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Design of FLAIR: a Phase 2b Study of the 5-Lipoxygenase Activating Protein Inhibitor AZD5718 in Patients With Proteinuric CKD

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Introduction: Patients with chronic kidney disease (CKD) remain at risk for kidney and cardiovascular events resulting from residual albuminuria, despite available treatments. Leukotrienes are proinflammatory and vasoconstrictive lipid mediators implicated in the etiology of chronic inflammatory diseases. AZD5718 is a potent, selective, and reversible 5-lipoxygenase activating protein (FLAP) inhibitor that suppresses leukotriene production.

Methods: FLAIR (FLAP Inhibition in Renal disease) is an ongoing phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of AZD5718 in patients with proteinuric CKD with or without type 2 diabetes. Participants receive AZD5718 at 3 different doses or placebo once daily for 12 weeks, followed by an 8-week extension in which they also receive dapagliflozin (10 mg/d) as anticipated future standard of care. The planned sample size is 632 participants, providing 91% power to detect 30% reduction in urinary albumin-to-creatinine ratio (UACR) between the maximum dose of AZD5718 and placebo. The dose–response effect of AZD5718 on UACR after the dapagliflozin extension is the primary efficacy objective. Key secondary objectives are the dose–response effect of AZD5718 plus current standard of care on UACR and acute effects of treatment on the estimated glomerular filtration rate. Safety, tolerability, AZD5718 pharmacokinetics, and analyses of biomarkers that may predict or reflect response to AZD5718 are additional objectives.

Conclusion: FLAIR will provide data on the effects of 5-lipoxygenase pathway inhibition in patients with proteinuric CKD with or without type 2 diabetes, and will form the basis for future clinical trials (ClinicalTrials.gov: NCT04492722).

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Chronic kidney disease affects 9% of the global population (700 million people) and is associated with significant morbidity and mortality.[1,2] In 2017, chronic kidney disease (CKD) was the 12th leading cause of death worldwide and accounted for an estimated 1.2 million deaths. Furthermore, an additional 1.4 million deaths per year from cardiovascular disease were attributed to impaired kidney function.[1,2] Diabetes and hypertension are strongly associated with the development of CKD.[1,3] The pathogenesis of CKD is multifactorial, and emerging evidence implicates inflammation in its development.[4,5]

The mainstay of treatment for patients with CKD is inhibition of the renin–angiotensin–aldosterone system through angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

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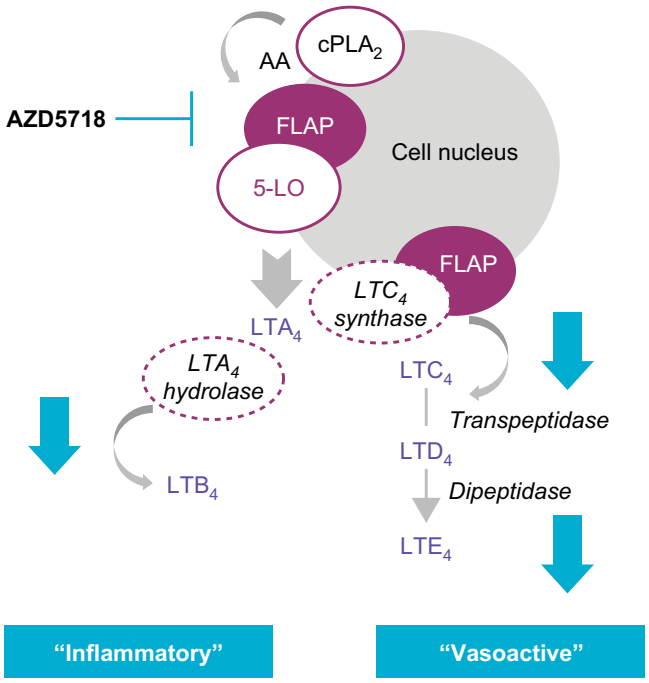


