- **Protocol number:** D6402C00003
- **Document title:** An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers
- **NCT number:** NCT04798222
- **Version number:** 1.0
- **Date of the document:** 28 Feb 2022

2 SYNOPSIS

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers	
Study Numbers:	Parexel Study No.: PXL257284 Sponsor Study No.: D6402C00003	
Investigational Medicinal Products:	Test Product: • AZD9977 + dapagliflozin capsule formulations • Dapagliflozin capsule Reference Product: • AZD9977 capsule • Dapagliflozin tablet	
Indication Studied:	Heart failure	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit – Berlin Campus DRK Kliniken Berlin Westend, Haus 31 Spandauer Damm 130 14050 Berlin Germany	
Publication:	None	
Study Duration:	First subject first visit: 29 Jun 2021	Last subject last visit: 03 Sep 2021

Study Objectives:

Primary objective:

- To evaluate the relative bioavailability of AZD9977 and dapagliflozin and compare the plasma concentration-time profiles after dosing with different capsule formulations containing both AZD9977 and dapagliflozin or solely dapagliflozin, the AZD9977 capsule, and dapagliflozin tablet under fasted conditions.

Secondary objectives:

- To evaluate the relative bioavailability of AZD9977 and dapagliflozin after dosing with 2 different capsule formulations (AZD9977 + dapagliflozin) under fed and fasted conditions.
- To evaluate the relative bioavailability of AZD9977 in different capsules against each other under fasted conditions.
- To evaluate the relative bioavailability of dapagliflozin in different capsules against each other under fasted conditions.
- To assess the safety and tolerability of single doses of AZD9977 and dapagliflozin in healthy subjects.

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Study Design:

This was a randomized, parallel group, open-label, four/five period, eight treatment, single-dose, cross-over study. Subjects were randomized to one of the 8 treatment sequences (4 unique sequences to Group 1 and 4 unique sequences to Group 2). In Group 1, subjects received 5 single-dose treatments (Treatments A, B, C, D, and E), while in Group 2, subjects received 4 single-dose treatments (Treatments A, F, G, and H). Treatment A was given to both Group 1 and Group 2. The study was planned to be conducted in 2-centers; however, it was conducted in only one center.

The study comprised of the following:

- A screening period of maximum 21 days.
- Four or five treatment periods during which subjects were resident at the study center from the day before dosing (Day -1 of Treatment Period 1) until at least 72 hours after the final dose (Day 4 of the final treatment period).
- A final visit within 5 to 7 days after administration of the last treatment.

Each subject received single-dose treatments under fasted or fed conditions. There was a washout period of at least 4 days between each investigational medicinal product (IMP) dose administration.

Dosing under fasted conditions

On Day 1 of each dosing day, subjects received the corresponding treatment following an overnight fast of at least 10 hours. No fluids were allowed apart from water which was given until 1 hour prior to administration of the IMP and then from 2 hours after administration of the IMP (excluding water used in conjunction with IMP administration). A standard meal was given 4 hours after administration of the IMP.

Dosing under fed conditions:

On Day 1 of each dosing day, following an overnight fast of at least 10 hours, a high-fat, high-calorie breakfast was served 30 minutes before administration of the IMP and was consumed in full at least 5 minutes before administration of the IMP. No fluids were allowed apart from water which was given until 1 hour prior to dosing and then from 2 hours after dosing (excluding milk served with the breakfast and water used in conjunction with IMP administration). A standard meal was given 4 hours after administration of the IMP.

Study Subjects:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
20 subjects	20 subjects	20 subjects

Main Inclusion Criteria:

Healthy, male and/or female subjects of non-childbearing potential aged 18 to 50 years, inclusive, with suitable veins for cannulation or repeated venipuncture. Subjects had to have a body mass index (BMI) between 18 and 29.9 kg/m^2, inclusive, and weigh at least 50 kg and no more than 100 kg, inclusive, at screening.

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Investigational Medicinal Product(s):

Formulation(s):	Strength/Concentrations:	Batch/Manufacturing Lot Number(s):	Expiry Date(s):
AZD9977 capsule	CCI	CCI	31 Aug 2023
AZD9977 capsule	CCI	CCI	31 Aug 2023
Dapagliflozin tablet	CCI	CCI	30 Apr 2022
Dapagliflozin capsule	CCI	CCI	28 Feb 2022
AZD9977 and Dapagliflozin, Capsule 1	CCI	CCI	28 Feb 2022
AZD9977 and Dapagliflozin, Capsule 2	CCI	CCI	28 Feb 2022
AZD9977 and Dapagliflozin, Capsule 3	CCI	CCI	28 Feb 2022
AZD9977 and Dapagliflozin, Capsule 4	CCI	CCI	28 Feb 2022

Duration of Treatment:

Each subject was involved in the study for approximately 6 to 7 weeks.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit in Berlin. The administration of IMP was recorded in Parexel's electronic source data capturing and information management system (ClinBase™). Compliance was assured by direct supervision and witnessing of IMP administration. After IMP administration, a check of the subject's mouth and hands was performed.

