clinic	United States	Cleveland, OH
University of California - Irvine Medical Center	United States	Irvine, CA
University of Mississippi Medical Center	United States	Jackson, MS
Westside Medical Associates of Los Angeles- NATIONAL HEART INSTITUTE	United States	Beverly Hills, CA
St. Louis Heart and Vascular Cardiology	United States	St. Louis, MO
InvivoCure LLC	United States	Mission Hills, CA

ECOGENE-21	Canada	Chicoutimi, Quebec
C-Endo - Calgary	Canada	Calgary, Alberta
Institut Universitaire de Cardiologie et de Pneumologie De Quebec	Canada	Quebec, Quebec
BC Diabetes	Canada	Vancouver, British Columbia
CHU de Nantes	France	Nantes Cedex 1
AP-HP Hopital Jean-Verdier	France	Bondy
Cardiologicum Pirna und Dresden	Germany	Dresden
Herz- und Diabeteszentrum NRW, Bad Oeynhausen Universitaetsklinik der Ruhr-Universitaet Bochum	Germany	Bad Oeynhausen
Klinische Forschung Berlin GbR	Germany	Berlin
ZKS - Zentrum Klinische Studien Sudbrandenburg GmbH	Germany	Elsterwerda
Klinikum Frankfurt (Oder) GmbH	Germany	Frankfurt
Diabetespraxis Dr. Braun	Germany	Berlin
Hospital Abente y Lago	Spain	La Coruna, Galicia
Hospital de la Santa Creu i Sant Pau	Spain	Barcelona
Hospital Universitario Virgen Macarena	Spain	Sevilla
Hospital Germans Trias i Pujol	Spain	Badalona
Ninewells Hospital & Medical School	United Kingdom	Dundee
Glenfield hospital	United Kingdom	Leicester
Barts and The London School of Medicine & Dentistry	United Kingdom	London
CPS Research	United Kingdom	Glasgow
Baker Heart and Diabetes Institute	Australia	Melbourne
AusTrials	Australia	Kippa Ring, Queensland
Barwon Health	Australia	Geelong, Victoria
CORE Research Group Pty. Ltd.	Australia	Milton, Queensland
Prince of Wales Hospital	Hong Kong	Shatin
Baker Heart and Diabetes Institute	Australia	Melbourne
Austin Health	Australia	Heidelberg, Victoria
Prince of Wales Hospital	Hong Kong	Shatin
Sir Charles Gairdner Hospital	Australia	Nedlands
University of Tasmania at Hobart	Australia	Hobart, Tasmania
Edumed s.r.o.	Czech Republic	Nachod
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4 Wojskowy Szpital Kliniczny z Poliklinika Samodzielny Publiczny ZOZ we Wrocławiu	Poland	Wrocław
NZOZ Specjalistyczny Osrodek Internistyczno - Diabetologiczny	Poland	Białystok

Supplemental Table 1: Full inclusion and exclusion criteria for the ARISE-HF Trial.

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

1. Diagnosis of Type 2 Diabetes Mellitus (T2DM)
2. One of the following age-related criteria:
 - Age \geq 60 years
 - OR
 - Age \geq 40 to $<$ 60 years AND at least **1** of the following 2 risk factors:
 - Duration of diabetes \geq 10 years
 - Estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m²
3. Demonstration of Diabetic Cardiomyopathy (DbCM) / Stage B Heart Failure (SBHF) defined by Left Ventricular Ejection Fraction (LVEF) \geq 45% and at least one of the following 3 criteria:
 - Echocardiographic demonstration of the following, as confirmed by either the central core lab or by local review at selected study centers:
 - At least 1 of the following 5 abnormalities:
 - Absolute value of global longitudinal strain (GLS) $<$ 16% (i.e., GLS $>$ -16%)
 - Left ventricular hypertrophy (LVH) defined as left ventricular mass index (LVMI) \geq 95 g/m² in women and \geq 115 g/m² in men
 - Left atrial enlargement (LAE) defined as left atrial volume index (LAVi) $>$ 34 mL/m²
 - Diastolic Dysfunction defined as E/E' \geq 13
 - Right ventricular systolic pressure (RVSP) $>$ 35 mmHg
 - OR
 - N-terminal pro B-type natriuretic peptide (NT-proBNP) \geq 50 pg/mL
 - OR
 - High-sensitivity troponin T (HsTnT) \geq 6 ng/L
4. Cardiopulmonary exercise test (CPET) demonstration of both, as confirmed by the CPET core lab:
 - Impaired functional capacity, i.e., peak oxygen uptake (VO₂) $<$ 75% of predicted, based on age and gender
 - Ability of maximal effort, i.e., achieve a respiratory exchange ratio (RER) \geq 1.05