Figure 1. Inhibition of FLAP by AZD5718 blocks the production of leukotriene B_4 and the cysteinyl leukotrienes (leukotriene C_4, leukotriene D_4, and leukotriene E_4). AA, arachidonic acid; $cPLA_2$, cytoplasmic phospholipase A_2; FLAP, 5-lipoxygenase activating protein; 5-LO, 5-lipoxygenase; LTA_4, leukotriene A_4; LTB_4, leukotriene B_4; LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new addition to standard of care for patients with diabetic kidney disease, and are likely to become standard of care for those with nondiabetic CKD.[6] SGLT2 inhibitors have been shown to reduce albuminuria and to slow the progression of CKD in patients with and without type 2 diabetes.[6–9] The Kidney Disease: Improving Global Outcomes (KDIGO) and the American Diabetes Association guidelines now recommend first-line treatment with SGLT2 inhibitors alongside metformin in patients with type 2 diabetes and CKD.[10,11] In patients with nondiabetic CKD, a protective effect of SGLT2 inhibitors has recently been demonstrated in the DAPA-CKD and EMPEROR-Reduced phase 3 trials.[6,12] Despite these recent recommendations and findings, the adoption of SGLT2 inhibitors in patients with diabetic and nondiabetic CKD remains low.[13,14] Furthermore, residual albuminuria in many patients receiving treatment with ACE inhibitors, ARBs and SGLT2 inhibitors suggests incomplete protection from kidney and cardiovascular risk.[15–17] Renin–angiotensin–aldosterone system blockers and SGLT2 inhibitors act primarily via their effects on glomerular hemodynamics. Additional drugs with novel mechanisms of action are therefore needed to slow the progression to kidney failure requiring kidney replacement therapy.

Inflammatory pathways offer pathophysiological targets for the development of new drugs for CKD.[5,18] Previous studies in diabetic kidney disease in particular have demonstrated increasing proinflammatory cytokine levels during disease progression.[4,5,19–22] Leukotrienes are potent proinflammatory and vasoconstrictive lipid mediators involved in the etiology of chronic inflammatory diseases.[23] Leukotrienes B_4, C_4, D_4, and E_4 derive from the precursor leukotriene A_4, which is biosynthesized from arachidonic acid by 5-lipoxygenase in conjunction with 5-lipoxygenase activating protein (FLAP) after an inflammatory stimulus (Figure 1).[24] Several lines of evidence implicate leukotrienes in the pathogenesis of CKD. First, expression of 5-lipoxygenase and FLAP is increased in the tubulointerstitial compartment of patients with CKD, which may be associated with increased inflammation and disease progression.[25,26] Second, leukotrienes B_4, C_4, and D_4 can cause endothelial dysfunction, leading to increased glomerular permeability to albumin; and leukotrienes C_4 and D_4 are vasoconstrictive and may reduce renal perfusion.[27] Third, preliminary evidence indicates that FLAP inhibition may reduce albuminuria and restore glomerular size selectivity in patients with glomerulonephritis.[28] Finally, a randomized controlled trial in 46 children with Henoch–Schonlein nephritis treated with the cysteinyl leukotriene receptor antagonist montelukast for 3 months demonstrated a significant reduction in proteinuria.[29]

AZD5718 is a potent, selective, and reversible FLAP inhibitor that acts at the first step of leukotriene biosynthesis to suppress production of all leukotrienes (Figure 1).[23] In healthy volunteers, AZD5718 was well tolerated at multiple oral doses, and dose-dependently reduced urinary leukotriene E_4 levels and *ex vivo* leukotriene B_4 production in blood.[30,31] The safety and efficacy of AZD5718 has recently been evaluated in FLAVOUR (NCT03317002), a phase 2a study in patients with recent myocardial infarction.[32]

Here, we describe the design of FLAIR (FLAP Inhibition in Renal disease), an ongoing phase 2b study of AZD5718 in patients with proteinuric CKD with or without type 2 diabetes. FLAIR aims to evaluate the effect of AZD5718 in reducing albuminuria as a surrogate for kidney failure.[33] The study will evaluate AZD5718 with both current and anticipated future levels of SGLT2 inhibitor use.

