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

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100

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110 **Abstract**

111 **Background:** Progression to symptomatic heart failure (HF) is a complication of type 2
112 diabetes; HF onset in this setting is commonly preceded by deterioration in exercise capacity.

113 **Objective:** To determine whether AT-001, a highly selective aldose reductase inhibitor, can
114 stabilize exercise capacity among individuals with diabetic cardiomyopathy (DbCM) and
115 reduced peak oxygen uptake (VO_2).

116 **Methods:** 691 individuals with DbCM meeting inclusion and exclusion criteria were randomized
117 to receive placebo or ascending doses of AT-001 twice daily. Stratification at inclusion included
118 region of enrollment, cardiopulmonary exercise test results, and use of sodium/glucose co-
119 transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RA). The
120 primary endpoint was proportional change in peak VO_2 from baseline to 15 months. Sub-group
121 analyses included measures of disease severity and stratification variables.

122 **Results:** The mean (standard deviation) age was 67.5 (7.2) years, and 50.4% of participants were
123 women. By 15 months, peak VO_2 fell in the placebo-treated patients by -0.34 mL/kg/minute
124 ($P=.005$ compared to baseline) while in those receiving high dose AT-001 peak VO_2 fell by -0.03
125 mL/kg/minute ($P=.21$); difference in peak VO_2 between placebo and high dose AT-001 was 0.30
126 ($P=.19$). In prespecified sub-group analyses among those not receiving SGLT2 inhibitors or
127 GLP-1RA at baseline, the difference between peak VO_2 in placebo versus high dose AT-001 at 15
128 months was 0.62 mL/Kg/minute ($P=.04$; interaction $P=.10$).

129 **Conclusions and Relevance:** Among individuals with DbCM and impaired exercise capacity,
130 treatment with AT-001 for 15 months did not result in significantly better exercise capacity
131 compared with placebo.

132 **Trial Registration:** ARISE-HF (NCT04083339)

133 **Key words:** heart failure, diabetes, aldose reductase inhibitor

134

135 **Abbreviations**

136 HF Heart failure

137 T2DM Type 2 diabetes mellitus

138 DbCM Diabetic cardiomyopathy

139 NT-proBNP N-terminal pro-B type natriuretic peptide

140 ARISE-HF Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart
141 Failure

142 VO₂ Oxygen uptake

143 CPET Cardiopulmonary exercise test

144 hs-cTnT High sensitivity cardiac troponin T

145 SGLT2 Sodium-glucose cotransporter 2

146 GLP-1RA Glucagon-like peptide-1 receptor agonist

147

148 **Condensed abstract**

149 This randomized controlled trial evaluated effect of aldose reductase inhibition with AT-001 on
150 exercise capacity in individuals with diabetic cardiomyopathy (DbCM) and well-controlled type
151 2 diabetes. Following 15 months of treatment, placebo-treated patients had a decline in peak
152 oxygen uptake while AT-001 treated patients experienced no decline. Despite this, the difference
153 in oxygen uptake between groups did not reach statistical significance. In a prespecified
154 secondary analysis, study participants not receiving SGLT2 inhibitors or GLP-1 RA at baseline
155 randomized to AT-001 had significantly better peak VO₂ at 15 months.

156

157 **Introduction**

158 Heart failure (HF) is an under-appreciated but increasingly recognized major cardiovascular
159 complication of individuals with diabetes mellitus¹. For example, it is estimated that individuals
160 with Type 2 diabetes mellitus (T2DM) have a more than doubling in their risk for incident HF
161 compared to those without DM, and when a person with T2DM develops HF, their risk for
162 mortality is considerably higher than someone without DM¹. Among individuals with DM, the
163 risk for HF onset persists even when adjusting for factors such as glycemic control, blood
164 pressure control, valvular heart disease or the presence and severity of ischemic heart disease²⁻⁴.
165 It is now recognized that DM itself may result in heart muscle disease related to chronicity and
166 severity of hyperglycemia, abnormalities in myocardial metabolism and oxidative stress^{5,6}.
167 These processes result in diabetic cardiomyopathy (DbCM)^{4,7-12}, a form of cardiac dysfunction
168 that is initially without overt HF symptoms, classified as Stage B HF³; this is associated with
169 high risk for progression to overt HF. No treatment is currently offered to DbCM in those
170 without overt HF, which is an ideal opportunity for intervention to reduce the considerable risk in
171 such individuals.

172 An important cause of DbCM is increased activity of the polyol pathway¹¹⁻¹⁵. Stimulated
173 by hyperglycemic conditions, the polyol pathway reduces glucose to sorbitol followed by further
174 conversion of sorbitol to fructose; this results in tissue injury and fibrosis. Aldose reductase is the
175 initial, rate limiting step in the polyol pathway¹⁶; accordingly inhibition of aldose reductase has
176 been proposed as a treatment for DbCM^{8,17,18}. AT-001 is a novel, highly selective aldose
177 reductase inhibitor that demonstrates higher target engagement than other compounds in its class.
178 In early-stage trials of individuals with DbCM, AT-001 lowered concentrations of N-terminal
179 pro-B type natriuretic peptide (NT-proBNP) and circulating sorbitol without dose-limiting

180 toxicity⁹. For this reason, it was hypothesized that AT-001 treatment would result in stabilization
181 of DbCM progression. This Phase 3 study evaluated the effect of AT-001 on exercise capacity
182 among individuals with DbCM and reduced exercise capacity at high risk for progression to
183 overt HF.

184 **Methods**

185 All research procedures were approved by local institutional review boards, and study
186 participants provided informed consent for their participation in the trial.

