Clinical Study Report Synopsis	
Drug Substance	Atuliflapon (AZD5718)
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A Phase IIb Randomised, Double-Blind, Placebo-Controlled, Multi Centre, Dose-Ranging Study of AZD5718 in Participants with Proteinuric Chronic Kidney Disease

Study dates:
First participant enrolled: 01 October 2020
Last participant last visit: 06 September 2022
Date of early study termination: 01 July 2022 due to lack of efficacy.
The analyses presented in this report are based on a clinical data lock date of 30 November 2022.

Phase of development: Therapeutic exploratory (IIb)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted in 116 study centres across 11 countries.

Publications

There were no publications reporting study results at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To evaluate the dose-response effect of AZD5718 on urine ACR at 20 weeks in participants with proteinuric CKD (on treatment with dapagliflozin as future standard of care from Weeks 12 to 20).	• Reduction of urine ACR from baseline to Week 20 compared with placebo. The primary estimand was a hypothetical estimand such that the treatment effect was quantified in the optimal situation where any potential confounder was avoided. The population of interest was the Per-Protocol population. The endpoint being assessed was the change in log-transformed urine ACR from baseline to Week 20. For the intercurrent event, if a participant discontinued treatment due to AE or lack of efficacy, or used prohibited medication, the urine ACR data were treated as missing after the event and no imputation was performed. The summary measure being evaluated was the geometric mean reduction of urine ACR from baseline to Week 20.
Secondary	
• To evaluate the dose-response effect of AZD5718 on urine ACR at 12 weeks (on current standard of care).	• Reduction of urine ACR from baseline to Week 12 compared with placebo. The clinical quantity of interest to be estimated was defined by the following 3 components: – Population Randomised participants who met all eligibility criteria and had valid non-missing urine ACR records at baseline and at least one post-treatment visit. – Endpoint Change in log-transformed urine ACR from baseline to Week 12. – Summary measure Geometric mean reduction of urine ACR from baseline to Week 12 compared with placebo.

Objectives	Estimand description/Endpoints
• To evaluate the safety and tolerability of AZD5718 in participants with proteinuric CKD	• AEs/SAEs. • Vital signs. • Clinical chemistry/haematology/coagulation/urinalysis parameters. • ECG assessments.
• To evaluate the effect of AZD5718 on Ambulatory Blood Pressure in participants with proteinuric CKD.	• Change in 24-hour mean SBP from baseline to Week 12.
• To assess the PK of AZD5718 after repeated oral dosing for 20 weeks in participants with proteinuric CKD.	• AZD5718 plasma concentrations (Note: following study termination and reduced scope of the analysis, the PK analysis has not been performed).
• To assess the effect of AZD5718 on renal function in participants with proteinuric CKD with and without the addition of dapagliflozin.	• Change in eGFR from baseline to Week 12 and from Week 12 to Week 20.

Abbreviations: ACR = albumin to creatinine ratio; AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; PK = pharmacokinetics; SAE = serious adverse event; SBP = systolic blood pressure.

Study design

This was a Phase IIb, randomised, double-blind, placebo-controlled, multi-centre, dose ranging study to evaluate the efficacy, safety, and pharmacokinetics (PK) of Atuliflapon (AZD5718) in participants with proteinuric chronic kidney disease (CKD). Furthermore, the additive effect of the sodium-glucose linked transporter-2 inhibitor (SGLT2i) dapagliflozin taken together with AZD5718 on albuminuria was assessed in an 8-week extension period where participants were treated with AZD5718 or placebo and dapagliflozin.

The study included 4 treatment groups: CCI mg AZD5718, CCI mg AZD5718, CCI mg AZD5718, or placebo for the first 12 weeks followed by the addition of dapagliflozin for all participants for 8 weeks. The study planned to include up to approximately 632 participants comprising 67% diabetic kidney disease (DKD) and 33% non-DKD participants to be randomised 1:1:1:1, to have 158 participants per treatment group. The plan was to have approximately 568 evaluable participants (142 per group) completing the study.

All participants were centrally randomised using Interactive Response Technology. Block randomisation was used to randomise participants in a 1:1:1:1 ratio to the 4 treatment groups. Randomisation was stratified by participants with and without diabetes mellitus (DM) at the time of randomisation in order to ensure approximate balance between treatment groups within each sub-population.

Following the results of an administrative interim analysis, the Sponsor decided to terminate the study early due to lack of efficacy. There were no safety concerns related to the study.