MATERIALS AND METHODS

Overview

FLAIR is a phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy,

safety, and pharmacokinetics of 3 different doses of AZD5718 in participants with proteinuric CKD with or without type 2 diabetes. Participants receive AZD5718 or placebo for 12 weeks in addition to their usual treatments, followed by an 8-week extension in which all participants also receive the SGLT2 inhibitor dapagliflozin. Patients who are already taking an SGLT2 inhibitor switch to dapagliflozin for the 8-week extension. The primary endpoint is the combined effect of AZD5718 and dapagliflozin on urinary albumin-to-creatinine ratio (UACR) after 20 weeks compared with placebo.

Ethics and Conduct

The study started in October 2020 and is recruiting patients at approximately 120 sites in 11 countries. FLAIR is registered on ClinicalTrials.gov (NCT04492722) and EudraCT (2020-002263-54), and is being conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonisation Good Clinical Practice, and all applicable regulatory requirements. Local ethics committees reviewed and approved the study protocol, and participants give their written informed consent before study enrollment.

Objectives

The primary objective is to evaluate the dose–response effect of AZD5718 plus dapagliflozin (anticipated future standard of care) on UACR in participants with CKD and increased albuminuria. The key secondary objective is to assess the dose–response effect of AZD5718 plus current standard of care on UACR. Other secondary objectives include assessing the safety, tolerability, and pharmacokinetics of AZD5718 (Table 1). Exploratory objectives include assessing the dose–response effect of AZD5718 on biomarkers of the 5-lipoxygenase pathway, and assessing additional biomarkers that may show response to or predict the response to treatment with AZD5718 (Table 1).

Participants

Eligible patients are men and women 18 years of age or older with a body mass index of 18–45 kg/m^2 and albuminuric CKD (estimated glomerular filtration rate [eGFR] of 20–75 ml/min per 1.73 m^2 and albuminuria of 200–5000 mg albumin/g creatinine). Although there is risk of renal events in individuals with lower levels of albuminuria, this was the range included in the DAPA-CKD study, which provides the only currently published data in support of efficacy of SGLT2 inhibitors in patients with nondiabetic CKD.[6] Patients must have stable, reasonably controlled blood pressure and must be on stable doses of ACE inhibitors and/or ARBs for at least 4 weeks before randomization (if able to tolerate these medications). Patients already receiving SGLT2 inhibitors or glucagon-like peptide 1 receptor agonists must be on a stable dose for at least 4 weeks before randomization. Approximately one-third of participants will have nondiabetic kidney disease, and two-thirds will have diabetic kidney disease (confirmed diagnosis of type 2 diabetes mellitus without specified hemoglobin A1c thresholds for inclusion or exclusion). There is no requirement for histological diagnosis confirmation by renal biopsy. At least 72 participants will be enrolled in Japan to meet Japanese regulatory requirements for the number of Japanese participants. Men must be surgically sterile or using highly effective contraceptives, and women must be unable to have children (surgically sterile or postmenopausal). Key exclusion criteria are listed in Table 2.