187 *Rationale and Design*

188 The rationale, design, and baseline characteristics of the Aldose Reductase Inhibition for
189 Stabilization of Exercise Capacity in Heart Failure (ARISE-HF) Trial (www.clinicaltrials.gov:
190 NCT04083339) have been recently reported^{9,10}. The study protocol and statistical analysis plan
191 are provided in the **Supplemental Appendix**, which also details trial leadership, committees, and
192 study sites.

193 ARISE-HF was a global, Phase 3, randomized, placebo-controlled double-blind study
194 performed in 62 sites to assess the efficacy of AT-001 compared with placebo for stabilization of
195 exercise capacity (as measured by peak oxygen uptake [VO₂] during cardiopulmonary exercise
196 testing, CPET), in adult study participants with T2DM and DbCM.

197 The full inclusion and exclusion criteria for participation in ARISE-HF are detailed in
198 **Supplemental Table 1**. In brief, study participants with T2DM were considered for enrollment if
199 they were age ≥ 60 years (or age ≥ 40 to < 60 years with duration of T2DM ≥ 10 years or with an
200 estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²) and had either abnormal
201 cardiac structure or function or increased concentration of either NT-proBNP or high-sensitivity

202 cardiac troponin T (hs-cTnT). Furthermore, study participants were required to have impaired
203 cardiac functional capacity defined by a peak $\text{VO}_2 \leq 75\%$ of predicted based on age and sex¹⁹,
204 and ability to achieve acceptable maximal effort during CPET (defined as a respiratory exchange
205 ratio [RER] ≥ 1.05 . Importantly, well-controlled blood pressure and hemoglobin A1c $< 7.5\%$ were
206 both required for enrollment to the trial. All glucose lowering treatments were allowed except for
207 thiazolidinediones. Use of sodium-glucose cotransporter-2 (SGLT2) inhibitors or glucagon-like
208 peptide-1 receptor agonists (GLP-1RA) was permitted.

209 Following baseline CPET, confirmation of eligibility, and provision of informed consent,
210 study participants were randomized in a 1:1:1 fashion to receive placebo, low dose AT-001 (1000
211 mg twice daily), or high dose AT-001 (1500 mg twice daily).

212 Randomization was stratified by region (North America versus Rest of World), by the
213 baseline CPET results (RER ≥ 1.15 versus RER < 1.15 ; peak $\text{V02} \leq 15$ mL/kg/min in study
214 participants with RER ≥ 1.15), and use of SGLT2 inhibitor or GLP1-RA at baseline). The
215 rationale for regional stratification was to evaluate for geographic heterogeneity in baseline
216 DbCM profiles and response to therapy, while the RER stratification was to ensure adequate
217 distribution of high and lower performing study participants. Stratification of SGLT2 inhibitors
218 and/or GLP-1RA use was based on previous evidence suggesting impact on exercise capacity of
219 these therapies^{20,21}.

220 The high dose of AT-001 was selected as the target dose, given its ability to lower NT-
221 proBNP in Phase I and II trials, while lower dose treatment was included to explore safety and
222 efficacy of lower doses of the drug. Study participants were treated for a planned 15 months with
223 routine study visits as described. A longer treatment duration was initially planned if a neutral

224 finding was returned at 15 months⁹; due to a 2 year study delay caused by the global COVID-19
225 pandemic, the trial was completed at 15 months, without continuation.

226 *Study Endpoints*

227 The primary endpoint of the ARISE-HF Trial was change in peak VO₂ from baseline to 15
228 months between placebo and high dose AT-001. Initial prespecified sub-groups analyzed
229 included region of enrollment, sex, baseline CPET parameters (peak VO₂, RER), baseline
230 hemoglobin A1c, and baseline use versus non-use of SGLT2 inhibitor and/or GLP-1 RA.

231 Key secondary outcomes of ARISE-HF included percentage of study participants with a
232 clinically-significant decrease ($\geq 6\%$) in peak VO₂, effect of low dose AT-001, change in NT-
233 proBNP concentrations, change in health status assessed using the 12-question Kansas City
234 Cardiomyopathy Questionnaire (KCCQ)²² and change in activity assessed using the Physical
235 Activity Scale for the Elderly (PASE)²³. Lastly, as described in the statistical analysis plan (see
236 **supplemental materials**), an additional pre-specified endpoint was progression to signs or
237 symptoms suggestive of HF (based on adverse event reporting by site investigators using
238 Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) together with
239 positively adjudicated events (a composite of cardiovascular death, HF hospitalization).

240 *Adverse Events*

241 All adverse events and serious adverse events were recorded. Potential cardiovascular serious
242 adverse events including possible cardiovascular deaths or HF hospitalizations were adjudicated
243 by a Clinical Events Adjudication Committee.

244 *Statistical Analyses*

245 Data frequencies are expressed as mean (SD) or median (Q1, Q3) depending on normality.
246 Original study planning included extension to 27 months if assessment at 15 months did not
247 demonstrate a statistically significant difference between AT-001 and placebo however all results
248 shown presently are based on the 15-month timepoint analyzed using $\alpha/2$. Assuming a 20% drop-
249 out rate within each group, a sample size of 181 patients per treatment group was calculated to
250 provide the analysis >90% power to detect a difference in peak VO_2 of 1.2 mL/kg/min between
251 active treatment and placebo assuming a common standard deviation of 3 mL/kg/min in each
252 stratum. This difference in peak VO_2 of 1.2 mL/kg/min is considered clinically significant for
253 patients with HF²⁴.