Criteria for Evaluation:

Pharmacokinetic (PK) Parameters:

Primary PK parameters: AUCinf, AUClast, Cmax, C24 for AZD9977 and dapagliflozin

Secondary PK parameters: AUCinf, AUClast, Cmax, C24 for AZD9977 and dapagliflozin, AZD9977 alone, and dapagliflozin alone.

Safety Variables:

- Adverse events (AEs)
- Laboratory assessments (hematology, clinical chemistry, and urinalysis)
- Physical examination (weight, height, and BMI)
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature)
- Electrocardiograms (ECGs).

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Statistical Methods:

Presentation and Analysis of Pharmacokinetic Data:

The plasma AZD9977 and dapagliflozin concentrations and the PK parameters were listed and presented in tabular and graphical form. In this CSR the terms PK analysis set and PK set are used interchangeably.

For AZD9977 and dapagliflozin, plasma concentrations for each scheduled time point were summarized by treatment group using appropriate descriptive statistics, based on the PK analysis set. A listing of all concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations was presented by treatment group for the safety analysis set. A listing of concentration versus scheduled time data was presented by treatment group for the PK analysis set.

All reportable AZD9977 and dapagliflozin PK parameters, including individual diagnostic and λz related parameters, were listed for each subject by treatment group, based on the PK analysis set.

All primary, secondary, and diagnostic PK parameters were summarized for AZD9977 and dapagliflozin by treatment group using appropriate descriptive statistics, based on the PK analysis set.

Presentation and Analysis of Safety Data:

All safety data were presented in the data listings. Continuous variables were summarized using descriptive statistics by treatment group and overall. Categorical variables were summarized in frequency tables by treatment group and overall. The analysis of the safety variables was based on the safety analysis set. In this CSR the terms safety analysis set and safety set are used interchangeably.

All AEs were summarized by Preferred Term and System Organ Class using the most recent version of the Medical Dictionary for Regulatory Activities vocabulary (Version 24.0).

The listings of serious adverse events (SAEs) and AEs leading to the discontinuation of IMP (DAEs) were made and the number of subjects who had any AEs, SAEs, DAEs and AEs with severe intensity were summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs (listings only), were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment were reported as an AE. Data were summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline is defined.

Out-of-range values for safety laboratory were flagged in individual listings as well as summarized descriptively using agreed reference ranges.

Determination of Sample Size:

CCI [redacted]

In order to ensure 16 evaluable subjects, 8 subjects in each Group, 20 subjects were randomized. Eight (8) evaluable subjects were planned to have 2 subjects per sequence. Additional subjects were enrolled as replacements if a sequence ends up with less than 2 subjects due to dropout.

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Protocol Deviations:

In total, two important deviations were reported in one subject PPD during the study:

- Pharmacokinetic plasma sampling for AZD9977 at 1-hour post treatment period 2 Day 1 was performed +28 minutes outside the tolerance window.
- Pharmacokinetic plasma sampling for dapagliflozin at 1-hour post treatment period 2 Day 1 was performed +28 minutes outside the tolerance window.

The subject was included in all analysis sets, but the affected data time points mentioned above was excluded from PK summary statistics for both AZD9977 and dapagliflozin.

Pharmacokinetic Results:

- Exposure to AZD9977 and dapagliflozin from all four capsules (Treatment B, D, F, G) under fasted conditions was generally comparable to the respective reference treatment (A1 and A2) in terms of AUClast and AUCinf. However, there was a trend towards a lower Cmax and a higher C24 than observed for the reference treatment.
- Administration of Capsule 1 and Capsule 2 with food resulted in a slightly delayed tmax for AZD9977. For Treatment C (Capsule 1, fed) the AUClast, AUCinf and Cmax of AZD9977 values were higher than that observed for Treatment B (Capsule 1, fasted), with the C24 value being lower in the fed state. For Treatment E (Capsule 2, fed) the AUClast, AUCinf of AZD9977 values were comparable to Treatment D (Capsule 2, fasted), with Cmax being possibly higher and C24 value being lower in fed than fasted state. Overall, the magnitude of the impact of food on AZD9977 PK appeared to be lower in Capsule 2 than in Capsule 1.
- For dapagliflozin in Treatment C (Capsule 1, fed) and Treatment E (Capsule 2, fed), the tmax in the fed state was slightly later than the fasted tmax, but exposure to dapagliflozin in terms of AUClast and AUCinf was comparable between fed and fasted states. For Treatment C the Cmax was lower than the Treatment B Cmax and the C24 was higher than the Treatment B C24. For Treatment E the Cmax was lower than the Treatment D Cmax and the C24 values were comparable.
- Exposure to AZD9977 variant 1 from Capsule 1 (Treatment B) was comparable with that from Capsule 3 (Treatment F) in terms of AUClast, AUCinf, Cmax and C24. Exposure to AZD9977 variant 2 from Capsule 2 (Treatment D) was comparable with that from Capsule 4 (Treatment G) in terms of AUClast and AUCinf. The Treatment D Cmax was possibly 11% higher than the Treatment G Cmax and the Treatment D C24 value was 29% lower than the Treatment G C24 value.
- Exposure to dapagliflozin variant 1 from Capsule 1 (Treatment B) was 6% lower than that from Capsule 4 (Treatment G) in terms of AUClast and AUCinf. The Treatment B Cmax was possibly 16% lower than the Treatment G Cmax and the C24 values were comparable.
- Exposure to dapagliflozin variant 2 from Capsule 2 (Treatment D) was comparable with that from Capsule 3 (Treatment F) in terms of AUClast and AUCinf. The Treatment D Cmax and C24 values were possibly 7-8% higher than the Treatment F values.