Table 1. Study objectives

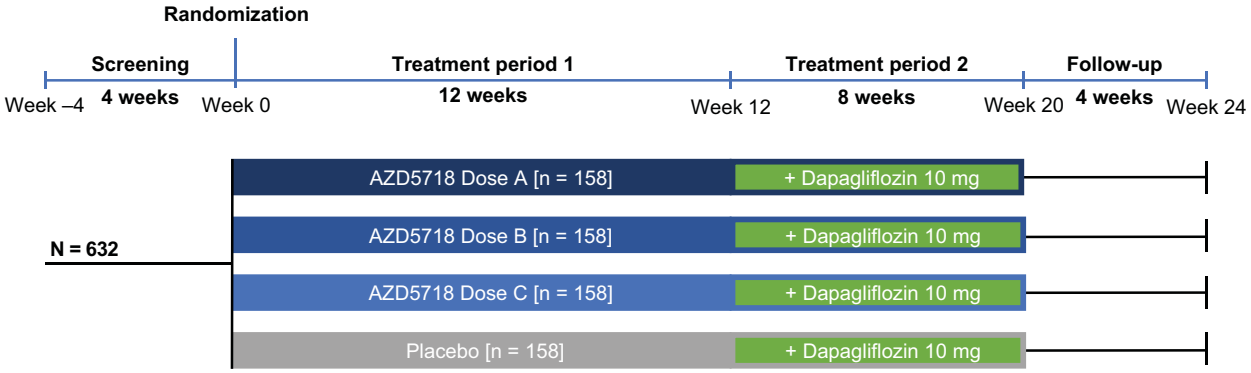
Objective	Assessment
Primary	Dose–response effect of AZD5718 on urinary albumin-to-creatinine ratio from baseline to 20 weeks (on treatment with dapagliflozin as future standard of care)
Secondary	Dose–response effect of AZD5718 on urinary albumin-to-creatinine ratio at 12 weeks (on current standard of care) Safety and tolerability of AZD5718 Effect of AZD5718 on ambulatory blood pressure Pharmacokinetics of AZD5718 Effect of AZD5718 on kidney function with and without dapagliflozin
Exploratory	Dose–response effect of AZD5718 on urinary and plasma leukotriene E_4 levels Sample collection for investigation of biomarkers that respond to treatment with AZD5718 Sample collection at baseline for investigation of biomarkers that may predict response to treatment with AZD5718 Effect of AZD5718 on diabetic retinopathy in patients with diabetic kidney disease Pharmacokinetics of dapagliflozin after 8 weeks

Randomization and Blinding

Enrolled participants are randomized 1:1:1:1 to receive oral AZD5718 at 3 different doses or matching placebo

Table 2. Key exclusion criteria

Hepatitis B or C
Polycystic kidney disease or anatomical causes of chronic kidney disease
Type 1 diabetes mellitus
Severe hepatic impairment (Child–Pugh class C)
Severe comorbidities or history of disease or disorder that would put patient at risk, affect participation, or influence study results
Confirmed COVID-19 in the past 4 weeks or severe COVID-19 at any point
Ongoing use of any biologic drug and/or small molecule targeting the immune system
Use of drugs that affect serum creatinine concentration in the past month
Concomitant use of medications associated with torsades de pointes or strong inducers/inhibitors of cytochrome P450 3A4
Treatment with zileuton, leukotriene receptor antagonists (e.g., montelukast) or cilastatin in the past month
Treatment with simvastatin, lovastatin, or atorvastatin at doses more than 40 mg per day in the past month
Hypersensitivity to drugs with a chemical structure or class similar to that of AZD5718
Pregnancy or breastfeeding



Visit number	1	2	3	4	5	6	7	8	9	10
Week	–4 to 0		0	2	4	8	12	16	20	24
UACR	X	X	X	X	X	X	X	X	X	X
eGFR	X		X	X	X	X	X	X	X	X
Cystatin-C	X		X	X	X	X	X	X	X	X
Pharmacokinetics (AZD5718)				X	X[a]	X	X	X	X	
Safety	X[b]	X[b]	X	X	X	X	X	X	X	X
Biomarkers		X	X		X		X		X	
Urine and plasma leukotriene E_4			X		X		X	X	X	
Ambulatory blood pressure monitoring[c]		X				X				