254 The primary end point of the change in VO_2 from baseline to 15 months was analyzed
255 using a mixed model for repeat measures (MMRM) analysis of covariance (ANCOVA) model
256 with an unstructured covariance matrix using $\alpha/2$; least-square (LS) mean changes (with standard
257 error; SE) in peak VO_2 were examined. Before utilizing the prespecified analysis method of
258 ANCOVA, graphical and visual inspection of the distribution of the primary endpoint was
259 performed to satisfy that the distribution was normal. There were no issues with using ANCOVA
260 also based on the evaluation of residuals.

261 There were three main sub-group analyses, based on measures of disease severity at
262 baseline and/or study stratification criteria. These included presence of abnormal NT-proBNP
263 (using a cut-point of 125 ng/L) or hs-cTnT (using a cut-point of 14 ng/L), baseline CPET result
264 ($\text{RER} \geq 1.15$ versus $\text{RER} < 1.15$; peak $\text{VO}_2 \leq 15$ mL/kg/min in study participants with $\text{RER} \geq$
265 1.15), region of enrollment, and use of SGLT2 inhibitor or GLP1-RA at baseline). These sub-
266 groups of interest were included as fixed effects, with a random effect at the patient level. All
267 efficacy analyses were conducted using the intent-to-treat principle.

268 Analysis of the percentage of patients with a decrease in peak VO₂ of ≥6% was
269 performed using a logistic regression model adjusting for covariates based on randomization
270 stratification factors. Estimated odds ratio (OR) and associated 2-sided 95% confidence intervals
271 (CI) were generated. Analysis of the changes in NT-proBNP, KCCQ score, and PASE score from
272 baseline to 15 months were assessed using an MMRM approach like that for the primary efficacy
273 outcome. The frequency of signs/symptoms suggesting HF with or without development of
274 positively-adjudicated HF events were compared using Chi-square testing.

275 All statistics were performed using SAS 9.4, with two-sided *P* values <.05 considered
276 significant.

277 *Role of the sponsor*

278 Applied Therapeutics, Inc participated in the design and conduct of the study; collection,
279 management, analysis, and interpretation of the data; review of the manuscript; and decision to
280 submit the manuscript for publication. All statistical analyses were independently confirmed by
281 the investigative team. The sponsor did not have the right to veto publication and did not have
282 control regarding which journal the paper was submitted. A medical writer was not used for
283 preparation of the manuscript.

284 **Results**

285 *Baseline Characteristics*

286 **Figure 1** details study flow and patient disposition. Between September 18 2019 and October 31
287 2022, 2081 individuals were screened for study participation; from these, 691 eligible study
288 participants with Stage B HF and reduced exercise capacity were randomized to receive placebo
289 (N=230) or AT-001 at low dose (N=230) and high dose (N=231), or placebo (N=230). At 15

290 months, there were 196 study participants in the placebo arm with data for analysis, 187
291 receiving low dose AT-001, and 188 receiving high dose AT-001.

292 Baseline characteristics of the study participants as a function of treatment allocation are
293 detailed in **Table 1**. Characteristics were well-balanced between study arms. Overall, the mean \pm
294 SD age was 67.5 ± 7.2 years, and 50.4% of participants were women. The race and ethnicity of
295 the study participants reflects the global enrollment; 82.5% were white (of which 21.9% were of
296 Hispanic ethnicity), 8.4% were Asian, and 7.2% were Black. On average, study participants had
297 obesity, with a body-mass index (BMI) of 30.6 ± 4.6 Kg/m². The average duration of T2DM was
298 14.5 ± 10.1 years. Consistent with expectations for well-controlled T2DM, the baseline
299 hemoglobin A1c was $6.98 \pm 0.79\%$; in a similar fashion, although a history of hypertension was
300 prevalent (75.7%), control of blood pressure was acceptable. Study participants received a
301 mixture of glucose-lowering therapies; notably, 32.0% were treated with SGLT2 inhibitors and
302 25% were receiving a GLP-1RA. The balance of use of SGLT2 inhibitors or GLP-1RA was
303 similar across study arms, at approximately 38%.

304 Overall, at baseline, the median (Q1, Q3) NT-proBNP was 71 (25, 135) ng/L, while the
305 corresponding hs-cTnT was 9 (6, 12) ng/L. Echocardiographic abnormalities were prevalent,
306 with global longitudinal strain $<16\%$ in 25.3%, $E/e' >14$ in 17.7%, increased indexed left atrial
307 volume (>34 mL/m²) or left ventricular mass (>95 g/m² in women; >115 g/m² in men) in 11.9%
308 each. The results of questionnaire testing at baseline are detailed in **Table 2**, which demonstrates
309 good balance of objective measures across study arms.

310 The baseline peak VO₂ was similar across treatment arms, averaging 15.7 ± 3.8
311 mL/kg/minute. A similar percentage of study participants had an RER ≥ 1.15 in each study arm,
312 at approximately 57%.

313 *Primary Endpoint*

314 As shown in **Figure 2**, from baseline to 15 months, LS-mean peak VO₂ fell in the placebo-
315 treated patients by -0.34 mL/kg/minute (SE=0.18), $P=.005$ compared to baseline. In those
316 receiving high dose AT-001 peak VO₂ was essentially unchanged, reduced by -0.03
317 mL/kg/minute (SE=0.18), $P=.21$ compared to baseline. Despite the difference in change between
318 placebo and high dose AT-001, the primary endpoint of LS-mean change difference (SE) between
319 placebo and high dose AT-001 was 0.30 (0.23), did not reach statistical significance ($P=.19$).