Target subject population and sample size

The study enrolled participants ≥ 18 years of age with proteinuric CKD defined as follows: estimated glomerular filtration rate (eGFR) 20 to 75 mL/min/1.73m^2 based on CDK epidemiology collaboration (CKD-EPI) equation at Screening Visit 1 and albuminuria defined as 200 to 5000 mg albumin/g creatinine based on the geometric mean of the replicated measurements using 3 sequential first morning void urine at Visit 2, and with diagnosis of Type 2 DM (for DKD sub-group only).

For the primary endpoint, a total of 142 evaluable participants per group was considered appropriate to provide CCI power to detect a placebo-adjusted CCI reduction in urine albumin to creatinine ratio (UACR) from baseline between AZD5718 CCI mg and placebo group with CCI, assuming a standard deviation (SD) of CCI on the natural log-scale. It was also considered appropriate to assure at least CCI power to detect the same UACR reduction and the significance of dose-response over multiple dose-response models in the DKD sub-population. To account for approximately CCI discontinuation, it was planned to enrol 158 participants per group. However, due to the early termination of the study, the total number of randomised participants was 613, with 318 participants completing the study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Investigational Products

Investigational Product	Dosage form and Strength	Route of Administration	Manufacturer
AZD5718	CCI mg, CCI mg and CCI mg tablets once daily	Oral	AstraZeneca
Placebo to AZD5718	Not applicable	Oral	AstraZeneca
Dapagliflozin	10 mg tablets once daily	Oral	AstraZeneca

Duration of treatment

The study included 4 periods:

- Screening Period of up to 4 weeks.
- Treatment Period 1 of 12 weeks where the participants received a once daily oral dose of the assigned dose of study drug taken with approximately 200 mL water in the morning with no restrictions on food intake.
- Treatment Period 2 of 8 weeks where the participants received a treatment of once daily oral dose of dapagliflozin 10 mg in addition to the assigned dose of study drug. Only

participants still taking their assigned treatment from Treatment Period 1 progressed to Treatment Period 2. Any participants with UACR < 30 mg/g at Week 12 were excluded from Treatment Period 2. The eligibility check to enter Treatment Period 2 was done at Visit 7 (Week 12) using the last available UACR result, calculated as the geometric mean of the replicated measurements using 3 sequential first morning urine voids.

- Follow-up Period of up to 4 weeks.

The expected total study duration, including the Screening Period, for each participant was at least 28 weeks.

Statistical methods

The primary efficacy endpoint for this study was to assess the dose-response effect of AZD5718 compared with placebo on reduction of UACR from baseline to Week 20 in participants with proteinuric CKD (on treatment with dapagliflozin as future standard of care). As UACR was assumed to follow a log-normal distribution, it was log-transformed for statistical analysis purposes. The mean log changes in UACR at Week 20 (Y1, Y2, Y3, Y4) for each of the 3 AZD5718 doses and placebo was estimated in a mixed model for repeated measures (Weeks 2, 4, 8, 12, 16, and 20). The values were back transformed onto the original scale to give the geometric mean relative change from baseline at Week 20. The analysis model included the fixed categorical effects of stratification factor, treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log (UACR) and baseline log (UACR)-by-visit interaction. An unstructured covariance structure was used for the within-participant errors. A homogeneity assessment between the DM and the non-DM sub-populations was performed. Denominator degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary endpoints were UACR at 12 weeks, eGFR, and Ambulatory Blood Pressure (BP) Monitoring (ABPM). The UACR at 12 weeks was evaluated using the same methods for the primary efficacy endpoint. Estimated GFR was analysed, comparing eGFR at baseline with that at 12 weeks, to determine whether there was any acute change with the introduction of AZD5718 to inform planning for an eGFR slope analysis in Phase III. This was analysed using a by-visit ANCOVA, adjusting for DM stratification factor, treatment group and baseline eGFR. Ambulatory BP was analysed to determine the effect of AZD5718 on BP relative to placebo. This was assessed by the change from baseline in 24-hour mean systolic blood pressure (SBP) at Week 12, analysed using an ANCOVA model, with change from baseline in 24-hour mean SBP as the dependent variable, adjusting for DM stratification factor, treatment group (AZD5718 CCI mg, AZD5718 CCI mg, AZD5718 CCI mg, placebo), plus baseline 24-hour mean SBP and body mass index as covariates.

