A Selective Aldose Reductase Inhibitor for the Treatment of Diabetic Cardiomyopathy

Primary Results of the Phase 3 Randomized Controlled ARISE-HF Study

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Disclosures

Dr. Januzzi:

- Board member ACC, Imbria Pharma
- Grant support from Abbott, Applied Therapeutics, AstraZeneca, BMS, Novartis Pharmaceuticals
- Consulting income from Abbott Diagnostics, Beckman-Coulter, Jana Care, Janssen, Novartis, Prevencio, Quidel, and Roche Diagnostics
- Clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, CVRx, Medtronic, Pfizer, and Roche Diagnostics

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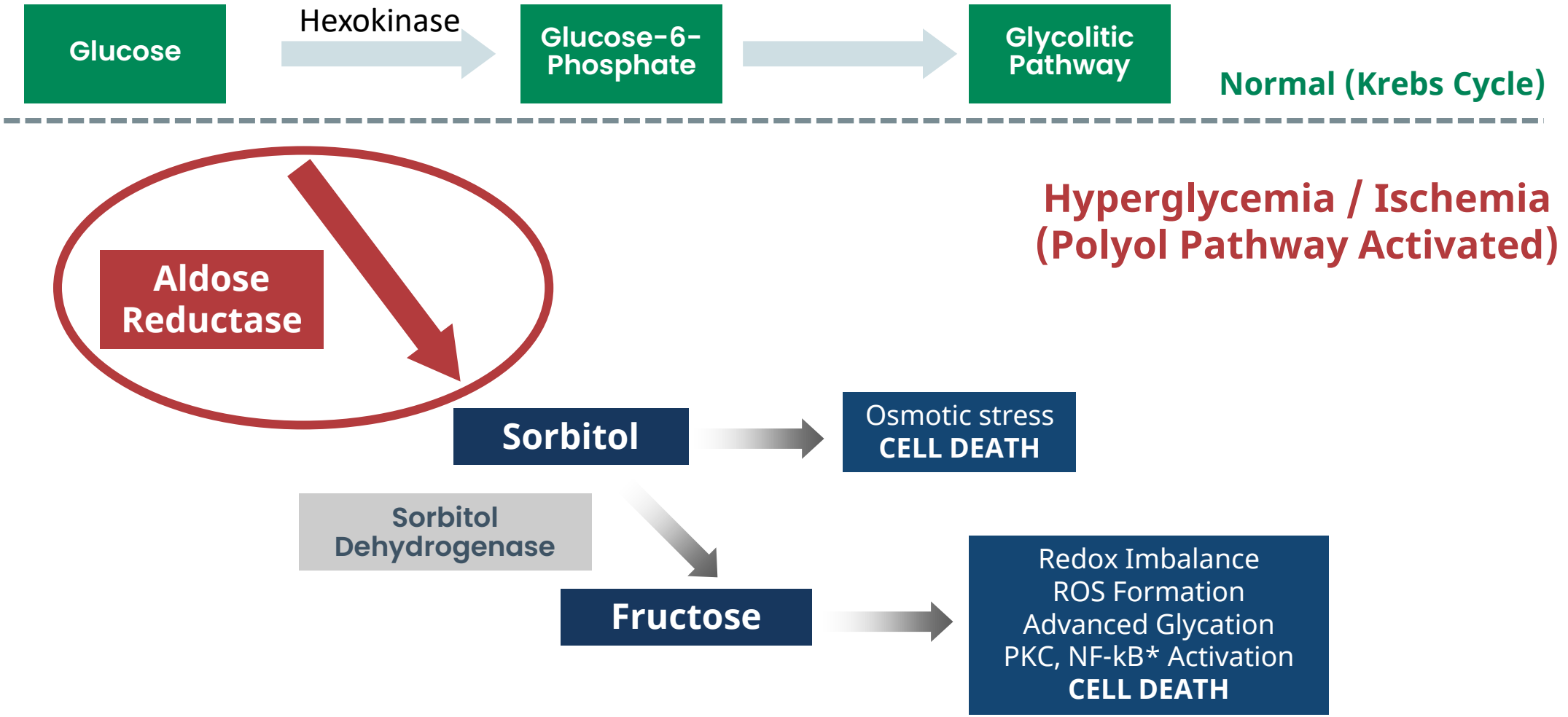
Introduction

