- **Protocol number:** D4325C00003
- **Document title:** A Phase I, Open-label Study with Two Independent Parts: Collecting Samples for Metabolites in Safety Testing Analysis of Zibotentan after Repeated Administration (Part 1); and a Randomised, Cross-over, Three-period, Three-treatment, Single-dose Study to Assess the Relative Bioavailability of Different Formulations of Zibotentan and Dapagliflozin (Part 2) in Healthy Adult Participants
- **NCT number:** NCT04991571
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2 SYNOPSIS

Title of Study:	A Phase I, Open-label Study with Two Independent Parts: Collecting Samples for Metabolites in Safety Testing Analysis of Zibotentan after Repeated Administration (Part 1); and a Randomised, Cross-over, Three-period, Three-treatment, Single-dose Study to Assess the Relative Bioavailability of Different Formulations of Zibotentan and Dapagliflozin (Part 2) in Healthy Adult Participants	
Study Numbers:	Parexel Study No.: 262565 Sponsor Study No.: D4325C00003	
Investigational Medicinal Products:	Test Product: Zibotentan and Dapagliflozin	
Indication Studied:	Chronic Kidney Disease	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit - Baltimore	
Publication:	Not applicable	
Study Duration:	First subject first visit: 29 July 2021	Last subject last visit: 22 October 2021

Study Objectives:

Primary Objectives:

Part 1

To collect samples for metabolites in safety testing analysis after administration of multiple oral doses of CCI zibotentan in healthy adult participants.

Part 2

To evaluate the relative bioavailability and plasma concentration time profiles of zibotentan and dapagliflozin administered as 2 different fixed dose combinations (FDC) formulations and the co-administered mono components zibotentan capsule CCI and dapagliflozin tablet CCI .

Secondary objectives:

Part 1

To assess the safety and tolerability of multiple oral doses of CCI zibotentan.

Part 2

To assess safety and tolerability of single doses of zibotentan and dapagliflozin in different formulations.

To evaluate further pharmacokinetics (PK) parameters of zibotentan and dapagliflozin.

Exploratory objective:

CCI

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Study Design:

This was a Phase I study conducted at a single-centre with two independent parts:

- Part 1 was an open-label, non-randomised, single-treatment period. Participants were administered CCI zibotentan orally once daily for 5 days.
- Part 2 was an open-label, randomised, 3-period, 3-treatment, cross-over, single dose study. Participants were randomised to one of 3 treatment sequences and received 3 single doses of study interventions (Treatment A, B or C). Participants who were enrolled in Part 1 could not be enrolled in Part 2.

On Day 1 of each treatment period, participants received the corresponding treatment following an overnight fast of at least 10 hours. In order to improve tolerability of the study interventions, subjects received prophylactic paracetamol (acetaminophen) in all treatment periods. No fluids were allowed apart from water which could be taken until 1 hour prior to administration of the study interventions and then from 2 hours after administration of the study intervention (excluding water used in conjunction with study intervention administration). A standard meal was given 4 hours after administration of the study intervention.

Part 1 of the study comprised:

- A screening period of maximum 28 days.
- A single treatment period during which participants were resident at the study centre from 2 days before dosing (Day -2) (due to COVID-19 pandemic restrictions) until the morning of Day 6 (24 hours after the last dose on Day 5 of the treatment period).
- A final Follow-up Visit 5 to 7 days after administration of the last dose.

Each participant in Part 1 received multiple oral doses of CCI zibotentan.

Part 2 of the study comprised:

- A screening period of maximum 28 days.
- Due to COVID-19 pandemic restrictions, participants were resident at the study centre from 2 days before dosing (Day -2) of the first treatment period until 72 hours after dosing in Treatment Period 3.
- A final Follow-up Visit within 5 to 7 days after administration of study intervention in Treatment Period 3.

Each participant received each of the following 3 single-dose study interventions, separated by a washout period of at least 7 days between treatment periods (ie, if the first dose is given on Day 1, the next dose was given on Day 8 at the earliest):

- Treatment A: CCI zibotentan (capsule) + CCI dapagliflozin (tablet)
- Treatment B: zibotentan/dapagliflozin CCI tablet – Formulation 1
- Treatment C: zibotentan/dapagliflozin CCI tablet – Formulation 2

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Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
7 subjects (Part 1) and 21 subjects (Part 2)	20 subjects (Part 2)	7 subjects (Part 1) and 19 subjects (Part 2)

Main Inclusion Criteria:

This study included healthy male, and female (non-childbearing potential) participants aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venipuncture, who had 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.

