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Brief Report

Myeloperoxidase Inhibition in Heart Failure With Preserved or Mildly Reduced Ejection Fraction: SATELLITE Trial Results

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ABSTRACT

Background: Inflammation is a key driver of heart failure with preserved left ventricular ejection fraction. AZD4831 inhibits extracellular myeloperoxidase, decreases inflammation, and improves microvascular function in preclinical disease models.

Methods and Results: In this double-blind phase 2a study (Safety and Tolerability Study of AZD4831 in Patients With Heart Failure [SATELLITE]; NCT03756285), patients with symptomatic heart failure, left ventricular ejection fraction of ≥40%, and elevated B-type natriuretic peptides were randomized 2:1 to once-daily oral AZD4831 5 mg or placebo for 90 days. We aimed to assess target engagement (primary end point: myeloperoxidase specific activity) and safety of AZD4831. Owing to coronavirus disease 2019, the study was terminated early after randomizing 41 patients (median age 74.0 years, 53.7% male). Myeloperoxidase activity was decreased by more than 50% from baseline to day 30 and day 90 in the AZD4831 group, with a placebo-adjusted decreased of 75% (95% confidence interval, 48, 88, nominal $P < .001$). No improvements were noted in secondary or exploratory end points, apart from a trend in Kansas City Cardiomyopathy Questionnaire overall summary score. No deaths or treatment-related serious adverse events occurred. AZD4831 treatment-related adverse events were generalized maculopapular rash, pruritus, and diarrhea (all $n = 1$).

Conclusions: AZD4831 inhibited myeloperoxidase and was well tolerated in patients with heart failure and left ventricular ejection fraction of 40% or greater. Efficacy findings were exploratory owing to early termination, but warrant further clinical investigation of AZD4831.

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Lay Summary: Few treatments are available for patients with the forms of heart failure known as heart failure with preserved or mildly reduced ejection fraction. Current treatments do not target inflammation, which may play an important role in this condition. We tested a new drug called AZD4831 (mitiperstat), which decreases inflammation by inhibiting the enzyme myeloperoxidase. Among the 41 patients in our clinical trial, AZD4831 had a good safety profile and inhibited myeloperoxidase by the expected amount. Results mean we can conduct further trials to see whether AZD4831 decreases the symptoms of heart failure and improves patients' ability to participate in physical exercise. (*J Cardiac Fail 2023;00:1−7*)
Key Words: Heart failure, preserved ejection fraction, mildly reduced ejection fraction, myeloperoxidase, inflammation, pharmacokinetics, pharmacodynamics, randomized controlled trial.

Heart failure (HF) affects 2% of adults, and its prevalence increases with advancing age, rising to more than 10% in those aged over 70 years. Few guideline-directed treatment options are available for the increasing number of patients with HF and preserved or mildly reduced ejection fraction (HFpEF/HFmrEF; left ventricular ejection fraction [LVEF] of >40%). A novel therapeutic approach is to target chronic inflammation and the resulting oxidative stress and microvascular dysfunction, which play key pathophysiological roles in HFpEF/HFmrEF.[1,2] In addition, inflammation impairs endothelial nitric oxide production in the heart and drives a vicious cycle of cardiomyocyte hypertrophy and fibrosis.[2,3]

Extracellular myeloperoxidase provides a mechanistic link between chronic inflammation and the development of HFpEF/HFmrEF. Myeloperoxidase inhibition is hypothesized to decrease free radical production, prevent microvascular dysfunction, improve cardiomyocyte relaxation, decrease fibrosis, and potentially improve heart function and clinical outcomes in patients with HFpEF/HFmrEF.[2,4] AZD4831 (mitiperstat) is a novel, selective, covalent inhibitor of myeloperoxidase with greater potency for extracellular than intracellular myeloperoxidase. This agent may preserve the protective microbicidal function of intragranular myeloperoxidase in neutrophils.[2] We have previously reported the pharmacokinetics, safety, tolerability, and target engagement after single and multiple ascending doses of AZD4831 in healthy volunteers.[5,6] The Safety and Tolerability Study of AZD4831 in Patients With Heart Failure (SATELLITE) study evaluated target engagement, safety and tolerability of AZD4831 in patients with HFpEF/HFmrEF.