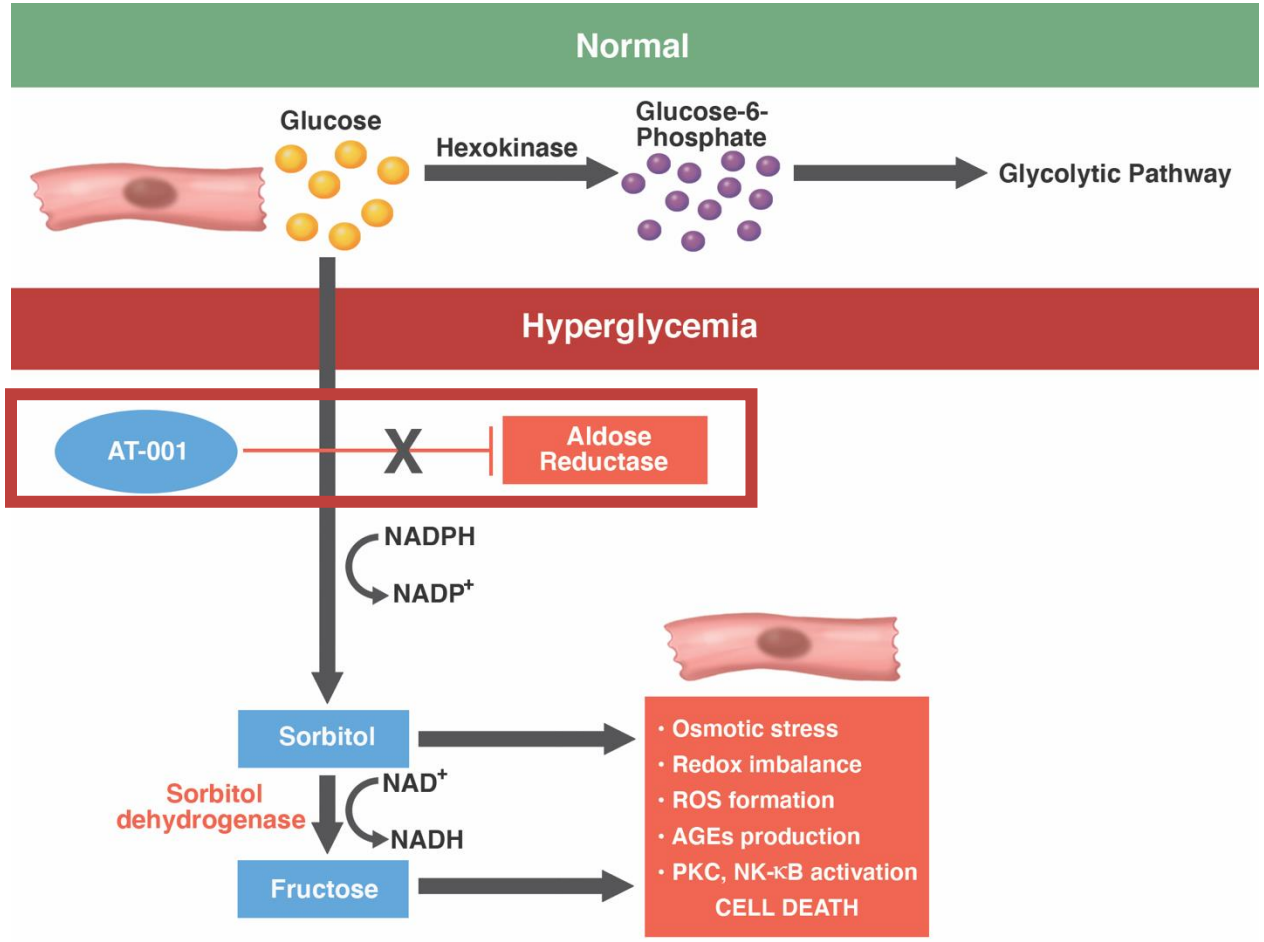
- Heart failure (HF) is a major cardiovascular complication among individuals with diabetes mellitus (DM)
  - ❖Persons with DM have 2X risk for HF development
  - ❖HF onset is often heralded by decline in exercise capacity
  - ❖Risk for HF persists even when adjusting for presence of classical risk HF risk factors
- DM itself may result in heart muscle disease, known as diabetic cardiomyopathy (DbCM)

Pathogenesis of DbCM & Hyperactivation of Polyol Pathway[1,2]



1. Brownlee M. Diabetes Care. 2005;54(6):1615-1625. 2. Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

Blocking aldose reductase in DBCM



- Aldose reductase inhibitors (ARIs) had previously been developed for treatment of microvascular complications
- Most 1st generation ARIs were low potency and poorly tolerated due to side effects
- AT-001 is a highly potent and well-tolerated ARI

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Hypothesis

- Treatment of individuals with DbCM and reduced exercise capacity at high risk for HF with an Aldose Reductase Inhibitor (AT-001) would limit progression of DbCM reflected in stabilization of peak VO_2

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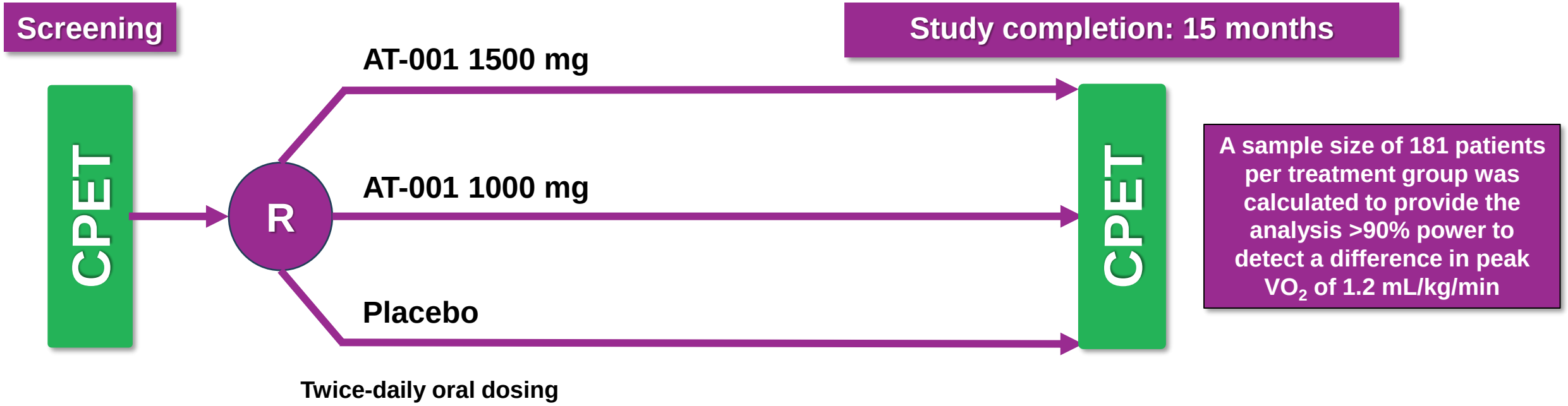
Key Inclusion/Exclusion Criteria

- To be included, participants had T2DM and:
  - ❖ Stage B HF
  - ❖ Reduced exercise capacity
  - ❖ No known ASCVD, valvular heart disease, or arrhythmia
- Study participants were required to have:
  - ❖ Controlled blood pressure
  - ❖ HbA1c <8.5%

Inclusion	Exclusion
• Diagnosis of T2DM • On stable glucose lowering and RAS inhibition • Age ≥ 60 years or Age ≥ 40 to < 60 years and either duration of T2DM ≥ 10 years or eGFR< 60 mL/min • DbCM/Stage B HF with at least 1: ❖ GLS < 16% ❖ Increased LVMi ❖ LAVi > 34 mL/m2 ❖ E/E' ≥ 13 ❖ RVSP> 35 mmHg ❖ NT-proBNP ≥ 50 ng/L ❖ hs-cTnT ≥ 6 ng/L • Peak VO_2 < 75% of predicted • RER ≥1.05	• Known or suspected Stage C HF • Loop diuretic use • BP > 140/> 90 mmHg • HbA1c >8.5% • Prior ACS • Severe CAD • Prior CABG or PCI • Severe valvular heart disease • Clinically significant arrhythmia including permanent AF or PAF requiring hospitalization • Prior stroke • BMI≥ 45 kg/m^2