320 In prespecified sub-group analyses, among non-users of SGLT2 inhibitors and/or GLP-
321 1RA peak VO₂ declined by 0.54 mL/kg/minute by 15 months, while treatment with high-dose
322 AT-001 was associated with improvement in peak VO₂ by 0.08 mL/kg/minute (LS-mean
323 difference between peak VO₂ in placebo versus high dose AT-001 in this prespecified subgroup=
324 0.62; $P=.04$; interaction P value =.10). The baseline characteristics of those study participants
325 not receiving SGLT2 inhibitor or GLP-1RA at baseline are detailed in **Supplemental Table 2**.
326 Other examined prespecified sub-groups showed no obvious differences in peak VO₂ related to
327 treatment with placebo versus AT-001.

328 *Secondary Endpoints*

329 Relative to secondary endpoints, in those receiving low dose AT-001 peak VO₂ declined by -0.29
330 mL/kg/minute (SE=0.18), which was similar to placebo ($P=.84$ for difference). Overall, a $\geq 6\%$
331 decline in peak VO₂ was observed in 41.8% of placebo-treated patients and 36.2% of those
332 treated with high dose AT-001 (OR=0.80, 95% CI=0.52, 1.21; $P=.29$). Among non-users of
333 SGLT2 inhibitors or GLP-1RA the difference was 46.0% versus 32.7% (OR=0.56; 95% CI=0.33,
334 0.96; $P=0.04$).

335 No significant differences were seen in NT-proBNP concentrations between study arms
336 from baseline to 15 months. For example, the difference in LS-mean change difference (SE)
337 between placebo and high-dose AT-001 was 10.2 (9.8), $P = .30$. Similarly, no significant
338 difference in PASE Score or consistent effect on KCCQ domains was seen from baseline to 15
339 months in those treated with AT-001 versus placebo (**Table 3**). There was one adjudicated HF
340 hospitalization in the placebo arm and 2 adjudicated cardiovascular deaths (both high-dose AT-
341 001). In a pre-specified analysis that considered potential cardiovascular adverse events
342 identified using MedDRA terms (**Supplemental Table 3**) together with adjudicated endpoints,
343 placebo-treated patients had 26 events, low dose AT-001 11 events, and high dose AT-001 14
344 events (chi square $P = 0.01$).

345 *Adverse events*

346 The most frequent adverse events were mild to moderate and with no major differences in
347 frequency between study groups (**Table 4**). Nausea and constipation events were numerically
348 slightly more frequent in those treated with AT-001, but these were typically mild and not
349 associated with a higher likelihood for treatment discontinuation. Treatment with AT-001 was not
350 associated with any evidence of significant liver injury (**Supplemental Table 4**). Frequency of
351 rise in serum creatinine at any time during the trial was infrequent (**Supplemental Table 5**). Rise
352 in serum creatinine (and other adverse events) was generally transient in people who
353 discontinued the study medication as well as in those who did not interrupt the daily intake of the
354 study medication; there was not an imbalance in drug discontinuation due to deterioration of
355 renal function between the patients on study drug (**Supplemental Table 6**) compared to placebo.

356 **Discussion**

357 DbCM is an increasingly recognized cause of HF in persons with T2DM but lacks a proven,
358 specific treatment^{7,12}. In this prospective, randomized controlled trial of individuals with well-
359 controlled T2DM complicated by Stage B HF and impaired exercise capacity, 15 months of a
360 highly selective, well tolerated, aldose reductase inhibitor (AT-001) did not result in higher peak
361 VO₂ versus placebo (**Central Illustration**). In a pre-specified subgroup of individuals not
362 prescribed an SGLT2 inhibitor or GLP-1RA at baseline (accounting for 62% of the study
363 population), AT-001 treatment was associated with better exercise capacity at 15 months;
364 although exploratory, such a finding is of note and suggests AT-001 may have an impact on a
365 relevant outcome measure in certain patients with DbCM.

366 The diagnosis of DbCM—a heart muscle disease related to chronic hyperglycemia—is
367 recognized as an important cause of HF in those with chronic DM^{2,4,7,11,12}. Changes in
368 myocardial substrate utilization have been implicated as a cause of DbCM²⁵, with over-activation
369 of the polyol pathway from chronic exposure to hyperglycemia a leading culprit. Such over-
370 activation of the polyol pathway has been linked to development of neuropathy and
371 nephropathy^{16,17,26}; it has also been implicated in the myocardial injury associated with DbCM.
372 Aldose reductase catalyzes the rate limiting step of the polyol pathway identifying it as an
373 important target for reducing complications of diabetes. In pre-clinical models, increased aldose
374 reductase activity has been shown to increase oxidative damage and deterioration of functional
375 activities of various cell types²⁷ while in human epidemiology studies, individuals over-
376 expressing aldose reductase are more likely to manifest various complications of the diabetes²⁸.
377 Attempts to develop inhibitors of aldose reductase for the treatment of diabetic complications
378 had been largely unsuccessful, due to low binding affinity and poor specificity for the target.
379 Many of the first generation agents in the class were withdrawn from clinical trials either

380 due to a lack of efficacy or adverse effects, including hepatotoxicity, fever, nausea, diarrhea and
381 Stevens-Johnson syndrome²⁹.

382 Despite these drawbacks, early studies of aldose reductase inhibition suggested a
383 potentially favorable impact on cardiac structure, function, and associated exercise capacity
384 among individuals with neuropathy from DM¹⁸. The development of AT-001, which has higher
385 potency and selectivity than other drugs in the class⁹, allowed for exploration of its use for
386 treatment of DbCM. In a transgenic mouse model of DbCM, treatment with AT-001 reduced
387 reduce cardiac fatty acid oxidation rates and cardiac oxygen consumption, preventing cardiac
388 structural and functional abnormalities present in DbCM with improved diastolic function and
389 reduced LV mass⁸.