All participants who were randomised and received any study treatment were included in the Full Analysis Set (FAS). The FAS was used for all analyses of demographic data, baseline

characteristics and efficacy data. The Safety Analysis Set (with participants analysed according to treatment actually received) was used for all safety analyses, unless otherwise specified. The Ambulatory Blood Pressure Monitoring Analysis Set included all participants in the FAS who had valid ambulatory BP data for change from baseline analyses.

Study population

A total of 1254 participants were enrolled. Of the enrolled participants, 613 were randomised to AZD5718 CCI mg (154 participants), AZD5718 CCI mg (153 participants), AZD5718 CCI mg (153 participants), or placebo (153 participants). A total of 608 (99.2%) received at least one dose of study treatment. In total, 438 (72.0%) participants completed Treatment Period 1 and 170 (28.0%) participants discontinued during Treatment Period 1. In total, 318 (52.3%) participants completed Treatment Period 2 and completed the study; 120 (19.7%) participants discontinued treatment in Treatment Period 2.

Summary of efficacy results

The aim of the study was to investigate if AZD5718 could reduce albuminuria in participants with proteinuric CKD both on treatment with dapagliflozin as future standard of care and on current standard of care with minimal SGLT2i use.

Of the 613 participants enrolled, 421 received additional treatment with dapagliflozin post-Week 12 and were included in the Per-Protocol Analysis Set.

At baseline, the geometric mean UACR (min, max, gSD) for the AZD5718 groups was 615.1 mg/g for CCI mg (min = 122.7, max = 4158.3, gSD = 2.14), 744.1 mg/g (min = 191.7, max = 4346.4, gSD = 2.12) for CCI mg, and 708.0 mg/g (min = 121.0, max = 4845.8, gSD = 2.24) for CCI mg compared to734.7 mg/g (min = 193.1, max = 3020.9, gSD = 2.15) for the placebo group.

The primary efficacy endpoint was to assess the dose-response effect of AZD5718 compared with placebo on UACR reduction from baseline to Week 20 in participants with proteinuric CKD (on treatment with dapagliflozin as future standard of care). The percentage change (95% Confidence intervals [CI]; p-value) in UACR reduction from baseline to Week 20 compared to placebo for the AZD5718 groups was: -5.49% (-21.37, 13.60; p-value = 0.5462) for CCI mg, -3.58% (-19.74, 15.82; p-value = 0.6956) for CCI mg, and -8.07% (-23.24, 10.10; p-value = 0.3596) for CCI mg. The percentage change in UACR reduction at Week 20 compared to placebo was not statistically significant in any treatment group. A trend for reduction in the percentage change of UACR was observed in all AZD5718 groups and also in the placebo group between Week 12 and Week 16, following administration of the dapagliflozin add-on treatment.

Change from baseline in UACR at Week 20 was also evaluated for DKD participants (with and without SGLT2i background) and for non-DKD participants. The expected decrease in UACR on introduction of treatment with an SGLT2i between Week 12 and Week 16 was not seen in participants who had been on SGLT2i treatment during the first 12 weeks of the study. In non-DKD participants, an apparently more prominent UACR reduction in the AZD5718 groups compared to the placebo group is likely to be due to an unexpected increase in UACR in the placebo group.

A secondary endpoint was the reduction of UACR from baseline to Week 12 compared to placebo. The percentage change in UACR reduction at Week 12 compared to placebo was statistically significant in the CCI mg AZD5718 group, for which the p-value (p-value = 0.0318) was just below the threshold of significance (p-value < 0.05). No significant UACR reduction at Week 12 compared to placebo was observed in the other treatment groups.

A further secondary efficacy endpoint was the change in eGFR from baseline to Week 12 and from Week 12 to Week 20, which was not statistically significant in any treatment group.

The third secondary endpoint was the change in 24-hour mean SBP from baseline to Week 12. No clinically relevant change from baseline to Week 12 was observed for SBP between the 3 AZD5718 groups and the placebo group.

Summary of safety results

The median duration of exposure (days) to placebo or AZD5718 was 138.0 days for the CCI mg AZD5718 group, 139.5 days for CCI mg AZD5718 group, and 139.0 days for the CCI mg AZD5718 and placebo groups, respectively. The median duration of exposure (days) to dapagliflozin was 56.0 days in all groups.