Study Design



Inclusion stratified by region, baseline CPET result, and use of SGLT2 inhibitor or GLP-1RA

Owing to COVID-19 related delays, a planned extension to 27 months if the primary endpoint was neutral at 15 months was removed

CPET denotes: cardiopulmonary exercise test; SGLT2 denotes: sodium/glucose cotransporter 2; GLP-1RA denotes: glucagon like peptide receptor agonist-1

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Endpoints

- **<u>Primary endpoint</u>**: change in peak VO_2 from baseline to 15 months between placebo and high dose AT-001
  - ❖Prespecified sub-groups:
    1. Region of enrollment
    2. Sex
    3. CPET parameters (peak VO_2, RER)
    4. Hemoglobin A1c
    5. Baseline NT-proBNP and/or hs-cTnT
    6. Baseline use versus non-use of SGLT2 inhibitor and/or GLP-1 RA

Endpoints

- **<u>Key secondary endpoints</u>**:
  - Percentage of study participants with ≥6% decrease in peak VO_2
  - Change in NT-proBNP concentration
  - Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score
  - Change in activity using the Physical Activity Scale for the Elderly (PASE)
  - Progression to symptomatic HF events
    - ❖Composite of CV death, HF hospitalization or development of signs/symptoms of HF
    - ❖Based on adjudicated endpoints plus adverse event reporting using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms

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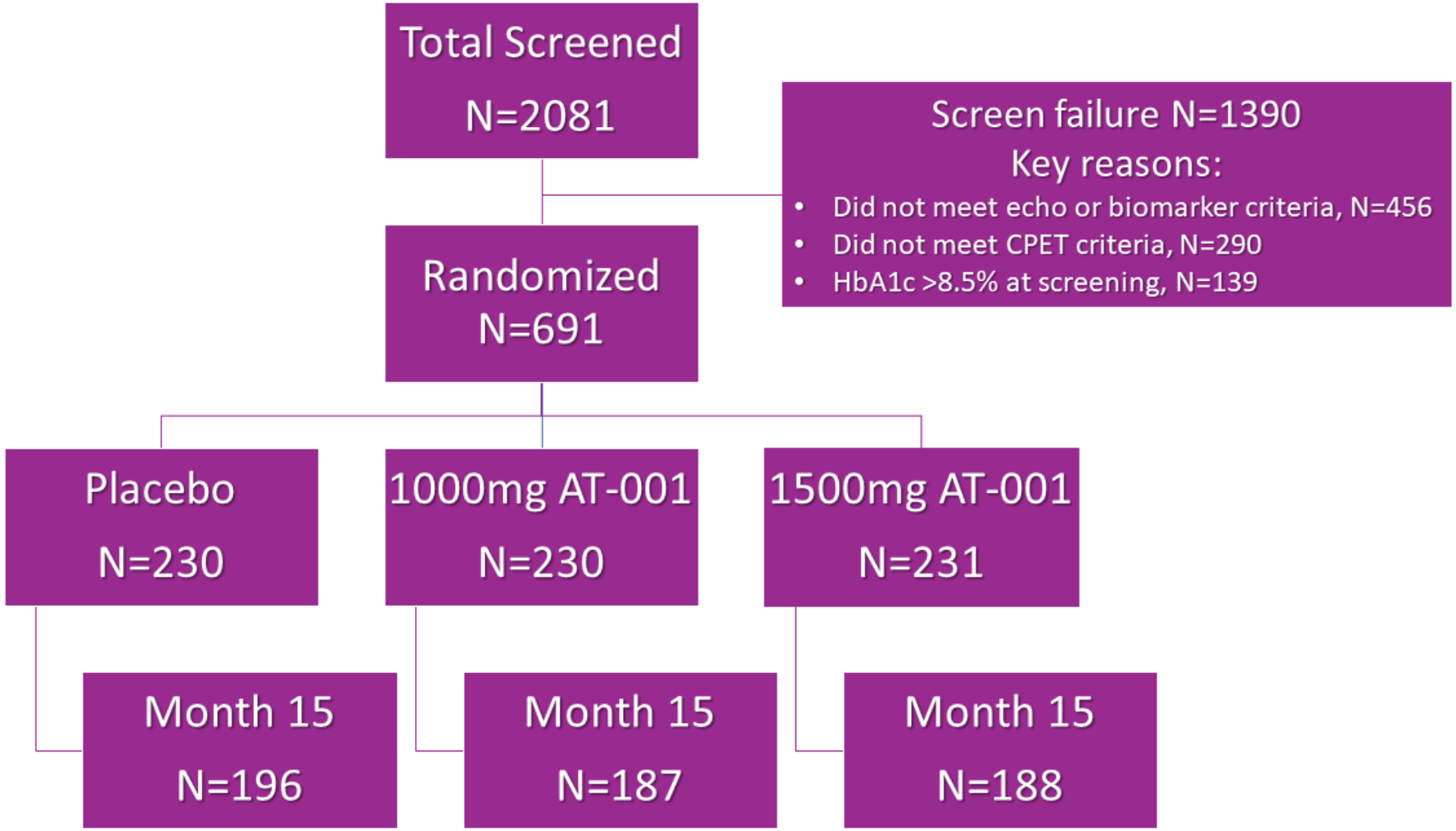
Sites/enrollment: 62 sites