390 Given the totality of evidence pointing toward benefit from inhibiting aldose reductase in
391 those with DbCM together with development of AT-001, this study examined effect of potent
392 aldose reductase inhibition with AT-001 in persons with chronic, well-controlled T2DM, DbCM
393 and reduced exercise capacity reflected by reduced peak VO₂ on CPET. Although impairment of
394 peak VO₂ is limited by cardiac and non-cardiac factors (including pulmonary and peripheral
395 muscle limitations), it is nonetheless a strong prognostic indicator for risk of HF onset^{19,30}. This
396 population with DbCM and impaired exercise tolerance therefore represents a high-risk group in
397 transition toward overt, severe HF.

398 In ARISE-HF, randomized allocation to high dose AT-001 was associated with no change
399 of peak VO₂ over 15 months, while those treated with placebo experienced a significant decline.
400 However, the difference in peak VO₂ between the two arms at 15 months was not statistically
401 significant. Whether a longer treatment time or inclusion of those with less well-controlled
402 T2DM would be expected to result in further divergence in exercise capacity remains uncertain.

403 As the overall study result was neutral, other outcomes are to be viewed as exploratory only.
404 However, in a prespecified and stratified subgroup analysis of the primary endpoint among those
405 study participants not receiving SGLT2 inhibitor or GLP-1RA therapy at baseline, high dose AT-
406 001 appeared to be associated with favorable impact on the primary endpoint, also reducing the
407 number of study participants in this sizeable subgroup experiencing a meaningful reduction in
408 peak VO₂. This finding was accompanied by an interaction P value of 0.10, implying lack of
409 heterogeneity; the non-significant trend in the interaction analysis may reflect reduced power in
410 this relatively small subgroup. Study participants were randomized stratified based on use of
411 SGLT2 inhibitors and/or GLP-1RA and this categorization was a pre-specified subgroup of
412 interest owing to the fact that these agents may affect exercise capacity through cardiovascular
413 and skeletal muscle effects^{20,21}. The possible efficacy of AT-001 in those not receiving these
414 drugs is thus of note.

415 Treatment with AT-001 was safe and well-tolerated in ARISE-HF. This is important,
416 given the off-target toxicities observed in other drugs within this class^{16,29}. Treatment with AT-
417 001 did not lead to liver injury during 15 months of treatment in ARISE-HF, while transient
418 changes in kidney function in the study associated with AT-001 were infrequent and did not lead
419 to discontinuation of treatment.

420 During the 15 months of treatment, serious adverse events such as HF hospitalization or
421 cardiovascular death were rare, reflecting the short follow up time of the trial. However, in
422 prespecified outcome analyses, the frequency of HF symptoms, physical findings, and site-
423 reported clinical adverse cardiovascular events as identified using MedDRA preferred terms
424 appeared higher among those study participants treated with placebo. More information is
425 needed regarding potential effect of AT-001 to reduce progression to overt, symptomatic HF.

426 **Limitations**

427 This study has limitations worth noting. First, the study participants in ARISE-HF were a unique
428 population with well-controlled T2DM and blood pressure, which may not reflect patients with
429 DbCM more generally. Restriction of uncontrolled T2DM or hypertension was a regulatory
430 requirement, imposed to remove influence of hyperglycemia or elevated blood pressure on CPET
431 performance or risk for overt HF. On the other hand, given the polyol pathway is activated (and
432 produces sorbitol) in the setting of hyperglycemia, it is possible AT-001 might be less effective in
433 individuals whose glucose is well-controlled. Indeed, as hyperglycemia is the main driver of
434 sorbitol generation, the near-normoglycemic control in our population may have mitigated
435 favorable effects of aldose reductase inhibition. The combination of tight blood pressure and
436 glycemic control is a unique aspect of the study participants in ARISE-HF compared to general
437 practice; thus, effects of AT-001 in a more generalizable population with T2DM and DbCM
438 remain unknown. It is plausible that among those with more advanced Stage B HF (such as those
439 with more elevated biomarker concentrations or worse echo parameters) that effect of AT-001
440 would be more evident. Baseline data from ARISE-HF reveals clusters of participants varying
441 clinical profiles, including those with worse biomarker concentrations and more remodeled
442 hearts¹⁰. Exploratory analyses based on these populations are planned. Second, the diagnosis of
443 DbCM lacks a gold-standard test for its identification and disease heterogeneity may be present.
444 The diagnosis of DbCM was made based on Stage B HF (characterized by structural heart
445 disease or elevated cardiac biomarkers without overt past or present symptoms of HF)³ and a
446 lack of other obvious causes of HF. It is plausible that study participants had a mixture of other
447 causes of Stage B HF besides DbCM or they may have had different manifestations of the
448 DbCM. Subgroup analyses based on phenotypic clusters are planned. Third, the time horizon of

449 this trial was only 15 months; during this time frame, those treated with high-dose AT-001
450 showed potential stabilization of exercise capacity while placebo-treated patients showed a
451 decline. We speculate a longer treatment duration might have been necessary to identify an
452 impact on exercise capacity in this population. Fourth, although peak VO₂ is a relevant and
453 important prognostic measure that predicts future events in chronic HF, it is possible that by the
454 point of such significant impairment (with an average peak VO₂) study participants might not
455 have been treatment responsive. Lastly, with increasing use of SGLT2 inhibitors and GLP-1RA
456 in the care of higher risk individuals with T2DM, the additive value of aldose reductase
457 inhibition requires further study.