A higher percentage of participants in the AZD5718 CCI mg group (104 [69.8%]) experienced at least one AE compared with the lower dose groups (82 [53.2%] for AZD5718 CCI mg and 81 [53.3%] for AZD5718 CCI mg) and the placebo group (80 [52.3%]). When combining all 3 AZD5718 treatment groups, 267 of 455 participants (58.7%) treated with AZD5718 experienced at least one AE.

One (0.7%) participant in the placebo group experienced an AE with fatal outcome. Overall, there was a higher percentage of participants with SAEs in the combined AZD5718 group (31 [6.8%]) compared to the placebo group (6 [3.9%]). Pneumonia was the only SAE Preferred Term (PT) that was reported in > 1 participant in any one treatment group (2 participants [1.3%] in the AZD5718 CCI mg group).

The most frequently reported (reported by ≥ 10% participants) AEs by System Organ Class among the 455 participants in the combined AZD5718 group were:

- Infections and infestations (86 [18.9%] compared to 26 [17.0%] in the placebo group).
- Gastrointestinal disorders (56 [12.3%] compared to 14 [9.2%] in the placebo group).
- Metabolism and nutrition disorders (51 [11.2%] compared to 25 [16.3%] in the placebo group).

The most frequently reported (≥ 5% participants in any treatment group) AEs by PTs in the combined AZD5718 group were hyperkalaemia (22 [4.8%]), urinary tract infection (19 [4.2%]), and glomerular filtration rate decreased (16 [3.5%]).

Most participants experienced AEs that were mild (212 [46.6%] in the combined AZD5718 group; 61 [39.9%] in the placebo group) or moderate (106 [23.3%] in the combined AZD5718 groups; 30 [19.6%] in the placebo group) in intensity. In total, 12 (2.6%) participants in the combined AZD5718 group and 6 (3.9%) participants in the placebo group experienced severe AEs.

The percentage of participants who experienced an AE assessed by the investigator as causally related to the study treatment was similar for the combined AZD5718 group (34 [7.5%]) and the placebo group (14 [9.2%]).

A similar percentage of participants in the combined AZD5718 groups (17 [3.7%]) and the placebo group (6 [3.9%]) experienced AEs leading to permanent discontinuation of study treatment. A higher percentage of participants that permanently discontinued the study treatment due to AEs was observed in the CCI mg AZD5718 group (12 [7.8%]) compared with the higher dose groups (2 [1.3%] for the AZD5718 CCI mg and 3 [2.0%] for the AZD5718 CCI mg).

The study began on 01 October 2020 (first participant enrolled) and was completed on 06 September 2022 (last participant last visit), which included the period during which the COVID-19 pandemic occurred globally. Overall, the disruptions related to the COVID-19 pandemic were considered to have had minimal impact on the participants' safety or data integrity.

There were no clinically meaningful trends over time from baseline in haematology, coagulation, clinical chemistry parameters or urinalysis.

No coagulation, clinical chemistry, and urinalysis abnormalities were reported as SAE. Two participants (both on AZD5718 CCI mg) experienced haematology abnormalities that were reported as SAEs (PTs: acute leukaemia and leukocytosis), but both were assessed by the investigator to be not related to study treatment.

There were 5 discontinuations due to clinical chemistry abnormal values (PTs: liver function test increased, and glomerular filtration rate decreased).

Many participants experienced vital signs treatment-related changes outside the pre-defined criteria. The percentage of participants who experienced abnormal vital signs was similar for the combined AZD5718 group and the placebo group. No clinically significant changes in vital signs were reported as SAE during the study.

Many participants experienced clinically significant ECG findings. The majority of participants had potentially clinically significant ECGs at Screening. No ECG abnormalities were reported as SAE during the study.

Conclusions

- The primary objective was not met. No response was observed in terms of albuminuria reduction following administration of AZD5718: the percentage change in UACR at Week 20 compared to placebo was not statistically significant in any treatment group.
- Lack of response to AZD5718 administration was also confirmed by the analysis of the secondary efficacy endpoint: UACR reduction from baseline to Week 12. The percentage change in UACR at Week 12 compared to placebo was not statistically significant in any treatment group (except for the [redacted] mg AZD5718 group).
- Generally, no clinically relevant differences between the AZD5718 and placebo groups were seen for any of the secondary endpoints relating to ABPM and renal function in participants with proteinuric CKD, with and without the addition of dapagliflozin.
- Treatment with AZD5718, and in combination with dapagliflozin add-on therapy, was generally well tolerated in all 3 AZD5718 groups; no safety concerns were raised.