Figure 2. Study design and assessments. [a]Four postdose (1–2, 2–5, 5–8, and 8–12 hours) samples will be collected for a subgroup of at least 80 participants. Each sample will be separated by at least 1 hour. [b]Serious adverse events only. [c]An ambulatory blood pressure monitoring cuff will be provided to participants at the indicated study visits to provide a 24-hour reading before the next study visit. eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

tablets once daily for 12 weeks, followed by the same treatment plus dapagliflozin 10 mg/d for 8 weeks (Figure 2). Randomization is stratified by participants with and without type 2 diabetes, pre-existing SGLT2 inhibitor use (for participants with type 2 diabetes), and whether participants are from Japan. Randomization is performed by Parexel Informatics using the sponsor's (AstraZeneca) algorithm. Participants and the study team are blinded to treatment assignments throughout the study. Investigators remain blinded unless they need to know a participant's assigned treatment in a medical emergency.

AZD5718 Dose Selection

AZD5718 doses were selected based on a previous clinical study that measured inhibition of leukotriene B_4 and E_4 biosynthesis and subsequent *post hoc* analyses (NCT02632526 and NCT02963116, respectively).[30,31]

Procedures

Potentially eligible participants are screened up to 4 weeks before randomization. Participants attend up to 10 study visits, including 2 during screening, 5 during weeks 1 to 12, 2 during weeks 13 to 20, and 1 during the 4-week follow-up period (Figure 2). At week 12, any participant with complete resolution of albuminuria (<30 mg/g) will be excluded from the second treatment period. The remaining participants receive dapagliflozin 10 mg/d during weeks 13 to 20 in addition to their randomly assigned dose of AZD5718 or placebo. Participants who were receiving SGLT2 inhibitors before randomization continue on their usual SGLT2 inhibitor and dose during weeks 1 to 12, then switch to dapagliflozin 10 mg during weeks 13 to 20. All participants receive the same SGLT2 inhibitor and dose during weeks 13 to 20 (dapagliflozin 10 mg/d) to minimize potential variation due to differences in drug efficacy or dose. Furthermore, dapagliflozin is currently the only SGLT2 inhibitor licensed for patients with nondiabetic CKD. Participants take oral tablets of AZD5718 or placebo (weeks 1–20) and dapagliflozin (weeks 13–20) every morning with water before or after food. Participants' adherence to the regimen is monitored using an e-Diary application or a paper dosing diary.

Efficacy Outcomes

Urinary Albumin-to-Creatinine Ratio

Change in UACR (UACR [mg/g] = urine albumin [mg/dl]/urine creatinine [g/dl]) after 20 weeks is the primary

efficacy outcome. To reduce variability in measurements, participants collect first morning urine samples for 3 consecutive days before each study visit (with the exception of the first visit). The geometric mean UACR will be calculated from the triplicate UACRs and will be used for all analyses. All analyses are conducted at a central laboratory (Covance).

Estimated Glomerular Filtration Rate

The eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[34,35] Serum cystatin-C measurements will also be collected as an exploratory biomarker for eGFR.

Safety Outcomes

Safety is assessed throughout the study (Figure 2). Safety assessments include monitoring of adverse events and serious adverse events, physical examinations, monitoring of vital signs (blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry), electrocardiography and clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis). All adverse events are followed up by the investigator until resolved or for as long as medically indicated. Investigators assess whether adverse events are causally related to the investigational medical product, and also whether serious adverse events are causally related to other medications and study procedures.

Other Secondary and Exploratory Outcomes

Pharmacokinetics and Pharmacodynamics

Pre-dose plasma samples are collected throughout the study to assess AZD5718 and dapagliflozin concentrations (Figure 2). A subgroup of at least 80 participants (n = 20 per treatment arm) will also provide 4 post-dose samples 1 to 2, 2 to 5, 5 to 8, and 8 to 12 hours after receiving AZD5718 at the week 4 study visit. Inhibition of the 5-lipoxygenase pathway will be assessed by measuring leukotriene E_4 concentrations in urine and plasma (Figure 2). In urine, leukotriene E_4 concentrations will be expressed relative to creatinine concentrations.

