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Safety and efficacy of the 5-lipoxygenase-activating protein inhibitor AZD5718 in patients with recent myocardial infarction: The phase 2a FLAVOUR study

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ABSTRACT

Background: Leukotrienes are pro-inflammatory vasoactive lipid mediators implicated in the pathophysiology of atherosclerotic cardiovascular disease. We studied the effect of the 5-lipoxygenase-activating protein inhibitor AZD5718 on leukotriene biosynthesis and coronary microvascular function in a single-blind, phase 2a study.
Methods: Patients 7–28 days after myocardial infarction (±ST elevation), with <50% left anterior descending coronary artery stenosis and Thrombolysis in Myocardial Infarction flow grade ≥ 2 after percutaneous coronary intervention, were randomized 2:1:2 to once-daily AZD5718 200 mg or 50 mg, or placebo, in 4- and 12-week cohorts. Change in urine leukotriene E_4 ($uLTE_4$) was the primary endpoint, and coronary flow velocity reserve (CFVR; via echocardiography) was the key secondary endpoint.
Results: Of 129 randomized patients, 128 received treatment (200 mg, $n = 52$; 50 mg, $n = 25$; placebo, $n = 51$). Statistically significant reductions in $uLTE_4$ levels of >80% were observed in both AZD5718 groups versus the placebo group at 4 and 12 weeks. No significant changes in CFVR were observed for AZD5718 versus placebo. Adverse events (AEs) occurred in 12/18, 3/6 and 6/13 patients receiving 200 mg, 50 mg and placebo, respectively, in the 4-week cohort, and in 27/34, 14/19 and 24/38 patients, respectively, in the 12-week cohort. Serious AEs in seven patients receiving AZD5718 and four receiving placebo were not treatment-related, and there were no deaths.

Abbreviations: 5-LO, 5-lipoxygenase; CFVR, coronary flow velocity reserve; FLAP, 5-lipoxygenase-activating protein; LAD, left anterior descending; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; $uLTE_4$, urine leukotriene E_4.

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Conclusions: In patients with recent myocardial infarction, AZD5718 was well tolerated, and leukotriene biosynthesis was dose-dependently inhibited. No significant changes in CFVR were detected. ClinicalTrials.gov identifier: NCT03317002.

1. Introduction

Cardiovascular disease accounts for around 17.9 million deaths per year and is the leading cause of death worldwide [1,2]. Survivors of acute coronary syndrome (ACS) remain at risk of recurrent cardiovascular events, and anti-inflammatory therapies may reduce the residual risk potentially related to specific inflammatory pathways, including the leukotriene cascade [3].

Leukotrienes are potent pro-inflammatory vasoconstrictive lipid mediators biosynthesized via the 5-lipoxygenase (5-LO) pathway and are implicated in the pathophysiology of atherosclerotic cardiovascular disease plaque rupture and infarction area remodelling [4]. Leukotriene biosynthesis occurs by the conversion of arachidonic acid to leukotriene A_4 (LTA_4) via 5-LO and 5-LO-activating protein (FLAP; Supplementary Fig. S1). LTA_4 is the precursor for the synthesis of leukotriene B_4 (LTB_4), a potent leukocyte activator and chemokine, and the cysteinyl leukotrienes (C_4, D_4 and E_4), potent vasoactive and inflammatory mediators [4,5].

ALOX5 (5-LO), *ALOX5AP* (FLAP) and *LTA4H* (LTA_4 hydrolase) are abundantly expressed in the arterial walls of patients with coronary artery disease [6,7]. Increased expression and activity of 5-LO pathway components are linked to atherosclerotic plaque inflammation and progression [4,6,8–10]. Individuals with 5-LO pathway gene variants have an increased risk of carotid atherosclerosis and myocardial infarction and an association with surrogate measures of coronary artery disease [11–14].