Baseline characteristics

	Placebo (N=230)	AT-001 1000 mg (N=230)	AT-001 1500 mg (N=231)
Age, years	68.2 ± 6.7	67.4 ± 7.8	66.9 ± 7.0
Female, n (%)	124 (53.9)	107 (46.5)	117 (50.6)
Race, n (%)			
White	195 (84.8)	191 (83.0)	184 (79.7)
Black	14 (6.1)	13 (5.7)	23 (10.0)
Hispanic ethnicity, n (%)	44 (19.1)	48 (20.9)	59 (25.5)
Body-mass index, kg/m^2	30.9 ± 4.8	30.4 ± 4.6	30.5 ± 4.4
SBP, mmHg	131 ± 17	132 ± 17	131 ± 16
Medical history, n (%)			
Hypertension	179 (77.8)	179 (77.8)	165 (71.4)
Dyslipidemia	45 (19.6)	36 (15.7)	35 (15.2)
Duration of T2DM, years	14.4 ± 9.2	14.6 ± 9.2	14.4 ± 9.0
SGLT2i or GLP-1RA, n (%)	86 (37.4)	89 (38.7)	88 (38.1)

- **Average age of 68 years**
- **Female predominant (50.4%)**
- **Race and ethnicity reflective of international enrollment**
- **Medical evaluation included a BMI of 31 but well-controlled blood pressure**
- **Long-standing history of T2DM**
- **62% were not receiving an SGLT2i or GLP-1RA at baseline**

SD denotes: standard deviation; kg denotes: kilogram; m^2 denotes: square meter; SBP denotes: systolic blood pressure; SGLT2i denotes: sodium/glucose cotransporter 2 inhibitor; GLP1-RA denotes: glucagon-like peptide-1 receptor agonist

Baseline characteristics, objective results

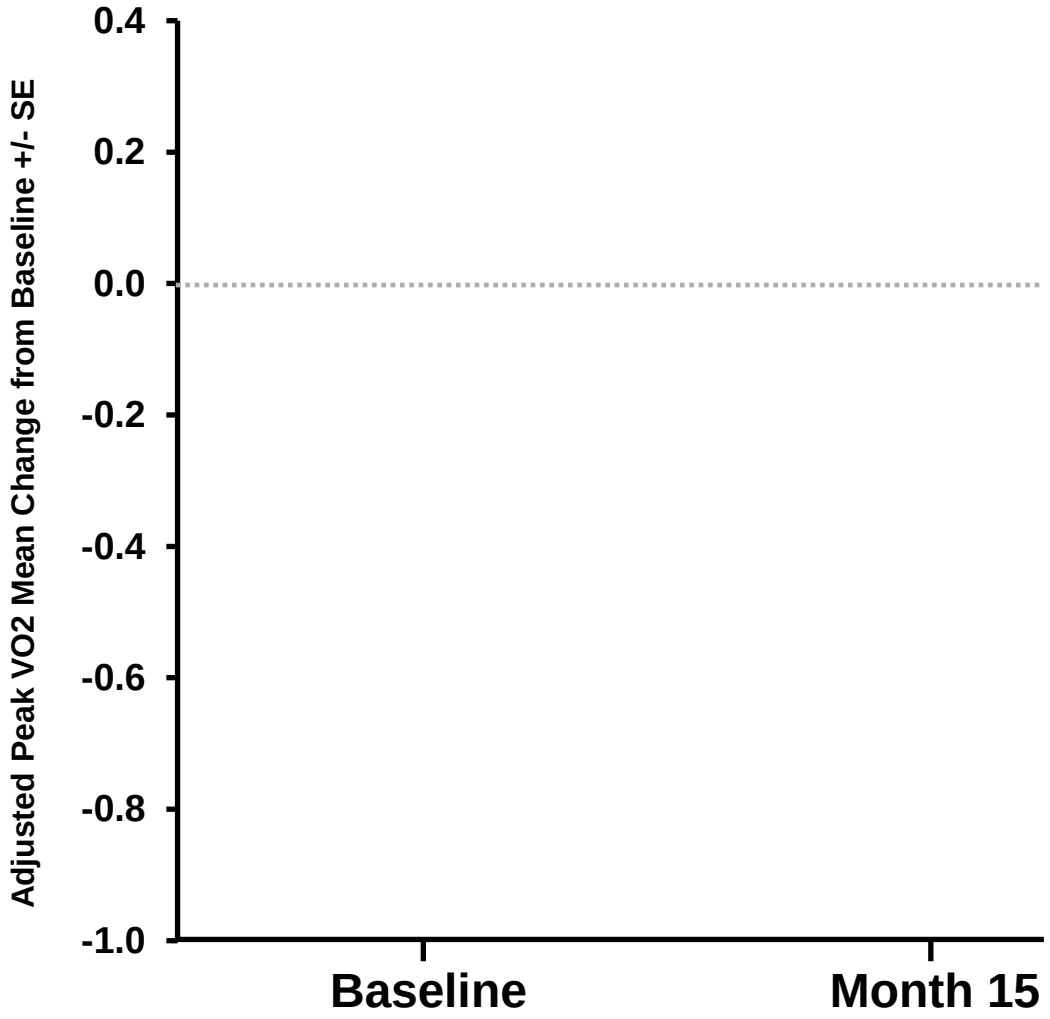
Parameter	Placebo (N=230)	AT-001 1000 mg (N=230)	AT-001 1500 mg (N=231)
Hemoglobin A1c, %	6.96±0.74	7.04±0.81	6.98±0.80
eGFR, mL/min/1.73m^2	81±16	81±16	80±17
NT-proBNP, ng/L, median (Q1,Q3)	76 (42,145)	74 (39,137)	63 (27,114)
hs-cTnT, ng/L, median (Q1,Q3)	8 (6,13)	9 (6,12)	9 (6,12)
PASE Score	159 ± 94	150 ± 90	157 ± 87
KCCQ Overall Summary Score	90 ± 16	90 ± 15	91 ± 13
KCCQ Clinical Summary Score	90 ± 15	91 ± 14	91 ± 13
KCCQ Total Symptom Score	92 ± 15	92 ± 15	94 ± 13
Baseline RER ≥1.15, n (%)	132 (57.4)	131 (57)	131 (56.7)
Baseline peak VO_2, mL/kg/min	15.6 ± 3.8	15.7 ± 3.8	16 ± 3.9

- **Well-controlled T2DM**
- **Preserved kidney function**
- **~25% with high-risk NT-proBNP or hs-cTnT**
- **PASE consistent with reduced activity but with well-preserved KCCQ scores**
- **Impairment in exercise capacity with average peak VO_2 of 15.7 mL/kg/min**