458 In conclusion, in this 15-month study, aldose reductase inhibition with AT-001 did not
459 result in a statistically significant difference in peak oxygen uptake among persons with very
460 well-controlled T2DM affected by DbCM and reduced exercise capacity. Despite these overall
461 results, given the urgency to reduce risk for HF in those with chronic DM, more investigation is
462 needed regarding the potential role of AT-001 to reduce HF risk. Future studies should evaluate
463 longer treatment with AT-001 in a more generalizable population of T2DM with hyperglycemia.
464 Furthermore, the additive value of AT-001 with SGLT2 inhibitors or GLP-1RA bears further
465 scrutiny.

466 **Clinical Perspectives**

467 *Competency in medical knowledge:* Diabetes mellitus may lead to heart failure through
468 development of a heart muscle disease known as diabetic cardiomyopathy (DbCM).

469 *Translational outlook:* Use of aldose reductase inhibition with AT-001 may be a means by which
470 to reduce progression of DbCM.

471 ***Translational outlook:*** Although 15 months of treatment with AT-001 did not stabilize exercise
472 capacity in DbCM overall, individuals not receiving SGLT2 inhibitors or GLP-1RA did show
473 better peak VO₂ at this time point. More data are needed to understand the role of AT-001 to
474 improve outcomes in DbCM.

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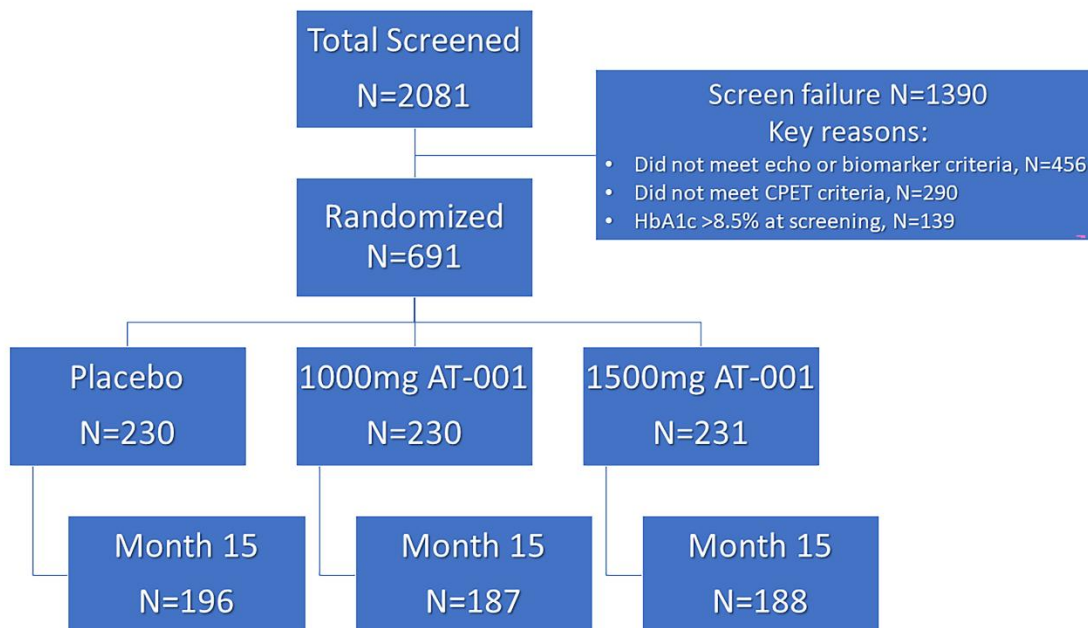
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556 **Figure Legends**

557 **Figure 1:** Study flow for the ARISE-HF Trial.

558 691 eligible individuals with DbCM and reduced exercise capacity were randomized. CPET

559 denotes: cardiopulmonary exercise test; HbA1c denotes: hemoglobin A1c.



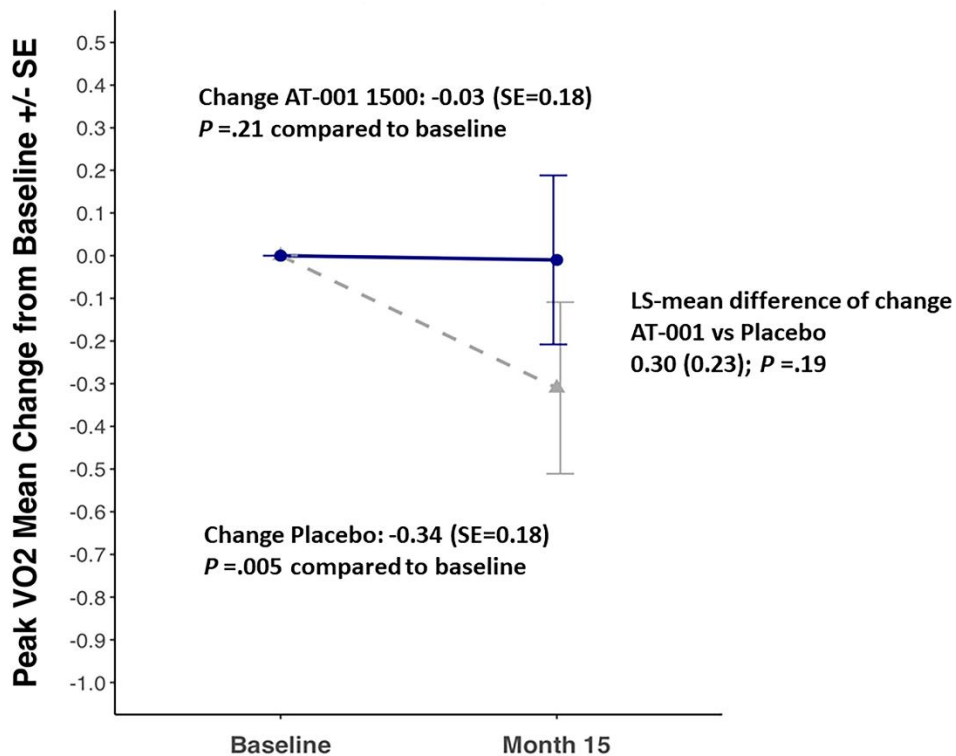
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563 **Figure 2:** Primary endpoint of the ARISE-HF Trial.