In patients with myocardial infarction, a FLAP inhibitor (DG-031) reduced the level of biomarkers associated with an increased risk of myocardial infarction [15]. VIA-2291 (atreleuton), a 5-LO inhibitor, reduced ex vivo stimulated LTB_4 production and plaque progression in patients with ACS [16,17], and the 5-LO inhibitor zileuton improved endothelial function in patients undergoing coronary angiography. [18] The site of cascade inhibition (of FLAP vs 5-LO) may also be of biological relevance: inhibition of FLAP increases the biosynthesis of potentially beneficial lipid proresolving mediators, which actively terminate inflammation and promote tissue healing and regeneration, while inhibition of 5-LO blocks proresolving mediator biosynthesis. [19]

AZD5718 is a FLAP inhibitor at the first step of leukotriene biosynthesis that suppresses all leukotriene production (Supplementary Fig. S1). [20] In phase 1 studies (NCT02632526; NCT02963116), multiple oral doses of AZD5718 60–600 mg were generally well tolerated and potently reduced endogenous urine leukotriene E_4 ($uLTE_4$) and ex vivo calcium ionophore-stimulated LTB_4 synthesis in whole blood. [5] A post hoc pharmacokinetic–pharmacodynamic model demonstrated 90% inhibition of plasma LTB_4 production over 24 h after once-daily administration of AZD5718 200 mg oral tablets. [21]

In the FLAVOUR study, we tested the effect of AZD5718 on leukotriene E_4 (LTE_4) biosynthesis and coronary flow velocity reserve (CFVR) in the left anterior descending (LAD) coronary artery in patients with recent myocardial infarction.

2. Methods

2.1. Study design and interventions

The FLAVOUR study (ClinicalTrials.gov: NCT03317002) started in October 2017 and was a 12-week, randomized, placebo-controlled, parallel-group, multicentre, phase 2a study. The original protocol defined a 4-week treatment period. In April 2018, a protocol amendment was made that extended the treatment period to 12 weeks for longer-term assessment of efficacy and safety. [22] Enrolled patients were randomized 2:1:2 to receive once-daily AZD5718 200 mg, AZD5718 50 mg or placebo, respectively, in 4- and 12-week treatment cohorts. Overall, the study was single-blind regarding treatment strengths but double-blind with regards to whether a participant received AZD5718 or placebo. Randomization, using algorithm-based block sequence generation, was stratified by type of myocardial infarction (ST-elevation myocardial infarction [STEMI] vs non-STEMI).

2.2. Patients

Eligible patients were adults aged 18–75 years with a body mass index of 18–35 kg/m^2 and with coronary artery disease. Patients had experienced STEMI or non-STEMI 7–28 days before randomization. [22] Patients were required to have <50% residual stenosis of the LAD coronary artery and a Thrombolysis in Myocardial Infarction (TIMI) flow grade of ≥2 after percutaneous coronary intervention (PCI). Patients with a left ventricular ejection fraction (LVEF) of <30%, atrial fibrillation, prior LAD coronary artery bypass grafting or stroke within 6 months were excluded. Complete exclusion criteria have been previously described. [22]

2.3. Endpoints

The primary efficacy endpoint was the assessment of $uLTE_4$ levels at 4 weeks, to test the null hypothesis that patients receiving AZD5718 200 mg would have <80% reduction of $uLTE_4$ levels compared with those given placebo. The key secondary endpoints were change in $uLTE_4$ at 12 weeks and change in coronary microvascular function, assessed by Doppler echocardiographic CFVR, during adenosine stress test at 4 and 12 weeks. Additional details are provided in the Supplementary Material section.

2.4. Statistical analyses

The study was powered to compare AZD5718 200 mg with placebo for the primary and three key secondary endpoints of $uLTE_4$ and CFVR. A sample size of 33 evaluable patients per group was determined to provide >99% power to detect an 80% decrease in $uLTE_4$ levels and 80% power to detect a 20% increase in CFVR in the AZD5718 200 mg group versus the placebo group (both one-sided $\alpha = 0.05$). A mixed model repeated measures analysis was used to test the changes from baseline in $uLTE_4$ levels and CFVR in AZD5718 groups versus placebo, with treatment, visit and treatment–visit interaction as fixed factors and type of myocardial infarction and baseline LTE_4 or CFVR values as covariates.