Investigational Medicinal Product(s):

Formulation(s):	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
Zibotentan (ZD4054) capsule	CCI	F Lot ID: CCI P Lot ID: CCI	CCI
Dapagliflozin tablet [a]	CCI	F Lot ID: CCI P Lot ID: CCI	CCI
Zibotentan/ Dapagliflozin tablet - Formulation 1	CCI	F Lot ID: CCI P Lot ID: CCI	CCI
Zibotentan/ Dapagliflozin tablet - Formulation 2	CCI	F Lot ID: CCI P Lot ID: CCI	CCI

[a] The tablets contained lactose in quantities not likely to cause discomfort in lactose-intolerant individuals.

Duration of Treatment:

The planned duration of subject involvement was approximately up to 40 days in Part 1 and up to 49 days in Part 2.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit. The administration of all investigational products (IPs) was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of IP administration. After IP administration, a check of the subject's mouth and hands was performed.

Criteria for Evaluation:

Pharmacokinetic Parameters:

Where possible, single-dose PK parameters were assessed for all participants in Part 2 following each of the 3 treatments.

The following PK parameters for zibotentan and dapagliflozin were derived from plasma concentrations:

AUCinf, AUClast, Cmax and C24 for zibotentan and dapagliflozin.

tmax, tlast, t1/2λ_z, λ_z, CL/F, and Vz/F for zibotentan and dapagliflozin.

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Safety Variables:

Adverse events (AEs), serious adverse events (SAEs), adverse events leading to the discontinuation of investigational product (DAEs), vital signs (systolic and diastolic blood pressure, pulse rate), resting 12-lead electrocardiograms (ECGs), physical examination, and laboratory assessments (haematology, clinical chemistry, and urinalysis).

Exploratory Variables:

CCI [redacted]

Statistical Methods:

Determination of Sample Size:

CCI [redacted]

Analysis Populations:

Enrolled Analysis Set

The enrolled set consisted of all participants who were enrolled and assigned to treatment.

Randomised Set

The randomised set consisted of all subjects randomised in Part 2 of the study.

Safety Analysis Set

The safety analysis set included all subjects who received at least one dose of IP zibotentan and/or dapagliflozin, and for whom any safety post-dose data were available. Unless otherwise stated, the safety analysis set was used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IP was also presented using the safety analysis set.

Pharmacokinetic Analysis Set

The PK analysis set consisted of all subjects in the safety analysis set of Part 2 who had at least 1 quantifiable post-dose concentration for zibotentan or dapagliflozin, with no important protocol deviations related to AEs considered to impact the PK data. Inferential statistics could be performed for a subset of participants with available PK data for all treatments relevant to the comparison.

Data could be excluded from the PK analysis set as a result of the following:

- Data from subjects who experienced vomiting during the course of the study were deleted from statistical analysis if vomiting occurred at or before median tmax.
- Data from participants for whom the pre-dose concentration was > 5% of Cmax for zibotentan and/or dapagliflozin in a specific treatment period.

A subject could be excluded from the analysis only for the specific treatment period in which the AE occurred.

The exclusion of any subjects or time-points from the calculation of the PK parameters was to be documented by the PK Scientist including the reason for exclusion.

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The available concentration data and PK parameter data for any subjects excluded from the PK analysis set were to be listed only. Concentration data for participants excluded from the PK analysis set were to be presented in the individual figures of concentration versus time plots.

Presentation and Analysis of Pharmacokinetic Data:

Part 1

No statistical analysis was performed for Part 1. The result of this AstraZeneca internal analysis was not reported in the clinical study report (CSR).

Part 2

For each analyte, plasma concentrations for each scheduled time-point were summarised for each analyte, PK Day/Visit and treatment, 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 Study Part and treatment for all randomised participants. A listing of concentration versus scheduled time data was presented by analyte, and treatment for the PK analysis set.

Individual concentrations with time deviations of greater than ± 10% from the clinical study protocol (CSP) scheduled time were used in the PK analysis but flagged for exclusion from the summary tables and corresponding figures.

All reportable PK parameters, including individual diagnostic and terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve (λz) related parameters, were listed for each participant by treatment, for each analyte separately, based on the safety analysis set.

All primary, secondary, and diagnostic PK parameters were summarised for each analyte by PK Day/Visit and treatment/dose group using appropriate descriptive statistics, based on the PK analysis set. Plasma PK parameters were summarised for the PK analysis set by treatment separately. Pharmacokinetic parameters were summarised for each treatment using the following descriptive statistics (where possible): n, geometric mean, geometric coefficient of variation (CV), arithmetic mean, arithmetic standard deviation (SD), median, minimum and maximum. The ratios of Cmax, AUCinf, AUClast, and C24 of test product to those of reference product in each individual were calculated. For tmax and tlast, only n, median, minimum and maximum were presented.