Methods

Conduct

SATELLITE was a randomized, double-blind, placebo-controlled, phase 2a study of AZD4831 (mitiperstat) in patients with HF and LVEF of at least 40%. Ethics committees at all centers approved the protocol. All patients gave written informed consent before enrollment and could withdraw at any time. The study took place from December 2018 to May 2020 with final analysis in November 2020, and was registered on clinicaltrials.gov (NCT03756285).

Patients

Eligible patients were aged 45−85 years with a history of symptomatic HF; New York Heart Association functional class of II−IV; LVEF of at least 40%; elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels in the past year; and at least 1 of the following: hospitalization owing to HF, structural heart disease,[7] high pulmonary capillary wedge pressure, or high E/e′. Key exclusion criteria were low estimated glomerular filtration rate, decompensated HF, primary cardiomyopathy, significant valve disease, indication for cardiac surgery/catheterization, tachycardia, and dysrhythmia (see clinicaltrials.gov NCT03756285 for complete inclusion and exclusion criteria).

Procedures

Patients (planned $N = 96$) were randomized 2:1 to once-daily oral AZD4831 or matching placebo film-coated tablets for 90 days. In part A (planned $n = 37$), the AZD4831 dose was 2.5 mg for 10 days and then 5 mg for 80 days. In part B (planned $n = 59$), the AZD4831 dose was 2.5 mg for 10 days and then 2.5 mg, 5 mg, or 10 mg for 80 days, depending on part A 30-day interim safety and pharmacodynamic results. Randomization was centrally computer-generated and stratified by atrial fibrillation status (maximum 50% of patients). Patients attended clinics on day 0 (baseline); days 10, 20, 30, 60, and 90 (treatment period), and day 120 (safety follow-up). Standard care was continued throughout the study as required.

End Points

The primary end point was myeloperoxidase specific activity, defined as myeloperoxidase activity

divided by myeloperoxidase protein concentration in an ex vivo whole-blood assay using zymosan stimulation to release intracellular myeloperoxidase. Values were normalized to maximal detectable inhibition with excess AZD4831 at baseline, as previously described.[6] Secondary end points were coronary flow velocity reserve (CFVR) and 6-minute walking distance (6MWD). Exploratory end points were NT-proBNP concentration and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS) and physical limitation score. Safety was monitored continuously with a special focus on maculopapular rash, based on findings in previous studies.[5,6]

Analyses

Statistical power was 95% for a 1.7-fold decrease in myeloperoxidase specific activity and 80% for a 20% increase in CFVR for AZD4831 vs placebo ($\alpha = 0.05$, 2-sided). A closed-test procedure preserved overall type 1 error at 5%. Prespecified efficacy analyses were performed as described in Fig. 1 using SAS v9.4 or later. Percentage changes for variables that were log-transformed before analysis were presented as geometric least-squares mean ratio -1×100.

Results

Early Termination

Part A was completed, and part B continued with AZD4831 5 mg selected at the interim analysis. Shortly afterward, the study was halted temporarily because of the impact of the coronavirus disease 2019 pandemic on participants' safety. Interim results indicated that the primary end point had been met, and the unblinded data review committee therefore stopped the study early. Final analyses were performed but were exploratory because the statistical assumptions were not met; *P* values were noninferential.

Patients

Both the efficacy and safety analysis sets comprised all 41 randomized patients (AZD4831 5 mg, $n = 27$: placebo, $n = 14$) (Table 1). Baseline demographics and disease characteristics were generally well balanced between groups. The majority of patients had atrial fibrillation and HFpEF (Table 1).