A hierarchical testing procedure was pre-specified to preserve the overall false positive rate at 0.05 or below for multiple comparisons of AZD5718 200 mg with placebo for the primary and key secondary endpoints. [22] Endpoints were tested in sequence: change in $uLTE_4$ levels at week 4; change in $uLTE_4$ at week 12; change in CFVR at 12 weeks; and change in CFVR at 4 weeks, until non-significance was reached ($p > 0.05$) and subsequent comparisons would be declared non-significant. Comparisons of AZD5718 50 mg with placebo were performed in parallel, but no adjustment for multiplicity was planned; therefore, p values are nominal.

For log-normally distributed endpoints (primary and key secondary endpoints) geometric means are presented. For normally distributed endpoints (other secondary and exploratory endpoints), means are presented. For log-normal variables, statistical analyses were performed on log-transformed data. The results were back transformed to original

scale for presentation, thus yielding geometric means and ratios in original scale for means and difference of means.

2.5. Study oversight

FLAVOUR was conducted at nine sites in Denmark, Finland and Sweden in accordance with the principles of the Declaration of Helsinki, the International Conference for Harmonisation on Good Clinical Practice, and all applicable ethical and regulatory requirements. All patients provided written informed consent before participating and could withdraw their consent at any time.

3. Results

3.1. Patients

The first patient was enrolled on 30 October 2017; study follow-up was completed on 8 April 2020. Overall, 129 patients were randomized to either the 4-week ($n = 38$) or the 12-week ($n = 91$) cohort to receive AZD5718 200 mg ($n = 52$), AZD5718 50 mg ($n = 25$) or placebo ($n = 52$); 128 patients received treatment (Table 1) and 121 patients completed treatment (AZD5718 200 mg, $n = 48$; AZD5718 50 mg, $n = 23$; placebo, $n = 50$). Baseline demographics and disease characteristics were well balanced across the treatment groups, with the exception that no female patients were randomized to the AZD5718 50 mg group (Table 1). The median age of the participants was 62.4 years, 86.7% were men and 99.2% were white. Most participants (97.7%) had undergone PCI, 47.7% had a history of hypertension and 45.3% had a history of dyslipidaemia. Baseline cardiovascular biomarker characteristics were comparable across treatment groups, except for a lower mean value for high-sensitivity C-reactive protein in the AZD5718 50 mg group. Overall, 54.7% of patients had experienced STEMI. All patients received statins and antiplatelet therapy, 63.3% received beta-blocking agents, and 51.6% received angiotensin-converting enzyme inhibitors (Table 1).

3.2. Efficacy

At 4 and 12 weeks, creatinine-adjusted $uLTE_4$ levels decreased from baseline in the AZD5718 200 mg and AZD5718 50 mg treatment groups, resulting in >80% inhibition of $uLTE_4$ compared with placebo (Table 2, Supplementary Table S1 and Fig. 1A). Significant differences in the ratio of least-squares (LS) mean change from endpoint to baseline versus placebo were observed (all $p < 0.001$; Fig. 1B). Plasma LTE_4 levels showed a similar decrease from baseline in the AZD5718 200 mg and AZD5718 50 mg treatment groups, but not in the placebo group (Fig. 1A and Supplementary Table S2).

No statistically significant changes in CFVR were observed in the AZD5718 200 mg or AZD5718 50 mg groups versus the placebo group at 4 or 12 weeks (Table 2, Supplementary Table S1 and Fig. S2). There were also no differences in several echocardiographic parameters between the AZD5718 200 mg or 50 mg and placebo groups at 4 or 12 weeks (Table 2 and Supplementary Table S1).

For resting LAD diastolic flow and left ventricular (LV)-global circumferential strain (GCS) at rest, there were nominally significant LS mean increases with AZD5718 200 mg compared with placebo at 12 and 4 weeks, respectively (Supplementary Table S1).

A post hoc subgroup analysis compared the efficacy of AZD5718 in patients who had low CFVR (<2.5) with those who had normal CFVR (≥2.5) at baseline (Supplementary Fig. S3A). [23] Patients with low CFVR at baseline demonstrated a non-significant, positive trend towards LVEF and LV-GLS improvement after 12 weeks of treatment with AZD5718 (Supplementary Fig. S3B and Table S3).