Exclusion Criteria

1. Prior diagnosis of overt/symptomatic heart failure/Stage C heart failure (SCHF), or prior or current symptom(s) or sign(s) that in the opinion of the investigator may be related to undiagnosed overt/symptomatic heart failure/SCHF. These symptoms and signs include, but are not limited to:
 - Breathlessness
 - Orthopnea
 - Paroxysmal nocturnal dyspnea
 - Fatigue or tiredness
 - Bilateral ankle edema
 - Rales
 - Jugular venous dilatation
2. Any prior echocardiographic measurement indicating ejection fraction (EF) < 40%
3. History of acute coronary syndrome (ACS), including acute myocardial infarction
4. History or planned coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI; e.g., stent or angioplasty)
5. Prior diagnosis of coronary artery disease (CAD) defined as $\geq 50\%$ stenosis of any major coronary artery
6. History of severe mitral, aortic, tricuspid, or pulmonary valve disease, or moderate valve disease requiring intervention
7. History of any clinically significant arrhythmia (including permanent atrial fibrillation or history of paroxysmal atrial fibrillation requiring hospitalization, unless successfully ablated with no episodes of recurrence for at least 3 years)
8. History of stroke
9. History of congenital, infective, toxic (e.g., chemotherapy or radiation), infiltrative (e.g., amyloidosis, sarcoidosis, or hemochromatosis), post-partum, or hypertrophic cardiomyopathy
10. Myocarditis induced by active autoimmune disease (e.g., Graves' disease or systemic lupus erythematosus)
11. Pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1)
12. Blood pressure > 140 mmHg (systolic) or > 90 mmHg (diastolic) at screening, treated or untreated
13. History of multiple (at least 2) hospitalizations for hypertensive emergency
14. Body mass index (BMI) $\geq 45 \text{ kg/m}^2$
15. Antihyperglycemic treatment has not been stable in the 4 weeks prior to screening in the opinion of the Investigator
16. Treatment with inhibitors of the renin-angiotensin-aldosterone system (RAAS) has not been stable in the 12 weeks prior to screening in the opinion of the Investigator
17. Use of thiazolidinediones at screening and/or after randomization
18. Planned start of a sodium glucose co-transporter 2 (SGLT2)-inhibitor after randomization (If a decision to start a SGLT2-inhibitor has already been made during the screening period, the treatment with a SGLT2-inhibitor should be initiated before randomization. Note that initiation of a SGLT2-inhibitor during the study is allowed at any time before and after randomization.)
19. Any current or prior use of a loop diuretic
20. Pregnant or breastfeeding women