564 Although peak VO₂ declined in placebo treated patients and remained the same in those treated
565 with high dose AT-001, the proportional change in peak VO₂ between study arms was not
566 significantly different at 15 months. Owing to trial termination, effect of AT-001 at 27 months



567 was not explored.

568





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570

571 **Central Illustration:** Design and main results from the ARISE-HF trial.

572 Persons with diabetic cardiomyopathy and reduced exercise capacity were treated with AT-001

573 for 15 months to explore impact of aldose reductase inhibition on peak oxygen uptake.

Study participants		691 individuals with Stage B heart failure from diabetic cardiomyopathy (50% women, mean age of 67.5 years) and reduced exercise capacity (peak VO_2 <75% of normal)
Intervention	 Placebo AT-001	Randomized to receive placebo versus aldose reductase inhibition with low and high dose AT-001 for a duration of 15 months
Outcomes		Change in peak VO_2 from baseline to 15 months
Results		<p>Peak VO_2 worsened by 15 months in placebo patients but not those receiving AT-001 but this difference was not statistically significant.</p> <p>In prespecified analyses, those not receiving SGLT2 inhibitors or GLP-1RA at baseline the difference between peak VO_2 in placebo versus high dose AT-001 at 15 months was 0.62 mL/Kg/minute (P =.04; interaction P =.10).</p>

574

575 **Table 1:** Baseline clinical characteristics of study participants randomized in the ARISE-HF Trial as a function of treatment allocation.

576

	All (N=691)	Placebo (N=230)	AT-001 1000 mg (N=230)	AT-001 1500 mg (N=231)
Age, years, mean ± SD	67.5 ± 7.2	68.2 ± 6.7	67.4 ± 7.8	66.9 ± 7.0
Female, N (%)	348 (50.4)	124 (53.9)	107 (46.5)	117 (50.6)
Race, N (%)				
White	570 (82.5)	195 (84.8)	191 (83.0)	184 (79.7)
Black	50 (7.2)	14 (6.1)	13 (5.7)	23 (10.0)
Asian	58 (8.4)	17 (7.4)	24 (10.4)	17 (7.4)
American Indian or Alaskan Native	5 (0.7)	2 (0.9)	0 (0)	3 (1.3)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0)	0 (0)	1 (0.4)
Other	5 (0.7)	1 (0.4)	1 (0.4)	3 (1.3)
Ethnicity, N (%)				
Hispanic	151 (21.9)	44 (19.1)	48 (20.9)	59 (25.5)
Non-Hispanic	532 (77.1)	183 (79.6)	179 (77.8)	170 (73.6)
Body-mass index, kg/m², mean ± SD	30.6 ± 4.6	30.9 ± 4.8	30.4 ± 4.6	30.5 ± 4.4
Smoking Status, N (%)				
Current Smoker	66 (9.6)	21 (9.1)	23 (10.0)	22 (9.5)
Previous Smoker	246 (35.6)	85 (37)	81 (35.2)	80 (34.6)
Never	394 (57)	132 (57.4)	130 (56.5)	132 (57.1)
Vital signs at baseline				
Systolic blood pressure, mmHg, mean ± SD	131 ± 17	131 ± 17	132 ± 17	131 ± 16
Diastolic blood pressure, mmHg, mean ± SD	77 ± 10	77 ± 11	77 ± 10	77 ± 10
Heart rate, beats/minute, mean ± SD	78 ± 13	78 ± 12	79 ± 13	78 ± 13
Medical history, N (%)				
Hypertension	523 (75.7)	179 (77.8)	179 (77.8)	165 (71.4)
Dyslipidemia	116 (16.8)	45 (19.6)	36 (15.7)	35 (15.2)
Duration of T2DM, years, mean ± SD	14.5 ± 9.1	14.4 ± 9.2	14.6 ± 9.2	14.4 ± 9.0
Geographical Region, n (%)				
North America	390 (56.4)	130 (56.5)	129 (56.1)	131 (56.7)

Rest of the World	301 (43.6)	100 (43.5)	101 (43.9)	100 (43.3)
Use of SGLT2i or GLP-1RA at baseline, n (%)	263 (38.1)	86 (37.4)	89 (38.7)	88 (38.1)
Baseline respiratory exchange rate, n (%)				
< 1.15	296 (42.8)	98 (42.6)	99 (43)	99 (42.9)
≥1.15	394 (57.2)	132 (57.4)	131 (57)	131 (56.7)
Baseline peak VO₂ (mL/kg/min), mean ± SD	15.7 ± 3.8	15.6 ± 3.8	15.7 ± 3.8	16 ± 3.9

577

578 SD denotes: standard deviation; kg denotes: kilogram; m² denotes: square meter; SGLT2i denotes: sodium/glucose cotransporter 2

579 inhibitor; GLP1-RA denotes: glucagon-like peptide-1 receptor agonist; VO₂ denotes: oxygen uptake; mL denotes: milliliters; min

580 denotes: minute

581

582

583 **Table 2:** Objective testing results at baseline as a function of treatment allocation.