Table 1
Baseline characteristics.

	AZD5718 200 mg ($n = 52$)	AZD5718 50 mg ($n = 25$)	Placebo ($n = 51$)	Overall ($N = 128$)
Treatment duration cohort				
4 weeks, *n*	18	6	13	37
12 weeks, *n*	34	19	38	91
Age, years – median (range)	64.1 (41–76)	60.6 (47–75)	60.9 (37–76)	62.4 (37–76)
Sex, male, *n* (%)	45 (86.5)	25 (100)	41 (80.4)	111 (86.7)
Ethnicity, *n* (%)				
White	52 (100)	25 (100)	50 (98.0)	127 (99.2)
Black or African American	0 (0)	0 (0)	1 (2.0)	1 (0.8)
Body mass index, kg/m^2, *n* (%)				
Normal (<25)	16 (30.8)	2 (8.0)	14 (27.5)	32 (25.0)
Overweight (≥25 to ≤30)	26 (50.0)	14 (56.0)	23 (45.1)	63 (49.2)
Obese (>30)	10 (19.2)	9 (36.0)	14 (27.5)	33 (25.8)
Medical and surgical history,[a] *n* (%)				
PCI	50 (96.2)	25 (100)	50 (98.0)	125 (97.7)
Hypertension	25 (48.1)	12 (48.0)	24 (47.1)	61 (47.7)
Dyslipidaemia	28 (53.8)	7 (28.0)	23 (45.1)	58 (45.3)
Cardiac disorders	13 (25.0)	4 (16.0)	7 (13.7)	24 (18.8)
Type 2 diabetes mellitus	4 (7.7)	4 (16.0)	7 (13.7)	15 (11.7)
Neoplasm malignant	4 (7.7)	0	3 (5.9)	7 (5.5)
Nervous system disorders	1 (1.9)	2 (8.0)	3 (5.9)	6 (4.7)
Baseline cardiovascular biomarkers				
Cholesterol, mmol/L, *n*	50	23	50	–
Mean (SD)	3.20 (0.70)	3.23 (0.57)	3.37 (0.71)	–
LDL-C, mmol/L, *n*	50	23	50	–
Mean (SD)	1.70 (0.53)	1.73 (0.49)	1.84 (0.67)	–
HDL-C, mmol/L, *n*	50	23	50	–
Mean (SD)	1.16 (0.33)	1.11 (0.35)	1.18 (0.36)	–
Triglycerides, mmol/L, *n*	52	24	50	–
Mean (SD)	1.07 (0.51)	1.09 (0.30)	1.09 (0.48)	–
hs-Troponin I, ng/mL, *n*	24	14	26	–
Mean (SD)	0.37 (1.55)	0.49 (1.70)	0.51 (2.10)	–
hs-CRP, mg/dL, *n*	48	25	50	–
Mean (SD)	0.79 (1.90)	0.21 (0.29)	0.79 (2.14)	–
NT-proBNP, pmol/L, *n*	47	23	49	–
Mean (SD)	63.47 (74.45)	45.53 (48.98)	54.01 (45.92)	–
Lipoprotein A, mg/L, *n*	39	19	38	–
Mean (SD)	348.51 (372.71)	331.47 (406.87)	323.13 (398.64)	–
Apolipoprotein A-I, g/L, *n*	51	23	47	–
Mean (SD)	1.29 (0.29)	1.31 (0.23)	1.32 (0.27)	–
Apolipoprotein B, g/L, *n*	41	23	41	–
Mean (SD)	0.68 (0.18)	0.68 (0.15)	0.70 (0.18)	–
Type of MI, *n* (%)				

(*continued on next page*)

Table 1 (*continued*)