Results are mean ± standard deviation unless otherwise specified

eGFR denotes: estimated glomerular filtration rate; mL denotes: milliliters; min denotes: minute; NT-proBNP denotes: N-terminal pro-B type natriuretic peptide; ng/L denotes: nanograms/liter; hs-cTnT denotes: high sensitivity cardiac troponin T; PASE denotes: Physical Activity Scale for the Elderly; SD denotes: standard deviation; KCCQ denotes: Kansas City Cardiomyopathy Questionnaire; RER denotes: respiratory exchange ratio; VO_2 denotes: oxygen consumption

Change in Peak VO_2 by 15 months



Baseline peak VO_2 = 15.7± 3.8

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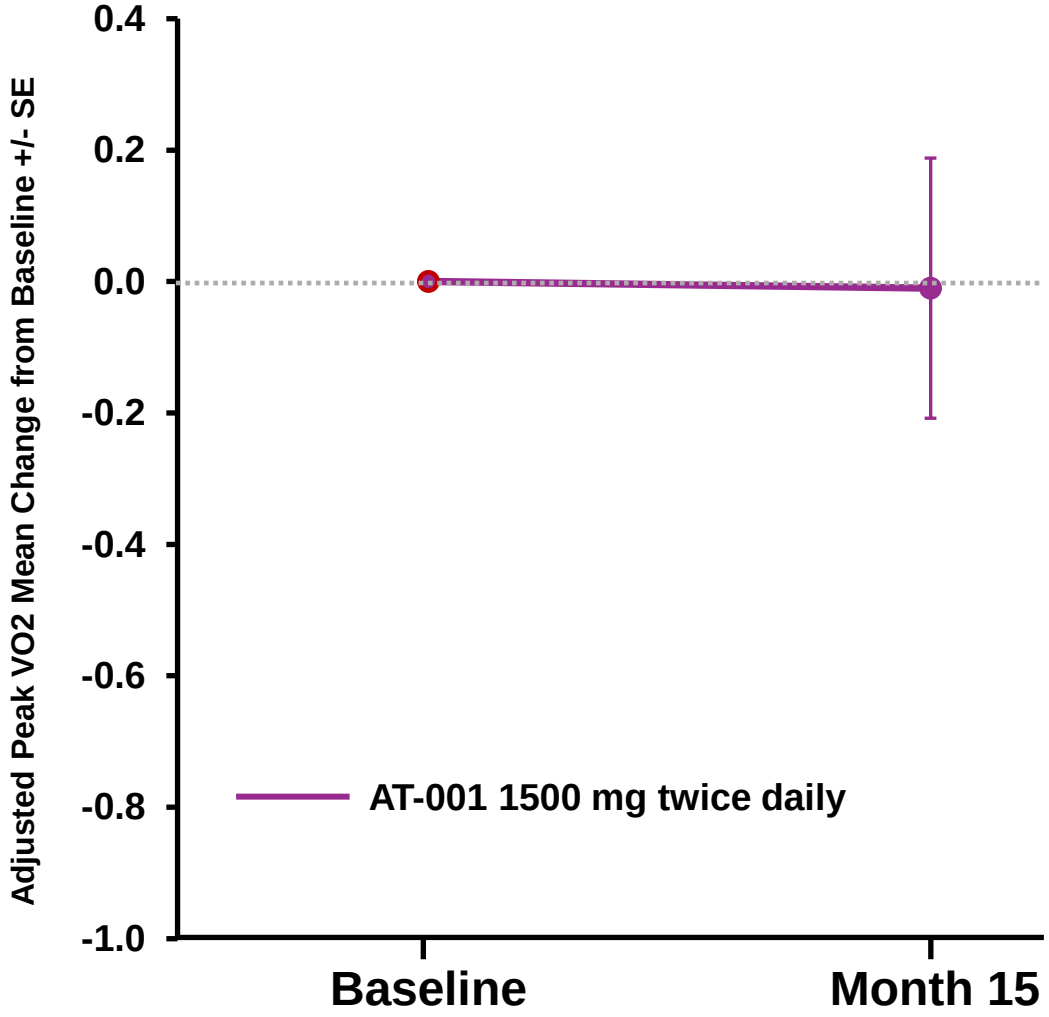
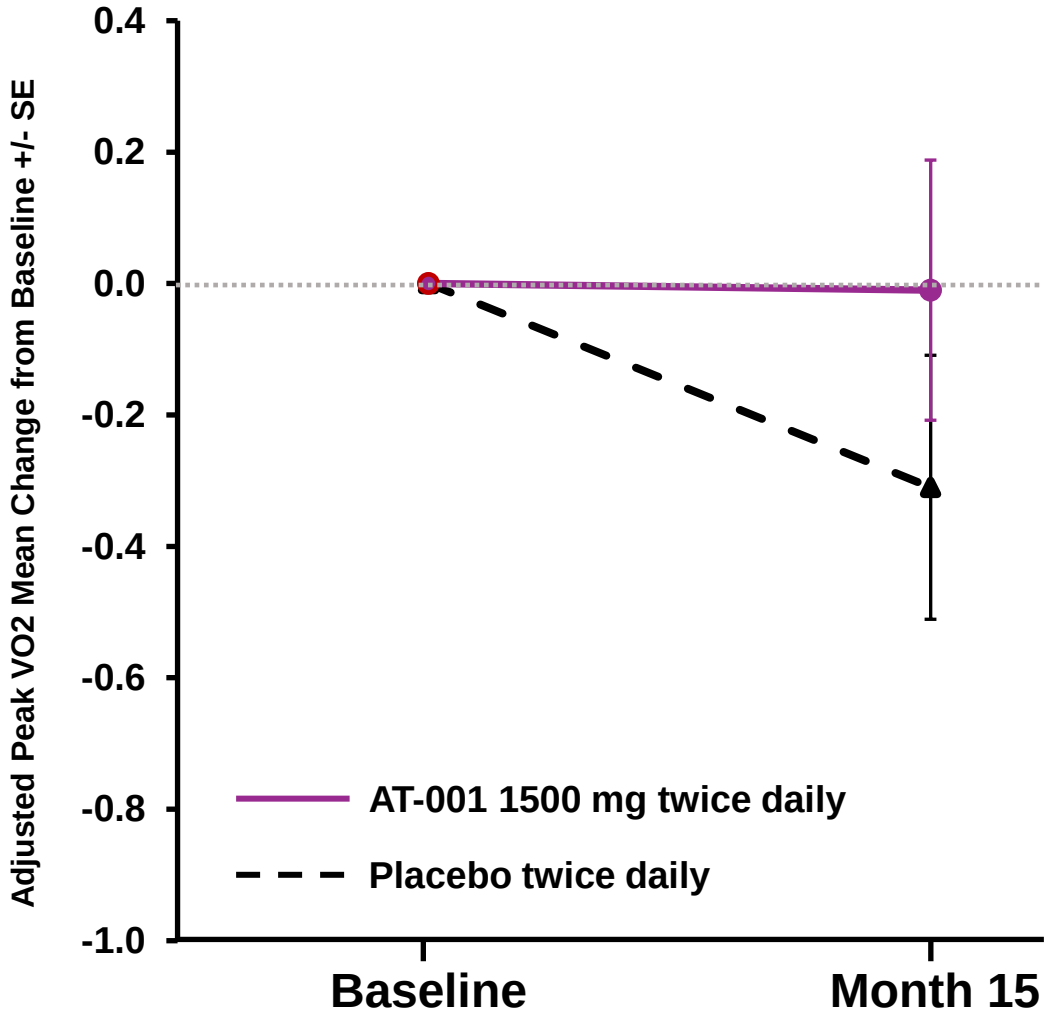
Change in Peak VO_2 by 15 months