Efficacy

Within the AZD4831 group, normalized ex vivo myeloperoxidase-specific activity was decreased from baseline by 67.5% to day 30 and 53.7% to day 90 (Fig. 1A). Myeloperoxidase specific activity was reduced in the majority of patients in the AZD4831 group and there were increases in the majority of patients in the placebo group (Fig. 1B). In the statistical analysis, the geometric least-squares mean ratio of end of treatment over baseline for AZD4831 vs placebo was 0.25 (95% confidence interval [CI] 0.12, 0.52, nominal $P < .001$) (Fig. 1C). This corresponds with a placebo-adjusted decrease in myeloperoxidase specific activity of 75% (95% CI 48, 88).

Placebo-adjusted changes from baseline to end of treatment in CFVR, NT-proBNP levels, 6MWD, KCCQ-OSS, and KCCQ-OSS were not significant (nominal $P > .05$) (Fig. 1C). The placebo-adjusted change in KCCQ-OSS from baseline to end of treatment was +6.283 points (95% CI −0.461, +13.027) (Fig. 1C). No changes were noted in echocardiographic parameters, including E/e′ and left atrial volume index.

Safety

Adverse events were reported in 17 of 27 patients (63.0%) receiving AZD4831 5 mg and 8 of 14 (57.1%) receiving placebo (Table 2). There were no treatment-related serious adverse events and no deaths. No clinically significant trends in vital signs, laboratory parameters, or electrocardiography parameters were observed. One patient (3.7%) in the AZD4831 5 mg group discontinued treatment after a nonserious, treatment-related grade 3 generalized maculopapular rash. This was reported 5 days after uptitration from AZD4831 2.5 mg to 5.0 mg and resolved after treatment with oral corticosteroid and antihistamine.

Discussion

AZD4831 inhibited released extracellular myeloperoxidase in patients with HFpEF/HFmrEF, with no new safety or tolerability concerns. Myeloperoxidase-specific activity was more than halved from baseline after 30 and 90 days, and the placebo-adjusted decrease at end of treatment was 75% (95% CI 48, 88). This met the prespecified target engagement level. There were no marked improvements in CFVR, 6MWD, KCCQ physical limitation score, or NT-proBNP levels, but a trend toward improvement in the KCCQ-OSS was potentially clinically meaningful in magnitude (>5 points vs placebo). Further studies are needed to investigate whether myeloperoxidase inhibition by AZD4831 translates into clinical benefit for patients with HFpEF/HFmrEF.

CFVR is a marker of coronary microvascular function in patients with HFpEF/HFmrEF and impairments correlate with mortality and hospitalization for HF. Standardized protocols and centralized training enable low variability, making CFVR an attractive multicenter study outcome.