	AZD5718 200 mg	AZD5718 50 mg	Placebo	Overall
	(*n* = 52)	(*n* = 25)	(*n* = 51)	(*N* = 128)
STEMI	29 (55.8)	14 (56.0)	27 (52.9)	70 (54.7)
Non-STEMI	23 (44.2)	11 (44.0)	24 (47.1)	58 (45.3)
Concomitant medication,[b] *n* (%)				
Statins	52 (100)	25 (100)	51 (100)	128 (100)
Platelet aggregation inhibitors	52 (100)	25 (100)	51 (100)	128 (100)
Beta-blocking agents	34 (65.4)	15 (60.0)	32 (62.7)	81 (63.3)
ACE inhibitors	24 (46.2)	15 (60.0)	27 (52.9)	66 (51.6)
Organic nitrates	16 (30.8)	9 (36.0)	23 (45.1)	48 (37.5)
Proton pump inhibitors	15 (28.8)	5 (20.0)	13 (25.5)	33 (25.8)
Angiotensin II receptor blockers	14 (26.9)	3 (12.0)	15 (29.4)	32 (25.0)
Dihydropyridine derivatives	8 (15.4)	3 (12.0)	12 (23.5)	23 (18.0)

ACE, angiotensin-converting enzyme; CRP, C-reactive protein; HDL—C, high-density lipoprotein cholesterol; hs, high-sensitivity; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

[a] Occurring in ≥4% of patients. Events were coded using the Medical Dictionary for Regulatory Activities Version 22.1.

[b] Reported by >20% of patients in any treatment group; coded using WHO-Drug 09 2019.

3.3. Exploratory outcomes

Patient-reported outcomes assessed using the 36-item Short-Form Health Survey (SF-36) version 2 showed a dose-independent increase in the physical component summary and physical functioning component in patients treated with AZD5718 compared with those given placebo at week 4 (Supplementary Table S4). At week 12, an improvement in general health, role limitations because of physical health problems and vitality components were observed for AZD5718 compared with placebo. A significant difference in LS means was observed for AZD5718 50 mg for the physical component summary, but not for AZD5178 200 mg (Supplementary Table S4).

3.4. Safety and tolerability

The mean (standard deviation [SD]) duration of exposure in the 4-week cohort for the AZD5718 200 mg, AZD5718 50 mg and placebo groups was 28.8 (1.04), 26.2 (9.47) and 29.2 (1.21) days, respectively. Mean duration of exposure in the 12-week cohort was 75.4 (24.68), 81.5 (10.89) and 83.6 (9.44) days, respectively.

3.4.1. Adverse events

The highest incidence of AEs occurred in the AZD5718 200 mg group in the 4-week and 12-week cohorts (Table 3). Treatment-emergent AEs occurring in >3% of participants are shown in Supplementary Table S5. The rates of treatment-related AEs were low, and treatment-related AEs in the AZD5718 groups were reported for one patient each (Table 3). In the 12-week cohort, one patient each from the AZD5718 200 mg and 50 mg groups discontinued treatment because of a treatment-related AE (diarrhoea and headache, respectively). Serious AEs occurred in seven patients receiving AZD5718 and four patients receiving placebo (Table 3). No serious AEs were treatment-related and there were no deaths.

4. Discussion

FLAVOUR is the first study to assess the effect of AZD5718, a first-in-class FLAP inhibitor, on LTE_4 suppression and CFVR in patients with coronary artery disease and recent myocardial infarction. [22] Treatment with AZD5718 dose-dependently inhibited leukotriene biosynthesis, as evidenced by significant reductions in $uLTE_4$ levels of >80%

Table 2
Primary and secondary endpoint measures at baseline, week 4 and week 12.