Change AT-001 1500 mg: -0.01 (SE=0.18)
***P* =.21 compared to baseline**

Baseline peak VO_2 = 15.7± 3.8

Change in Peak VO_2 by 15 months



Change AT-001 1500 mg: -0.01 (SE=0.18)
***P* =.21 compared to baseline**

Change Placebo: -0.31 (SE=0.18)
***P* =.005 compared to baseline**

Baseline peak VO_2 = 15.7± 3.8

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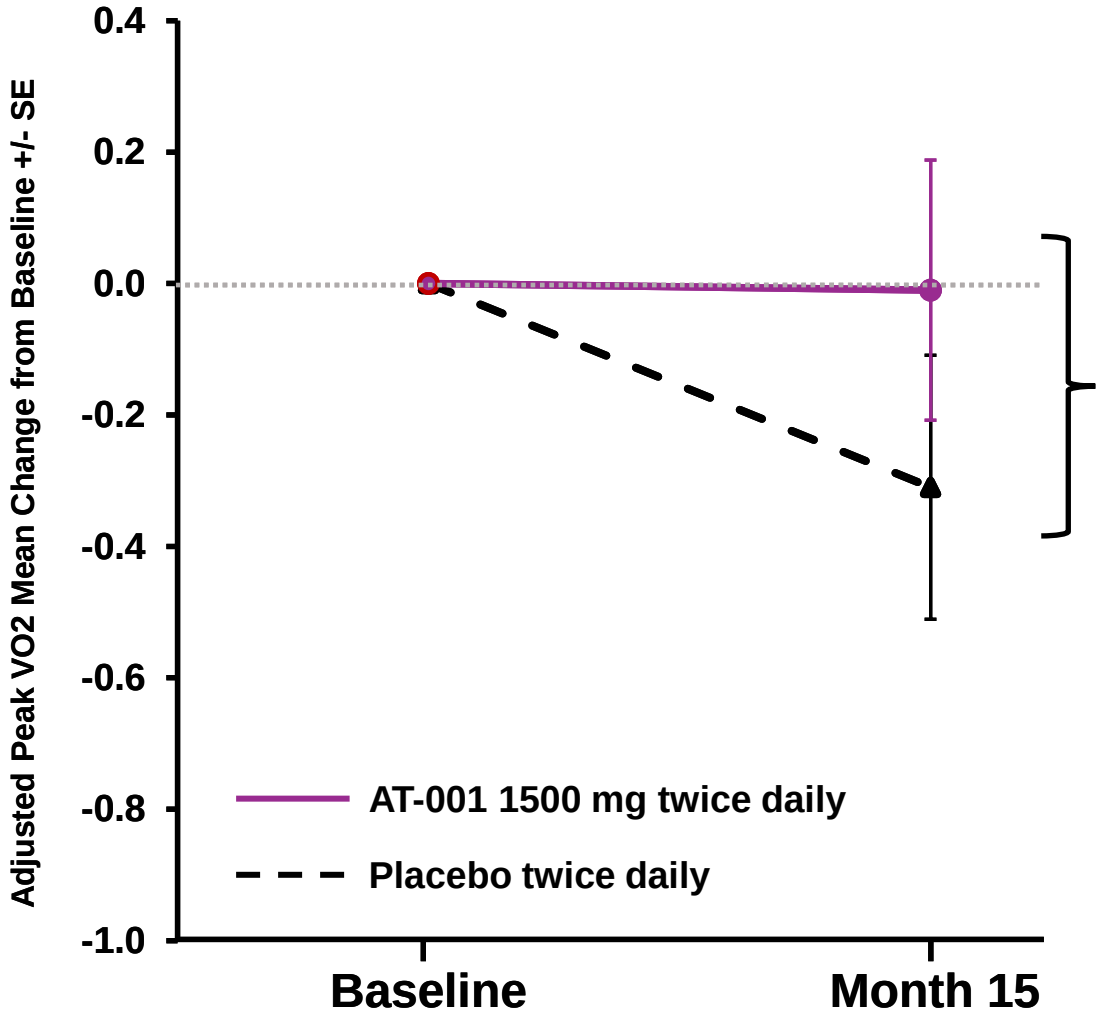
Change in Peak VO_2 by 15 months