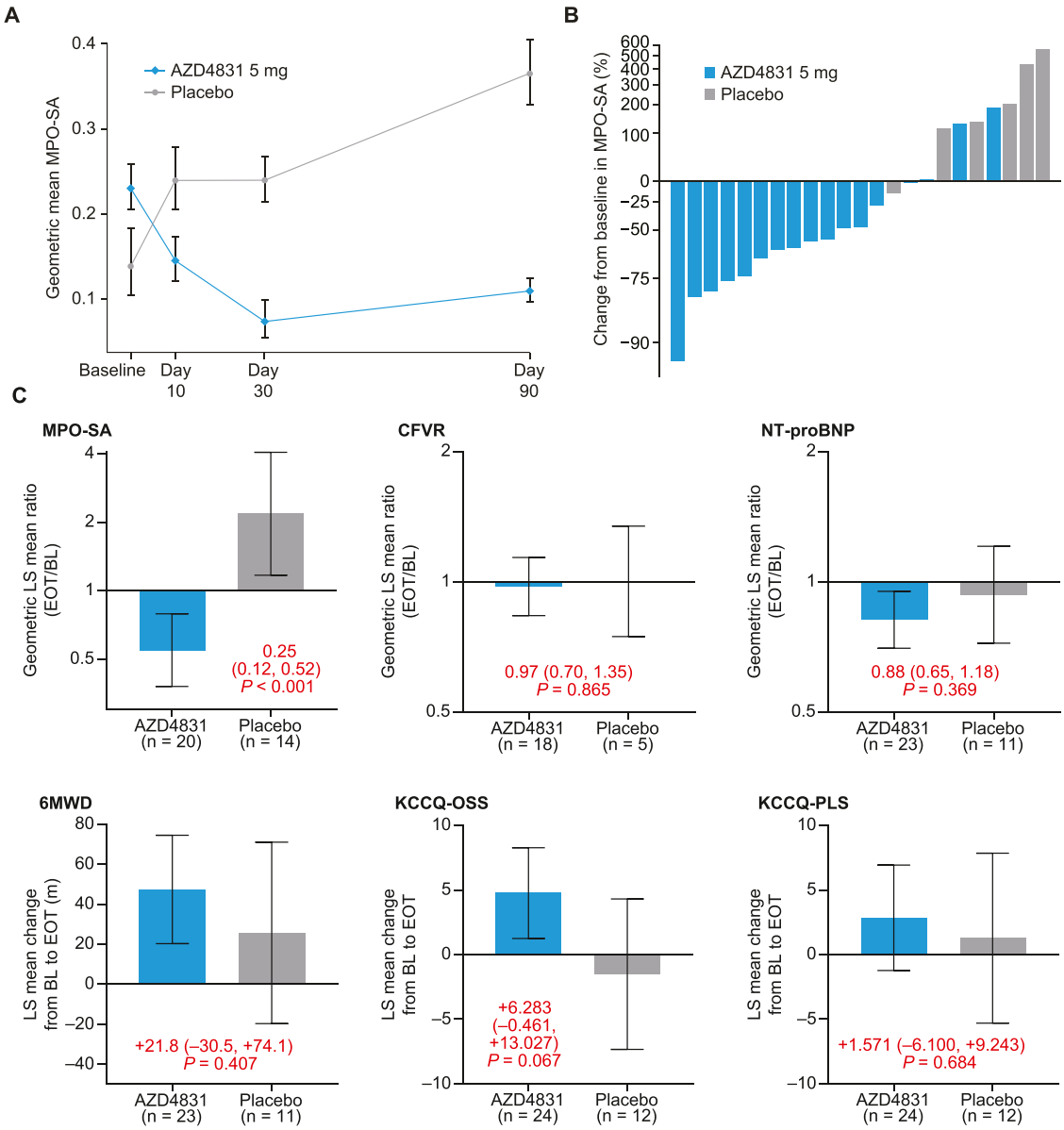

Figure 1. (**A, B**) Target engagement. (**C**) Exploratory statistical analyses of efficacy end points. (**A**–**C**) MPO-SA is ex vivo zymosan-released myeloperoxidase activity divided by myeloperoxidase protein mass, normalized to maximal detectable inhibition in the presence of excess AZD4831 at baseline. (**A**) Error bars show geometric SEM. (**B**) Geometric mean ratio of EOT/BL − 1 × 100. (**C**) Mixed-model repeated measures for change from BL to EOT (fixed factors: atrial fibrillation, treatment, visit, treatment–visit interaction; covariate: baseline value) or analysis of covariance for change from BL to EOT (fixed factors: atrial fibrillation, treatment; covariate: baseline value). LS mean change calculated as geometric ratio of EOT/BL for log-transformed variables and EOT−BL for other variables. Error bars show 95% CI. Red text shows placebo-adjusted changes (geometric LS mean ratio of AZD4831/placebo for log-transformed variables; AZD4831−placebo for other variables) with 95% CIs and nominal *P* values. Analyses are noninferential because of early study termination. 6MWD = 6-minute walking distance; BL = baseline; CFVR = coronary flow velocity reserve; CI = confidence interval; EOT = end of treatment; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire – overall summary score; KCCQ-PLS = Kansas City Cardiomyopathy Questionnaire – physical limitation score; LS = least squares; MPO-SA = myeloperoxidase specific activity; NT-proBNP = N-terminal pro B-type natriuretic peptide; SEM = standard error of the mean.