Ambulatory Blood Pressure Monitoring

The US Food and Drug Administration (FDA) recommends that ambulatory blood pressure monitoring be used to assess the sustained effects on blood pressure of drugs intended for chronic use.[36] Participants are given an ambulatory blood pressure monitoring cuff during screening and at week 8 to provide 24-hour readings at week 0 and week 12 (Figure 2). The analysis will assess the change in 24-hour mean systolic blood pressure from baseline to week 12, using a noninferiority margin of 3 mm Hg based on the results of PRECISION-ABPM.[37] Assuming a between-group difference of 0 mm Hg and a standard deviation of 10 mm Hg, and using a 2-sample, 1-sided *t*-test with 5% type I error, a sample size of 139 evaluable participants per group is estimated to provide 80% power.

Retinal Substudy

The retinal substudy comprises an optional exploratory efficacy assessment in participants with diabetic kidney disease at baseline and at 12 weeks. The effect of AZD5718 on the integrity of retinal blood vessels is assessed at participating sites with access to Early Treatment Diabetic Retinopathy Study (ETDRS) charts to test visual acuity, and optical coherence tomography facilities to measure central subfield thickness.

Biomarker Analysis

Plasma, serum, and urine samples are collected for the analysis of biomarkers that may show response to or predict the response to treatment with AZD5718 (Figure 2). Biomarkers assessed include high-sensitivity C-reactive protein, interleukin-6, and PRO-C6.

Statistical Methods

Sample Size Calculation

The target sample size is 632 participants (158 per group). Assuming a discontinuation rate of approximately 10%, a sample of 142 participants per group provides 91% power to detect a 30% reduction in UACR from baseline between the AZD5718 maximum dose and placebo groups (2-sided $\alpha = 0.1$). This also provides at least 80% power to detect a reduction in UACR across AZD5718 doses in the stratum of participants with diabetic kidney disease.

Current Status

As of March 2021, we have enrolled and randomized 24 participants. The first patient was enrolled in October 2020, and the first dose was taken in December 2020. We expect to enroll the last patient in mid 2022 and to complete the last follow-up visit in late 2022.

DISCUSSION

Leukotrienes are important proinflammatory mediators.[23] 5-Lipoxygenase is a key enzyme involved in the synthesis of leukotrienes and has been associated with kidney disease.[24–26] However, although there are 2 small published clinical studies that provide preliminary data for the efficacy of either cysteinyl leukotriene or FLAP inhibition in reducing albuminuria/proteinuria in patients with kidney disease, there was no further development of these drugs for a renal indication.[28,29] FLAIR is the first phase 2 clinical trial of a FLAP inhibitor in adults with CKD. Existing treatments provide incomplete protection against the

development and progression of CKD and do not primarily target inflammation, a key element of the etiology. By suppressing the biosynthesis of leukotrienes, AZD5718 has the potential to improve outcomes in patients with CKD via a novel anti-inflammatory mechanism of action.

Most previous studies of drugs that may slow the progression of CKD have exclusively enrolled patients with diabetic kidney disease,[38–40] despite evidence for common mechanisms underlying CKD progression irrespective of diabetes. A key strength of the present study, therefore, is that patients with CKD with and without type 2 diabetes are eligible to participate.

Clear evidence for the efficacy of SGLT2 inhibitors in patients with diabetic kidney disease was available when the present study was designed, but data from ongoing studies in patients with nondiabetic CKD were awaited.[6,12] We therefore designed FLAIR to assess the safety and efficacy of AZD5718 as an add-on both to current standard of care with minimal SGLT2 inhibitor use and to anticipated future standard of care with universal SGLT2 inhibitor use, in separate treatment periods. Enrolling only participants receiving SGLT2 inhibitors would not have enabled the evaluation of AZD5718 as an alternative add-on therapy in patients receiving current standard of care with antihypertensives. The primary objective of the study is to test the hypothesis that treatment with AZD5718 will have an additive effect on albuminuria when given in combination with SGLT2 inhibitors. Alternative possibilities include an equivalent but non-additive effect, potentially in different responder populations, or antagonism of the albuminuria reduction seen with SGLT2 inhibitors. The secondary study outcomes are designed to address these possibilities.