Parameter	Placebo	AT-001 1000 mg	AT-001 1500 mg
PASE Score, mean \pm SD	159 \pm 94	150 \pm 90	157 \pm 87
KCCQ Overall Summary Score, mean \pm SD	90 \pm 16	90 \pm 15	91 \pm 13
KCCQ Clinical Summary Score, mean \pm SD	90 \pm 15	91 \pm 114	91 \pm 13
KCCQ Total Symptom Score, mean \pm SD	92 \pm 15	92 \pm 15	94 \pm 13
KCCQ Physical Limitation Score, mean \pm SD	88 \pm 17	90 \pm 17	89 \pm 16
KCCQ Symptom Stability Score, mean \pm SD	52 \pm 10	52 \pm 11	51 \pm 9
KCCQ Symptom Frequency Score, mean \pm SD	91 \pm 15	91 \pm 15	93 \pm 13
KCCQ Symptom Burden Score, mean \pm SD	92 \pm 15	92 \pm 15	94 \pm 13
KCCQ Self Efficacy Score, mean \pm SD	85 \pm 22	85 \pm 25	86 \pm 22
KCCQ Quality of Life Score, mean \pm SD	87 \pm 20	88 \pm 20	87 \pm 18
KCCQ Social Limitation Score, mean \pm SD	92 \pm 18	92 \pm 18	93 \pm 15

584

585 PASE denotes: Physical Activity Scale for the Elderly; SD denotes: standard deviation; KCCQ denotes: Kansas City Cardiomyopathy
 586 Questionnaire

587 **Table 3:** Change in physical activity and health status from baseline to 15 months.

Questionnaire	Measure	Change from Baseline to 15 months		
		Placebo	AT-001 1000 mg	AT-001 1500mg
PASE Score	LS mean (SE)	-5.84 (7.34)	-6.96 (7.24)	-7.46 (7.22)
	LS mean difference (SE)		-1.12 (9.2)	-1.62 (9.11)
	<i>P</i>		.90	.86
KCCQ Overall Summary Score	LS mean (SE)	-1.62 (1.02)	-0.18 (1.02)	-2.61 (1)
	LS mean difference (SE)		1.44 (1.29)	-0.99 (1.27)
	<i>P</i>		.27	.44
KCCQ Clinical Summary Score	LS mean (SE)	-2.99 (0.99)	-1.05 (0.99)	-3.72 (0.97)
	LS mean difference (SE)		1.94 (1.26)	-0.74 (1.24)
	<i>P</i>		.12	.55
KCCQ Total Symptom Score	LS mean (SE)	-3.3 (1.03)	-0.49 (1.03)	-4.42 (1.01)
	LS mean difference (SE)		2.81 (1.31)	-1.12 (1.29)
	<i>P</i>		.03	.39
KCCQ Physical Limitation Score	LS mean (SE)	-2.72 (1.21)	-1.85 (1.21)	-2.65 (1.18)
	LS mean difference (SE)		0.88 (1.54)	0.07 (1.51)
	<i>P</i>		.57	.96
KCCQ Symptom Stability Score	LS mean (SE)	-1.01 (1.2)	-0.44 (1.2)	-0.36 (1.18)
	LS mean difference (SE)		0.57 (1.52)	0.65 (1.5)
	<i>P</i>		.71	.67
KCCQ Symptom Frequency Score	LS mean (SE)	-3.34 (1.12)	-0.06 (1.12)	-4.05 (1.1)
	LS mean difference (SE)		3.28 (1.42)	-0.71 (1.4)
	<i>P</i>		.02	.61
KCCQ Symptom Burden Score	LS mean (SE)	-3.25 (1.08)	-0.96 (1.09)	-4.8 (1.06)
	LS mean difference (SE)		2.28 (1.37)	-1.55 (1.35)
	<i>P</i>		.10	.25
KCCQ Self Efficacy Score	LS mean (SE)	-1.55 (2.01)	2.68 (2)	-2.43 (1.96)

	LS mean difference (SE)		4.23 (2.54)	-0.89 (2.5)
	<i>P</i>		.10	.72
KCCQ Quality of Life Score	LS mean (SE)	0.21 (1.45)	0.72 (1.45)	-0.52 (1.42)
	LS mean difference (SE)		0.51 (1.84)	-0.73 (1.81)
	<i>P</i>		.78	.69
KCCQ Social Limitation Score	LS mean (SE)	-0.62 (1.52)	0.97 (1.49)	-2.44 (1.49)
	LS mean difference (SE)		1.59 (1.94)	-1.82 (1.93)
	<i>P</i>		.41	.34

588

589 PASE denotes: Physical Activity Scale for the Elderly; LS denotes: least square; SE denotes: standard error; KCCQ denotes: Kansas
590 City Cardiomyopathy Questionnaire

591 **Table 4:** Adverse events occurring >5% during 15 months of treatment in ARISE-HF.

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)
Urinary tract infection	96 (13.9)	25 (10.9)	34 (14.9)	37 (16.0)
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 estimated glomerular filtration rate	39 (5.7)	2 (0.9)	16 (7.0)	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 (7.0)	11 (4.8)	15 (6.5)
Headache	35 (5.1)	11 (4.8)	10 (4.4)	14 (6.1)
Upper respiratory tract infection	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)

592