Other techniques or imaging modalities may, however, have provided more sensitive assessment of coronary perfusion.

NT-proBNP was the only prespecified biomarker in SATELLITE. In an exploratory proteomic analysis, inflammatory biomarker pathways that were most strongly associated with clinical outcomes in HFpEF observational cohorts were decreased in the AZD4831 group vs placebo in SATELLITE.[8] These findings support an association between chronic inflammation and HFpEF/HFmrEF, with myeloperoxidase as a central player in this pathophysiology.

Table 1. Patient Disposition and Baseline Characteristics

	Randomized Patients ($N = 41$)*	
	AZD4831 5 mg ($n = 27$)	Placebo ($n = 14$)
Disposition		
Enrolled in part A | part B, *n*	24 | 3	13 | 1
Received treatment, *n*	27	14
Discontinued treatment, *n*	4	6
Adverse event	1	0
Lost to follow-up	0	1
Protocol noncompliance	0	2
Disruption owing to the COVID-19 pandemic†	3	3
Completed 90 days of treatment, *n*	23	8
Completed follow-up, *n*	24	9
Baseline demographics and disease characteristics		
Age, years, median (range)	74.0 (55–85)	74.5 (54–81)
Male, *n* (%)	15 (55.6)	7 (50.0)
Female, *n* (%)	12 (44.4)	7 (50.0)
White, *n* (%)	27 (100)	13 (92.9)
Black or African American, *n* (%)	0	1 (7.1)
Body mass index, kg/m^2, median (range)	26.9 (18.3–37.7)	28.0 (23.8–38.8)
Atrial fibrillation, *n* (%)	15 (55.6)	8 (57.1)
HFmrEF, *n* (%) ‡ §	7 (25.9)	4 (28.6)
HFpEF, *n* (%) ‡ ‖	20 (74.1)	10 (71.4)
Relevant comorbidities in >10% of patients overall, *n* (%) ¶		
Hypertension	24 (88.9)	10 (71.4)
Cardiac failure	22 (81.5)	11 (78.6)
Hypercholesterolemia	4 (14.8)	3 (21.4)
Angina pectoris	6 (22.2)	1 (7.1)
Concomitant medications in >50% of patients overall, *n* (%)		
ß-blockers	18 (66.7)	9 (64.3)
Statins	17 (63.0)	8 (57.1)
Angiotensin II receptor blockers	16 (59.3)	6 (42.9)
Furosemide	13 (48.1)	8 (57.1)
Baseline efficacy parameters		
Myeloperoxidase specific activity, geo. mean (%CV) ‡‡	0.230 (61.7) **	0.138 (140.3)
Coronary flow velocity reserve, geo. mean (%CV)	2.114 (42.3) **	1.708 (34.8) ††
NT-proBNP, pg/mL, geo. mean (%CV) §§	918.0 (100.4)	1018.8 (66.5)
Six-minute walking distance, m, mean (SD)	392.7 (103.50)	364.4 (102.62)
KCCQ overall summary score, mean (SD)	74.38 (18.625)	70.92 (21.791)
KCCQ physical limitation score, mean (SD)	75.93 (19.314)	70.71 (21.550)

COVID-19 = coronavirus disease 2019; CV = coefficient of variation; Geo. = geometric; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; SD = standard deviation.

*Of 64 patients who consented and enrolled, 23 were not randomized because the study was terminated early.

†For example, patients unable to attend study visits; no adverse events of coronavirus infection occurred during the study.