LS-mean difference of change
AT-001 vs Placebo = 0.30 (0.23)
***P* =.19**

Baseline peak VO_2 = 15.7± 3.8

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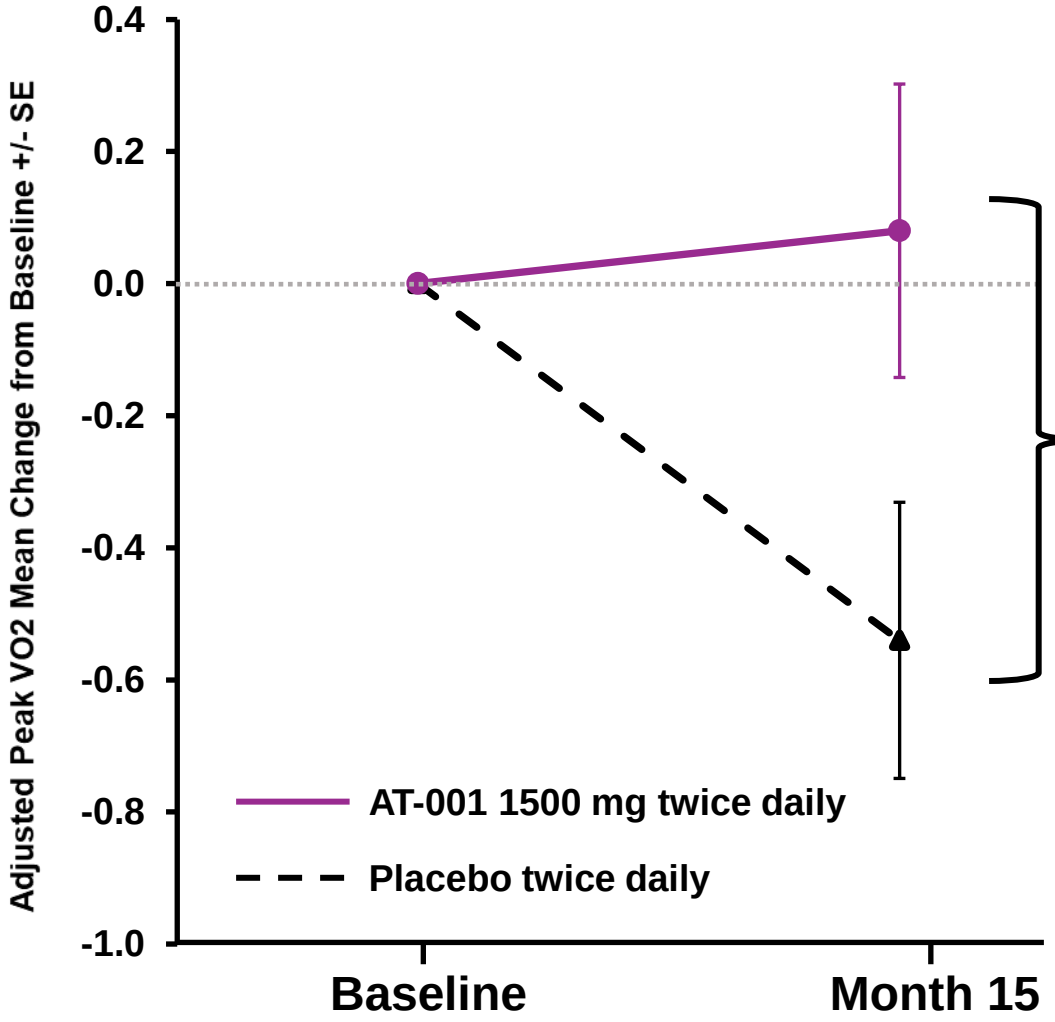
Change in Peak VO_2 in those not receiving SGLT2 inhibitors or GLP1-RA*

ARISE-HF

*Prespecified subgroup and study participants stratified on enrollment



Change AT-001 1500 mg: +0.08 (SE=0.22)

LS-mean difference of change AT-001 vs Placebo =0.62 (0.30)
***P* =.04**

Change Placebo: -0.54 (0.21)

Baseline peak VO_2 = 15.7± 3.8

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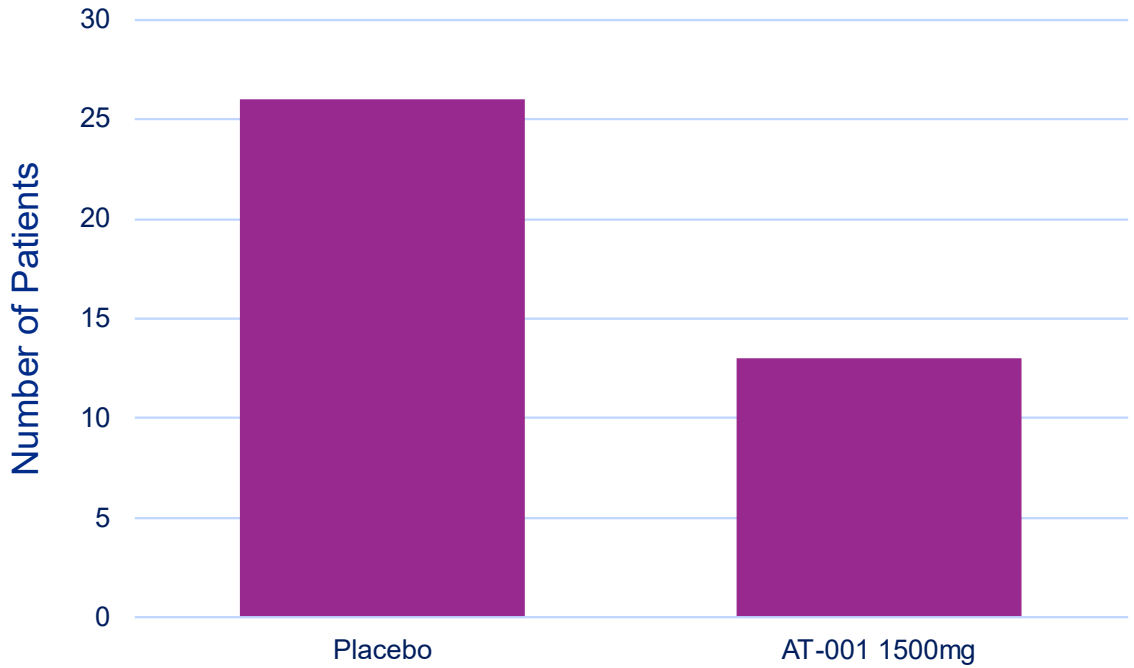
Secondary endpoints