21. Females of childbearing potential not willing to use a highly effective form of birth control from screening until the Study Closeout Visit, or Post-Treatment Follow-up Visit, whichever occurs later
22. Severe disease making implementation of the protocol or interpretation of the study results difficult. This includes clinically significant hematopoietic, renal, hepatic (including hepatitis B and C), endocrine, pulmonary, neurological, psychiatric, immunological (including human immunodeficiency virus – acquired immunodeficiency syndrome [HIV-AIDS]), dermatological, or gastrointestinal diseases or active malignant tumor (except for non-melanoma skin cancer), as well as conditions that would impact the performance of a CPET (e.g., claudication, chronic lung, musculo-skeletal or neuro-muscular disease).
23. Any condition that prevents the obtainment of a good quality echocardiogram at baseline
24. History of substance abuse including alcohol within 3 years (Use of cannabinoids is not an exclusion criterion).
25. History of clinically significant drug hypersensitivity reactions
26. Severe lower extremity complications (such as critical limb ischemia leading to skin ulcers, osteomyelitis and gangrene) and/or history of non-traumatic amputations
27. Short life expectancy (<12 months) making implementation of the protocol or interpretation of the study results difficult.
28. Investigators, site personnel directly affiliated with this study, and their immediate families (Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.)
29. Any other condition that, in the opinion of the Investigator, precludes the patient from following and completing the protocol
30. Use of any investigational drug within 5 half-lives prior to screening
31. Hemoglobin A1c (HbA1c) > 8.5% at screening
32. Hemoglobin (Hb) < 10.0 g/dL at screening
33. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or total bilirubin (except in case of Gilbert's syndrome) > 1.5 x upper limit of normal (ULN) at screening
34. An eGFR < 45 mL/min/1.73 m² (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) at screening
35. Interventions/conditions capable of altering the absorption, metabolism, or elimination of drugs or significantly impacting body weight (e.g., bariatric surgery)
36. History of hospitalization due to coronavirus disease 2019 (COVID-19) that required ventilation, or with residual pulmonary symptoms
37. Treatment with any sensitive substrates of organic anion transporter (OAT) 3 (OAT3) or inhibitors of OAT1 or OAT3 from randomization to the Study Closeout Visit. This includes, but is not limited to the following: **OAT3 substrates:** adefovir, cefaclor, ceftizoxime, famotidine, ganciclovir, oseltamivir carboxylate, penicillin G; and **OAT inhibitors:** probenecid. (for additional information, consult the Food and Drug Administration Drug-Drug Interaction [FDA DDI] website: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).
38. Treatment with any inhibitors of OATP1B1 or OATP1B3 from randomization to the Study Closeout Visit. This includes, but is not limited to the following: clarithromycin,

erythromycin, gemfibrozil, rifampin, simeprevir. (for additional information, consult the FDA DDI website: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).

39. History of kidney stones with >1 clinical recurrence requiring a surgical intervention during one of the recurrences (e.g., uroscopy with stone fragments removal/stent placement, nephrolithotomy, lithotripsy or open surgery)

Supplemental Table 2: Characteristics of study participants not receiving sodium/glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonist at baseline.

Characteristic	Overall (N=427)	Placebo (N=144)	AT-001 1000 mg (N=141)	AT-001 1500 mg (N=142)
Age, years, mean \pm SD	68 \pm 7.2	68.4 \pm 6.7	67.8 \pm 8.0	67.8 \pm 6.9
Female sex, n (%)	229 (53.6)	83 (57.6)	68 (48.2)	78 (54.9)
Race, n (%)				
White	354 (82.9)	121 (84)	121 (85.8)	112 (78.9)
Black	38 (8.9)	11 (7.6)	11 (7.8)	16 (11.3)
Asian	26 (6.1)	8 (5.6)	8 (5.7)	10 (7)
American Indian or Alaska Native	3 (0.7)	2 (1.4)	0 (0.0)	1 (0.7)
Hawaiian or Pacific Islander	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.7)
Other	4 (0.9)	1 (0.7)	1 (0.7)	2 (1.4)
Ethnicity, n (%)				
Hispanic or Latino	127 (29.7)	38 (26.4)	40 (28.4)	49 (34.5)
Not Hispanic or Latino	296 (69.3)	104 (72.2)	100 (70.9)	92 (64.8)
Not reported	2 (0.5)	1 (0.7)	0 (0.0)	1 (0.7)
Unknown	2 (0.5)	1 (0.7)	1 (0.7)	0 (0.0)
Geographical Region, n (%)				
North America	266 (62.3)	89 (61.8)	88 (62.4)	89 (62.7)
Rest of the World	161 (37.7)	55 (38.2)	53 (37.6)	53 (37.3)
Body-Mass Index (kg/m²), mean \pm SD	30.6 \pm 4.7	30.9 \pm 5.0	30.4 \pm 4.7	30.4 \pm 4.5
Baseline respiratory exchange rate, n (%)				
< 1.15	193 (45.2)	65 (45.1)	64 (45.4)	64 (45.1)
\geq 1.15	234 (54.8)	79 (54.9)	77 (54.6)	78 (54.9)
Peak VO₂ (mL/kg/min), mean \pm SD	15.3 \pm 3.8	15.2 \pm 3.8	15.4 \pm 3.8	15.3 \pm 3.9

SD denotes: standard deviation; kg denotes: kilogram; m² denotes: square meter; SGLT2i denotes: VO₂ denotes: oxygen consumption; mL denotes: milliliters; min denotes: minute

Supplemental Table 3: Medical Dictionary for Regulatory Activities preferred terms identified during post hoc analyses of clinical events.