‡Values from prebaseline screening assessment (unspecified method).

§LVEF <50% and ≥40%.

‖LVEF ≥50%.

¶Metabolic and cardiovascular comorbidities, excluding atrial fibrillation.

**$n = 24$.

††$n = 11$.

‡‡Ex vivo zymosan-released myeloperoxidase activity divided by myeloperoxidase protein mass, normalized to maximal detectable inhibition in the presence of excess AZD4831.

§§NT-proBNP 1 pg/mL = 0.118 pmol/L.

Table 2. Summary of Adverse Events

	No. of Patients (%)	
	AZD4831 ($n = 27$)	Placebo ($n = 14$)
Any adverse event	17 (63.0)	8 (57.1)
Treatment-related	3 (11.1)*	1 (7.1)
Any serious adverse event	2 (7.4)	1 (7.1)
Treatment-related	0	0
Adverse event leading to discontinuation of study treatment	1 (3.7) †	0
Adverse events reported in ≥2 patients		
Dizziness	3 (11.1)	1 (7.1)
Pruritus	3 (11.1)	1 (7.1)
Fatigue	2 (7.4)	0
Nasopharyngitis	2 (7.4)	0
Nausea	2 (7.4)	0
Pyrexia	2 (7.4)	0
Cough	1 (3.7)	1 (7.1)
Influenza	1 (3.7)	1 (7.1)

Adverse events were classified using MedDRA version 23.0.
CTCAE = Common Terminology Criteria for Adverse Events.

*Generalized maculopapular rash, pruritus, and diarrhea (all $n = 1$).

†Treatment-related generalized maculopapular rash of CTCAE grade 3 in part A; also reported as treatment-related severe dermatitis allergic (original reported term: allergic skin reaction).

Other inflammatory pathways may, however, also contribute to development of HFpEF/HFmrEF.

Overall, AZD4831 was well tolerated, with no new safety signals, no treatment-related serious adverse events, and no deaths. Maculopapular rash led to the discontinuation of AZD4831 5 mg in 1 patient, but resolved rapidly with steroid treatment. Maculopapular rash is most likely an off-target effect, although the mechanism remains unclear.[5,6]

Early termination of SATELLITE because of the coronavirus disease 2019 pandemic made it challenging to interpret the findings. The smaller than planned sample size meant that statistical analyses were exploratory instead of inferential. The small sample size may have also led to the imbalance in some baseline efficacy parameters. Myeloperoxidase-specific activity increased in the placebo group, but few patients had evaluable data, and some had low baseline values. Normalization and log-transformation of myeloperoxidase-specific activity reduced the number of patients with evaluable data and prevented comparison with levels published elsewhere. Another limitation was that baseline impairments in CFVR, 6MWD, and KCCQ were not required for enrollment.

In conclusion, once-daily AZD4831 5 mg decreased myeloperoxidase-specific activity in patients with HF and a LVEF of 40% or higher. Efficacy findings were exploratory and inconclusive, and the safety profile was consistent with previous studies.[5,6] Together, these data support continued clinical development

of AZD4831. ENDEAVOR is an ongoing sequential phase 2b−3 study of the efficacy and safety of AZD4831 in patients with HFpEF/HFmrEF with primary end points of change in KCCQ-OSS and 6MWD (NCT04986202).

How this work applies to patients

- Patients with heart failure and preserved or mildly reduced left ventricular ejection fraction have few treatment options.
- Multiple lines of evidence support targeting inflammation as a novel therapeutic approach in these patients, and indicate that myeloperoxidase is a key driver of inflammation.
- In this phase 2a study (SATELLITE), AZD4831 inhibited released extracellular myeloperoxidase in patients with heart failure and a left ventricular ejection fraction of at least 40%, with a good safety profile, supporting its continued development as a potential new treatment.

Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Carolyn Lam.

Declaration of Competing Interest

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