The PK parameters of zibotentan and dapagliflozin were compared. Analyses were performed using ANOVA model using the natural logarithm of AUCinf, AUClast, Cmax, and C24 as the response variables, sequence, period and treatment as fixed effects, and participant nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2 sided 95%) for AUCinf, AUClast, Cmax, and C24 were calculated and presented. Also, ratios of geometric means together with CIs (2 sided 90%) were estimated and presented. Additionally, the 90% CI for the difference in tmax was calculated and presented.

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Primary Comparison:

To evaluate the relative bioavailability of different FDCs against the individual components:

- Treatment B versus Treatment A
- Treatment C versus Treatment A

Secondary Comparison:

To evaluate the relative bioavailability of zibotentan and dapagliflozin in different FDCs against each other

- Zibotentan:
  - Zibotentan in Treatment B versus Treatment C
- Dapagliflozin:
  - Dapagliflozin in Treatment B versus Treatment C

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment (both Part 1 and Part 2). Categorical variables were summarised in frequency tables (frequency and proportion) by treatment (both Part 1 and Part 2). The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarised by preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA). Furthermore, listings of SAEs and DAEs were made and the number of subjects who had any AEs, SAEs, and AEs with severe intensity were summarised.

Tabulations and listings of data for vital signs, clinical laboratory tests, and ECGs, were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE.

Protocol Deviations:

There was no individual with any important protocol deviations (Appendix 16.2.2.1.1). No important protocol deviations, including COVID-19 related protocol deviations were identified (Table 14.1.2.1).

Pharmacokinetic Results:

Zibotentan exposure was similar across all three CCI -treatments, with GLSM ratios near 100% (range of 96.7% to 109.78%) and 90% CI within the bounds of 80-125% for AUCinf, AUClast, Cmax, and C24, except for C24 comparisons of Treatment B (Formulation 1) versus Treatment A (CCI capsule), where the GLSM (90% CI) was 106.16% (88.92, 126.73), and C24 comparisons of Treatment C (Formulation 2) vs. Treatment A, where the GLSM (90%CI) was 109.78% (91.87, 131.19). There were no differences in tmax among treatments.

Dapagliflozin exposure was similar across all three CCI -treatments, with GLSM ratios near 100% (range of 95.66% to 118.19%) and 90% CI within the bounds of 80-125% for AUCinf, AUClast, Cmax, and C24, except for Cmax comparisons of Treatment B (Formulation 1) vs. Treatment A (CCI tablet), where the GLSM (90% CI) was 115.32% (110.64, 132.13), and for Cmax comparisons of Treatment C (Formulation 2)

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vs. Treatment A, where the GLSM (90% CI) was 118.19% (102.99, 135.62). There were no differences in tmax among treatments.

Safety Results:

- There were no SAE or death reported in the study and no subject had DAEs of IP or withdrawal from the study.
- Overall, 5 (71.4%) of 7 subject reported 10 AEs in Part 1 and 6 (30.0%) of 20 subjects reported 15 AEs in Part 2. The reported AEs were of mild (2 subjects [28.6%] in Part 1 and 3 subjects [15.0%] in Part 2) or moderate (3 subjects [42.9%] in Part 1 and 3 subjects [15.0%] in Part 2) intensity and no severe AE was reported in any subjects.
- The events that were assessed as possibly related to IP were headache, constipation, and dry mouth in Part 1 and headache and nausea in Part 2.
- There were no clinically relevant changes in vital signs, ECG, safety laboratory variables or physical examination.
- There were mild abnormal findings in the ECG; however, none of the findings were clinically significant or reported as AE.

Discussion and Conclusion:

With Regards to PK

Exposure to zibotentan and dapagliflozin was generally similar among all treatment in terms of AUCinf, AUClast, Cmax, C24, and tmax.

With Regards to safety

A total of 5 (71.4%) of the 7 subjects had AEs in Part 1 and a total of 6 (30.0%) of the 20 subjects had AEs in Part 2. No SAEs, deaths, or any DAEs were reported for both Part 1 and 2. Subjects with reported AEs were of mild or moderate intensity and no severe AE was reported in any subjects.

Conclusion

Part 1

Zibotentan administered daily over 5 days was well tolerated with no safety concerns.

Part 2

Zibotentan and dapagliflozin whether administered individually or in combination as an FDC formulation were well tolerated by all the subjects in the study and there were no safety concerns observed in the study.

Exposure to zibotentan and dapagliflozin was generally similar among all treatments in terms of AUCinf, AUClast, Cmax, C24, and tmax.

Version and Date of Report: Final, dated 01 Apr 2022

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