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Safety Results:

- Overall, 10 of 20 subjects (50.0%) had at least one AE, of 10 subjects 8 (40.0%) had at least one possibly related AE.
- Overall, 26 AEs were reported, of the 26 AEs 21 were possibly related to IMP.
- The most common AE (including those possibly related to IMP) was headache, which is a frequently reported event in residential studies.
- All AEs were either mild or moderate in intensity.
- There were no SAEs, deaths or AEs leading to discontinuation of IMP or withdrawal from the study.
- AEs were not influenced by treatment or sequence.
- No clinically relevant trends were observed for laboratory results, vital signs, and ECGs.
- The coronavirus disease 2019 (COVID-19) pandemic did not impact the safety results of this study (no COVID-19 cases reported during the study).
- Single doses of AZD9977 and dapagliflozin were safe and well tolerated in healthy male subjects and there were no safety concerns observed.

Title of Study:	An Open-label, Randomized, Parallel Group, Four/Five Period, Eight Treatment Cross-over, Single Oral Dose Study to Assess the Relative Bioavailability of Different Formulations of AZD9977 and Dapagliflozin and Influence of Food in Selected Formulations in Healthy Volunteers

Discussion and Conclusion:

Treatments were generally considered comparable for a given PK parameter if the geometric mean ratio was close to 100% (ie, within ± 5%) and if the 90% CI included 100%. As the study had no pre-defined criteria, had a large number of statistical comparisons, and the variability of some PK parameters was greater than for others, it cannot necessarily be concluded that some treatments genuinely result in higher or lower exposure to AZD9977 and dapagliflozin than other treatments.

Pharmacokinetics

- Exposure to AZD9977 and dapagliflozin from all four capsules (Treatment B, D, F, G) under fasted conditions was generally comparable to the respective reference treatment (A1 and A2) in terms of AUClast and AUCinf. However, there was a trend towards a lower Cmax and a higher C24 than observed for the reference treatment.
- Administration of Capsule 1 and Capsule 2 with food resulted in a slightly delayed tmax for AZD9977. For Treatment C (Capsule 1, fed) the AUClast, AUCinf and Cmax of AZD9977 values were higher than that observed for Treatment B (Capsule 1, fasted), with the C24 value being lower in the fed state. For Treatment E (Capsule 2, fed) the AUClast, AUCinf of AZD9977 values were comparable to Treatment D (Capsule 2, fasted), with Cmax being possibly higher and C24 value being lower in fed than fasted state. Overall, the magnitude of the impact of food on AZD9977 PK appeared to be lower in Capsule 2 than in Capsule 1.
- For dapagliflozin in Treatment C (Capsule 1, fed) and Treatment E (Capsule 2, fed), the tmax in the fed state was slightly later than the fasted tmax, but exposure to dapagliflozin in terms of AUClast and AUCinf was comparable between fed and fasted states. For Treatment C the Cmax was lower than the Treatment B Cmax and the C24 was higher than the Treatment B C24. For Treatment E the Cmax was lower than the Treatment D Cmax and the C24 values were comparable.
- Exposure to AZD9977 variant 1 from Capsule 1 (Treatment B) was comparable with that from Capsule 3 (Treatment F) in terms of AUClast, AUCinf, Cmax and C24. Exposure to AZD9977 variant 2 from Capsule 2 (Treatment D) was comparable with that from Capsule 4 (Treatment G) in terms of AUClast and AUCinf. The Treatment D Cmax was possibly 11% higher than the Treatment G Cmax and the Treatment D C24 value was 29% lower than the Treatment G C24 value.
- Exposure to dapagliflozin variant 1 from Capsule 1 (Treatment B) was 6% lower than that from Capsule 4 (Treatment G) in terms of AUClast and AUCinf. The Treatment B Cmax was possibly 16% lower than the Treatment G Cmax and the C24 values were comparable.
- Exposure to dapagliflozin variant 2 from Capsule 2 (Treatment D) was comparable with that from Capsule 3 (Treatment F) in terms of AUClast and AUCinf. The Treatment D Cmax and C24 values were possibly 7-8% higher than the Treatment F values.

Safety

Single doses of AZD9977 and dapagliflozin were safe and well tolerated in healthy male subjects and there were no safety concerns observed.

COVID-19 Pandemic

The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final, dated 28 February 2022

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.