- A ≥6% decline in peak VO_2 was observed in 41.8% of placebo-treated patients and 36.2% of those treated with high dose AT-001 (OR=0.80, 95% CI=0.52, 1.21; *P* =.29)
  - ❖Among non-users of SGLT2 inhibitors or GLP-1RA: 46.0% versus 32.7% (OR=0.56; 95% CI=0.33, 0.96; *P* =.035)
- No significant differences in change of NT-proBNP, KCCQ domains or PASE results were observed

Progression to overt HF



26 Patients in the placebo-treated vs 13 patients in the high dose AT-001 group experienced events of HF (Chi-squared *P* =.0285)

Safety, adverse events occurring in >5%

Characteristic	Overall	Placebo	AT-001 1000 mg	AT-001 1500 mg
COVID-19	131 (19.0)	44 (19.1)	53 (23.2)	34 (14.7)
UTI	96 (13.9)	25 (10.9)	34 (14.9)	37 (16)
Constipation	49 (7.1)	11 (4.8)	17 (7.5)	21 (9.1)
Nausea	51 (7.4)	13 (5.7)	20 (8.8)	18 (7.8)
Decrease in eGFR	39 (5.7)	2 (0.9)	16 (7)	21 (9.1)
Diarrhea	58 (8.4)	23 (10)	20 (8.8)	15 (6.5)
Fatigue	54 (7.8)	22 (9.6)	12 (5.3)	20 (8.7)
Back pain	40 (5.8)	9 (3.9)	14 (6.1)	17 (7.4)
Nasopharyngitis	45 (6.5)	15 (6.5)	19 (8.3)	11 (4.8)
Dizziness	37 (5.4)	10 (4.3)	5 (2.2)	22 (9.5)
Arthralgia	42 (6.1)	16 (7)	11 (4.8)	15 (6.5)
Headache	35 (5.1)	11 (4.8)	10 (4.4)	14 (6.1)
URI	37 (5.4)	13 (5.7)	12 (5.3)	12 (5.2)
Fall	37 (5.4)	14 (6.1)	7 (3.1)	16 (6.9)
Peripheral edema	36 (5.2)	14 (6.1)	10 (4.4)	12 (5.2)

- **AT-001 was generally well-tolerated**
- **Treatment with AT-001 was not associated with any evidence of significant liver injury**
- **Rise in serum creatinine at any time during the trial was infrequent and transient**
  - ❖ **There was no imbalance in drug discontinuation due to deterioration of kidney function**

All results n (%); UTI denotes: urinary tract infection; eGFR denotes: estimated glomerular filtration rate; URI denotes: upper respiratory tract infection

Conclusions

- Treatment with AT-001 was safe and well-tolerated but did not result in a statistically significant difference in peak VO_2 among persons with DbCM and reduced exercise capacity
  - ❖The study participants in ARISE-HF had very well-controlled T2DM (**A1c=6.98%**), which may not reflect persons with DbCM more generally
  - ❖A longer study duration might have been necessary
- More investigation is needed regarding the potential role of AT-001 to improve cardiovascular outcomes in this high-risk population
  - ❖Future studies should evaluate longer treatment with AT-001 in a more generalizable population of DbCM
  - ❖The finding of superior outcomes in those not receiving SGLT2 inhibitors or GLP-1RA is exploratory in nature but bears further study

Conclusions

- The investigators wish to thank our sites, investigators, and especially the patients for their participation in the ARISE-HF Trial
- ARISE-HF is online now at

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Randomized Trial of a Selective Aldose Reductase Inhibitor in Patients With Diabetic Cardiomyopathy

James L. Januzzi, Jr, MD,[a,b] Javed Butler, MD, MPH, MBA,[c,d] Stefano Del Prato, MD,[e] Justin A. Ezekowitz, MB, BCh,[f] Nasrien E. Ibrahim, MD, MPH,[g] Carolyn S.P. Lam, MBBS, PhD,[b,h] Gregory D. Lewis, MD,[i] Thomas H. Marwick, MBBS, PhD, MPH,[j] Riccardo Perfetti, MD, PhD,[k] Julio Rosenstock, MD,[l] Scott D. Solomon, MD,[g] W.H. Wilson Tang, MD,[m] Faiez Zannad, MD, PhD[n]

ABSTRACT

BACKGROUND Progression to symptomatic heart failure is a complication of type 2 diabetes; heart failure onset in this setting is commonly preceded by deterioration in exercise capacity.

OBJECTIVES The study sought to determine whether AT-001, a highly selective aldose reductase inhibitor, can stabilize exercise capacity among individuals with diabetic cardiomyopathy (DbCM) and reduced peak oxygen uptake (Vo_2).

METHODS A total of 691 individuals with DbCM meeting inclusion and exclusion criteria were randomized to receive placebo or ascending doses of AT-001 twice daily. Stratification at inclusion included region of enrollment, cardiopulmonary exercise test results, and use of sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists. The primary endpoint was proportional change in peak Vo_2 from baseline to 15 months. Subgroup analyses included measures of disease severity and stratification variables.

RESULTS The mean age was 67.5 ± 7.2 years, and 50.4% of participants were women. By 15 months, peak Vo_2 fell in the placebo-treated patients by -0.31 mL/kg/min ($P = 0.005$ compared to baseline), whereas in those receiving high-dose AT-001, peak Vo_2 fell by -0.01 mL/kg/min ($P = 0.21$); the difference in peak Vo_2 between placebo and high-dose AT-001 was 0.30 ($P = 0.19$). In prespecified subgroup analyses among those not receiving sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists at baseline, the difference between peak Vo_2 in placebo vs high-dose AT-001 at 15 months was 0.62 mL/kg/min ($P = 0.04$; interaction $P = 0.10$).

CONCLUSIONS Among individuals with DbCM and impaired exercise capacity, treatment with AT-001 for 15 months did not result in significantly better exercise capacity compared with placebo. (Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy [ARISE-HF]; NCT04083339) (J Am Coll Cardiol 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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