	AZD5718 200 mg (*n* = 52)			AZD5718 50 mg (*n* = 25)			Placebo (*n* = 51)		
	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12
Creatinine-normalized $uLTE_4$, pmol/mmol, *n*	52	49	29	25	24	18	51	50	36
Mean (SD)	33.245 (31.130)	1.619 (1.420)	1.415 (0.902)	27.259 (21.272)	3.456 (4.036)	3.466 (2.659)	31.646 (17.556)	35.624 (26.076)	35.656 (24.520)
CFVR, ratio, *n*	43	38	18	19	18	12	45	39	25
Mean (SD)	2.88 (0.91)	3.04 (0.90)	3.14 (0.65)	2.80 (0.83)	3.14 (0.95)	2.95 (0.97)	2.89 (1.06)	3.04 (0.97)	3.55 (1.06)
Resting LAD mean diastolic flow velocity, m/s, *n*	43	38	18	19	18	12	45	39	25
Mean (SD)	0.21 (0.06)	0.20 (0.06)	0.21 (0.05)	0.20 (0.06)	0.19 (0.06)	0.20 (0.05)	0.19 (0.06)	0.19 (0.05)	0.18 (0.05)
LAD hyperaemic flow velocity, m/s, *n*	43	38	18	19	18	12	45	39	25
Mean (SD)	0.57 (0.19)	0.60 (0.19)	0.63 (0.10)	0.54 (0.15)	0.56 (0.17)	0.58 (0.19)	0.54 (0.20)	0.56 (0.18)	0.64 (0.22)
LVEF at rest, %, *n*	50	46	30	24	22	17	48	47	34
Mean (SD)	53.99 (5.79)	53.90 (4.76)	54.55 (4.92)	55.04 (6.38)	57.69 (8.28)	55.79 (5.90)	54.84 (5.77)	54.86 (5.89)	54.63 (6.13)
LV-GLS, %, *n*	49	45	29	23	17	14	47	43	32
Mean (SD)	−16.46 (2.87)	−16.91 (2.54)	−17.27 (2.69)	−17.59 (2.59)	−17.33 (2.96)	−16.99 (2.46)	−17.05 (2.47)	−17.37 (2.70)	−17.47 (3.05)
LV-GLS at hyperaemia, %, *n*	40	36	15	18	13	11	33	30	26
Mean (SD)	−18.10 (3.36)	−19.15 (3.65)	−19.03 (3.34)	−19.55 (4.01)	−19.68 (3.75)	−20.16 (2.47)	−18.00 (2.67)	−18.93 (2.52)	−18.95 (3.43)
LV-GCS at rest, %, *n*	47	42	22	22	16	13	45	37	30
Mean (SD)	−25.33 (5.91)	−25.43 (6.96)	−26.57 (5.10)	−27.70 (7.50)	−26.58 (5.02)	−27.36 (4.96)	−25.97 (7.20)	−28.25 (5.67)	−26.71 (6.24)
LV longitudinal early diastolic strain rate, per second, *n*	49	45	30	23	19	15	48	44	32
Mean (SD)	0.84 (0.29)	0.81 (0.18)	0.83 (0.21)	0.87 (0.21)	0.88 (0.26)	0.79 (0.20)	0.80 (0.22)	0.80 (0.22)	0.79 (0.20)

CVFR, coronary flow velocity reserve; GCS, global circumferential strain; GLS, global longitudinal strain; LAD, left anterior descending; LV, left ventricular; LVEF, LV ejection fraction; SD, standard deviation; $uLTE_4$, urine leukotriene E_4.