A key consideration in the study design was the minimum duration for efficacy assessment on albuminuria. A meta-analysis presented at the National Kidney Foundation–FDA–European Medicines Agency workshop has become the benchmark for the design of phase 2 trials in CKD; the study found that a 30% reduction in UACR after 6 months predicts hard renal endpoints in phase 3 trials.[41] We reviewed the subset of trials included in the meta-analysis with 3-month data. In all studies reporting significantly reduced albuminuria at 6 months, reductions were also detected at 3 months when data were available across the full spectrum of etiology and drug mechanism of action.[41] Based on these data, 12 weeks was selected as the duration for the first treatment period (AZD5718 alone). This duration is in accordance with other phase 2 dose-finding studies with albuminuria-lowering drugs.[42] The effect of dapagliflozin on albuminuria reaches a maximum by 4 weeks of treatment,[43] so a duration of 8 weeks was selected for the second treatment period (AZD5718 plus dapagliflozin).

Experimental data in rats indicate a decrease in renal blood flow and glomerular filtration rate (GFR) upon administration of leukotriene C_4 that was blocked by a leukotriene antagonist.[44] Although it is conceivable that an increase in renal blood flow may be a consequence of FLAP inhibition in patients with CKD, there was no change in measured renal plasma flow or GFR in a small short-term study of 5-lipoxygenase inhibition in patients with glomerulonephritis.[28] Given the uncertainty of the effect of FLAP inhibition on GFR in patients with CKD, assessing potential acute changes in eGFR with AZD5718 treatment in FLAIR will help to inform the design of phase 3 trials using eGFR slope as a surrogate endpoint for kidney disease progression.[45] We have elected to use the creatinine-based CKD-EPI equation for this analysis as the most widely used equation for estimating GFR, but will undertake an exploratory analysis using the combined creatinine/cystatin C equation.[46]

Assessing different dose levels of AZD5718 can enable analysis of the correlation between 5-lipoxygenase pathway suppression and changes in albuminuria. Exploratory biomarker analysis may reveal subgroups that respond better to treatment with AZD5718. Biomarkers that predict treatment response could guide the future development of a precision medicine strategy for AZD5718.

In line with FDA recommendations, FLAIR will also assess the effect of AZD5718 on blood pressure using ambulatory monitoring to ensure that there is not a potentially harmful hypertensive effect.[47] The study is well powered to detect a difference of 3 mm Hg between the AZD5718 and placebo groups in the first treatment period. Assessment of temporal changes in blood pressure, and therefore the risk of major adverse cardiovascular events, will support future development, including AZD5718 dose selection and identification of patients at potential risk for increased blood pressure.[47]

The exploratory diabetic retinopathy substudy will examine the potential for microvascular benefit outside the kidney using simple objective measurements. If the substudy yields positive results, retinopathy assessment could be an important secondary efficacy endpoint in a phase 3 trial of AZD5718.

In conclusion, FLAIR will provide data on potentially clinically meaningful effects of FLAP inhibition with AZD5718 in patients with albuminuric CKD with or without type 2 diabetes, and the results will form the basis for future clinical trials.

DISCLOSURE

HJLH reports consulting for Abbvie, AstraZeneca, Boehringer Ingelheim, Chinook, CSL Pharma, Dimerix, Fresenius, Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novo Nordisk, and Travere Therapeutics and has a policy of honoraria going to his employer. He has also received grant support from Boehringer Ingelheim, AstraZeneca, and Janssen (funding to his employer). GL, KP, KC, CW, HE, JK, E-LL and IM are employees of AstraZeneca and may own stock or stock options.

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