Outcome measure
Asthenic condition
Atrial fibrillation
Breathing abnormalities
Cardiac failure
Cardiogenic shock
Diastolic dysfunction
Dyspnea
Dyspnea exertional
Dyspnea paroxysmal nocturnal
Fatigue
Joint swelling
Left ventricular dysfunction
Left ventricular hypertrophy
Oedema peripheral
Right ventricular dilatation
Venous pressure jugular increased

Supplemental Table 4: Measures of liver injury or cholestasis as a function of treatment assignment.

Category	Placebo	AT-001 1000 mg	AT-001 1500 mg
> 1x ULN ALT or > 1x ULN AST, N (%)	19 (8.26)	20 (8.77)	17 (7.36)
> 3x ULN ALT or > 3x ULN AST, N (%)	0 (0)	1 (0.44)	1 (0.43)
> 5x ULN ALT or > 5x ULN AST, N (%)	0 (0)	0 (0)	0 (0)
> 1x bilirubin, N (%)	6 (2.61)	15 (6.58)	12 (5.19)
> 1.5x bilirubin, N (%)	2 (0.87)	1 (0.44)	2 (0.87)
> 2x bilirubin, N (%)	0 (0)	0 (0)	0 (0)
(> 1x ULN ALT or > 1x ULN AST) AND > 1x bilirubin, N (%)	1 (0.43)	3 (1.32)	1 (0.43)
(> 3x ULN ALT or > 3x ULN AST) AND > 1x bilirubin, N (%)	0 (0)	1 (0.44)	1 (0.43)
(> 1x ULN ALT or > 1x ULN AST) AND > 1.5x bilirubin, N (%)	0 (0)	1 (0.44)	0 (0)
(> 3x ULN ALT or > 3x ULN AST) AND > 1.5x bilirubin, N (%)	0 (0)	0 (0)	0 (0)

ULN denotes: upper limit of normal; ALT denotes: alanine aminotransferase; AST denotes: aspartate aminotransferase

Supplemental Table 5: Trajectory of serum creatinine across study visits expressed as the number (%) of study participants with serum creatinine ≥ 1.5 milligrams/deciliter at the study visit.

visit	Placebo	AT-001 1000 mg	AT-001 1500 mg
1	1 (0.5)	5 (2.3)	3 (1.4)
2	0 (0)	5 (2.4)	1 (0.5)
3	1 (0.5)	6 (2.9)	0 (0)
6	0 (0)	3 (1.5)	2 (1)
9	0 (0)	4 (2)	2 (1)
12	1 (0.5)	2 (1)	1 (0.5)
15	2 (1.1)	2 (1.2)	2 (1.1)
18	0 (0)	3 (2.3)	4 (2.9)
21	0 (0)	1 (1.2)	1 (1.3)
24	0 (0)	0 (0)	0 (0)
27	0 (0)	0 (0)	0 (0)
33	0 (0)	0 (0)	2 (15.4)
39	0 (0)	0 (0)	0 (0)
45	0 (0)	0 (0)	0 (0)

Supplemental Table 6: Adverse events leading to discontinuation of treatment.

	Placebo	AT-001 1000mg	AT-001 1500mg
Gastrointestinal disorders	6	17	14
Nervous system disorders	2	5	7
General disorders and administration site conditions	4	4	4
Renal and urinary disorders	1	5	4
Respiratory, thoracic, and mediastinal disorders	2	4	0
Skin and subcutaneous tissue disorders	0	2	2
Cardiac disorders	3	1	0
Infections and infestations	1	2	1
Investigations	0	1	3
Neoplasms benign, malignant and unspecified	0	0	4
Metabolism and nutrition disorders	1	2	0
Vascular disorders	1	1	0
Psychiatric disorders	0	0	1
Reproductive system and breast disorders	0	1	0
Musculoskeletal and connective tissue disorders	0	1	0