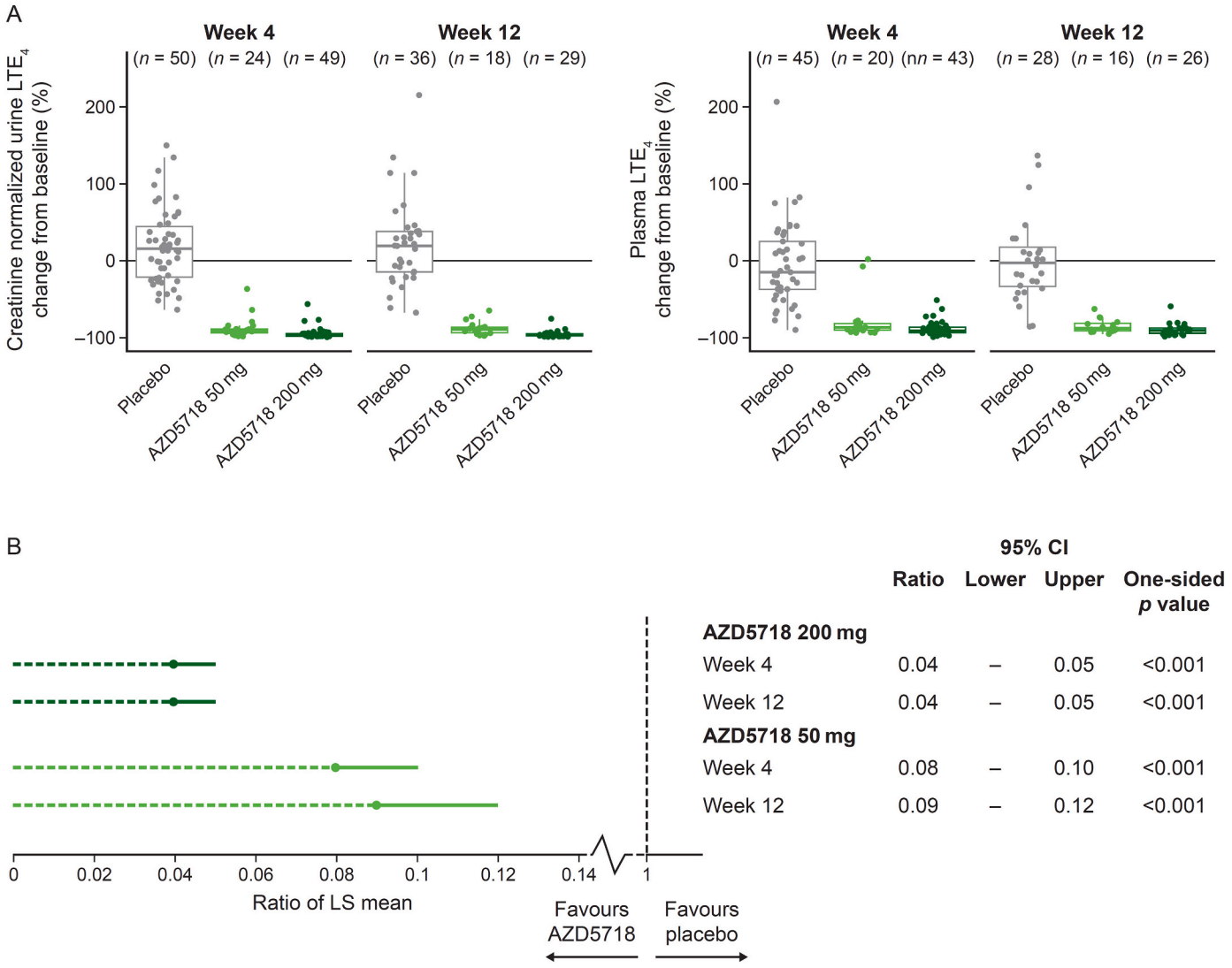

Fig. 1. (A) Change in creatinine-adjusted $uLTE_4$ levels from baseline (left panel), and change in plasma LTE_4 levels from baseline (right panel); (B) placebo-adjusted least-squares mean ratios of endpoint to baseline $uLTE_4$ levels. CI, confidence interval; LS, least-squares; LTE_4, leukotriene E_4; $uLTE_4$, urine LTE_4.

Table 3
Treatment-emergent adverse events.

	4-week cohort			12-week cohort		
Adverse event, *n* (%)	AZD5718 200 mg (*n* = 18)	AZD5718 50 mg (*n* = 6)	Placebo (*n* = 13)	AZD5718 200 mg (*n* = 34)	AZD5718 50 mg (*n* = 19)	Placebo (*n* = 38)
Any	12 (66.7)	3 (50.0)	6 (46.2)	27 (79.4)	14 (73.7)	24 (63.2)
Any drug-related	2 (11.1)	1 (16.7)	0	3 (8.8)	1 (5.3)	5 (13.2)
Serious	1 (5.6)	0	1 (7.7)	3 (8.8)	3 (15.8)	3 (7.9)
Serious drug-related	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0
Leading to interruption	0	0	0	1 (2.9)	0	0
Leading to discontinuation	0	0	0	1 (2.9)	1 (5.3)	0

after 4 and 12 weeks of treatment, compared with placebo, accompanied by a similar sustained reduction in plasma LTE_4 levels. Treatment with AZD5718 was generally well tolerated.

Inhibition of pro-inflammatory and vasoactive leukotrienes is hypothesized to improve microvascular function, minimize the risk of atherosclerotic plaque progression and reduce the risk of cardiovascular events in patients with established cardiovascular disease. There was no significant AZD5718 treatment-related change in echocardiographic CFVR. This was an all-comers study; therefore only a small proportion of patients had an impaired CFVR at baseline (<2.5). The population average at baseline (mean CFVR, 2.87; SD, 0.96) was not grossly impaired and may have reduced the possibility to observe changes during the study.

There were no significant differences in other secondary parameters, including LV longitudinal early diastolic strain rate, LVEF, LV-GLS and LAD hyperaemic flow velocity, in the AZD5718 200 mg or 50 mg groups

compared with the placebo group at either week 4 or 12. Resting LAD mean diastolic flow velocity showed a minor but statistically significant increase after AZD5718 200 mg at 12 weeks compared with placebo. However, the clinical significance and mechanism(s) are unclear. Some patients with higher leukotriene-driven coronary vascular tone and remodelling may respond to AZD5718 with a decrease in coronary vascular resistance and increased flow at rest after 12 weeks, but a longer treatment period may be needed to observe changes in flow under adenosine vasodilator stress conditions. A statistically significant increase in LV-GCS at rest was also observed in the AZD5718 200 mg group at 4 weeks compared with placebo. The clinical significance, however, remains unclear. Importantly, no adjustment for multiple testing was made; therefore, significant differences may be chance findings.

Despite a slightly higher frequency of AEs in the AZD5718 groups compared with placebo, AZD5718 was generally well tolerated, with few serious AEs or AEs leading to discontinuation.

Limitations of the study include first, a limited number of patients, not including women, were enrolled in an all-comers setting, which did not require participants to have high levels of leukotrienes or other inflammatory biomarkers, or impaired CFVR or cardiac function, at baseline. In addition, inclusion required <50% stenosis of the LAD coronary artery and a TIMI flow grade of ≥2. This could have potentially influenced measured responses. Second, the 12-week trial period may have been too short to observe changes in some of the variables measured. Third, the study was not powered to show statistical significance for secondary variables other than CFVR. Finally, the effect of AZD5718 on upstream leukotrienes (A_4, C_4 and D_4) was not assessed in this study because they are rapidly metabolized; however, successful inhibition of the production of LTE_4 indicates that production of these upstream leukotrienes is also inhibited. Robust measurements of plasma LTB_4 levels were also not possible in this study; however, ex vivo inhibition assays have previously demonstrated a potent reduction of LTB_4 synthesis by leukocytes upon treatment with AZD5718. [5]

Ongoing studies will investigate the effect of AZD5718 on coronary plaque volume in patients with ACS (PASSIVATE; NCT04601467) and the dose–response safety, efficacy and pharmacokinetics of AZD5718 in patients with chronic kidney disease (CKD) (FLAIR; NCT04492722). [24]

The FLAVOUR study results demonstrate that AZD5718 provides robust inhibition of leukotriene biosynthesis via the 5-LO pathway, which has been implicated as a key pathological driver in several disease states, including CVD and CKD. AZD5718 was well tolerated in a population with ACS.

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Data availability

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

Declaration of Competing Interest

OA, DE and AA have received speaker fees and/or consultancy fees from AstraZeneca. ELG has received speaker fees and/or consultancy fees from Abbott, Alexion Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Lundbeck Pharma, Merck Sharp & Dohme, Mundipharma, Organon, Pfizer, Portola Pharmaceuticals and Roche, and unrestricted research grants from Boehringer Ingelheim. MH has received speaker fees from Siemens Healthineers AG and GE Healthcare. LOJ has received unrestricted grants to her institution from Biotronik and Biosensors. AS has received speaker fees and/or consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim and Pfizer. AR, JK, ELL, PG, LMG and AG are employees of AstraZeneca; LMG has received research grants from AstraZeneca. EP, SS and JP have nothing to disclose.

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Appendix A. Supplementary data

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