2. SYNOPSIS

Study centre(s)

A total of 170 sites in 19 countries participated (ie, screened participants) into this study.

Publications

Heerspink HJL, Greasley PJ, Ahlström C, Althage M, Dwyer JP, Law G, et al. Efficacy and safety of zibotentan and dapagliflozin in patients with chronic kidney disease: study design and baseline characteristics of the ZENITH-CKD trial. Nephrol Dial Transplant. 2023. Aug 25;gfad183. doi: 10.1093/ndt/gfad183. Online ahead of print.

Heerspink HJL, Kiyosue A, Wheeler DC, Lin M, Wijkmark E, Carlson G, et al. Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial. Lancet. 2023. Nov 2:S0140-6736(23)02230-4. doi: 10.1016/S0140-6736(23)02230-4. Online ahead of print.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To evaluate the effect of zibotentan 1.5 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on UACR.	• Change in log-transformed UACR from baseline to Week 12. The primary estimand is a hypothetical estimand such that the treatment effect is quantified in the optimal situation where any potential confounder is avoided. The population of interest is the Full Analysis population. Participants are included in the analysis if they have a non-missing baseline and at least one post-treatment visit UACR measurement. For the intercurrent events, if a participant is lost to follow-up, prematurely discontinues study treatment, or uses prohibited medication, the UACR data are treated as missing after the event and no imputation is performed. The summary measure being evaluated is the geometric mean reduction of UACR from baseline to Week 12.
Secondary [a]	
• To evaluate the effect of zibotentan 0.25 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on UACR.	• Change in log-transformed UACR from baseline to Week 12.
• To determine the change in office systolic and diastolic BP for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy.	• Change in BP from baseline (Visit 2) to Week 12.
• To characterise the dose-response relationship (relationship between different doses of zibotentan/a fixed dose of dapagliflozin and UACR reduction).	• Change in log-transformed UACR from baseline to Week 12.
• To determine the effect of different doses of zibotentan and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy on eGFR.	• Change in eGFR from baseline to Week 1. • Change in eGFR from baseline to Week 12. • Change in eGFR from baseline to Week 14. • Change in eGFR from Week 1 to Week 12.
Safety	
• To assess the safety and tolerability of all doses of zibotentan combined with dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy.	• AEs/SAEs/DAEs. • Vital signs. • Clinical laboratory tests. • 12-lead ECG assessment. • Event of special interest (changes in fluid-related measures).

[a] The estimand for the secondary objectives is defined with the same approach as for the primary objectives.

Abbreviations: AE = adverse event; BP = blood pressure; DAE = adverse event leading to the discontinuation of study intervention; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; SAE = serious adverse event; UACR = urinary albumin to creatinine ratio.

Study design

This was a Phase 2b, multicentre, randomised, double-blind, active-controlled, parallel group dose-ranging study to assess the efficacy, safety and tolerability of zibotentan and dapagliflozin in participants with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2, and urinary albumin to creatinine ratio (UACR) ≥ 150 mg/g and ≤ 5000 mg/g.

Following a 4 week screening period, participants were randomised to 12 weeks of treatment plus 2 weeks follow-up. All the variables were collected to verify the inclusion criteria and additional demographic data such as race/ethnicity, serum creatinine, and height.

Participants who met the eligibility criteria were randomised to study intervention in addition to receiving background local standard of care (SoC) therapy. To ensure blinding to treatment and zibotentan dose, daily dosing consisted of one dapagliflozin tablet, containing dapagliflozin 10 mg and one zibotentan capsule containing zibotentan 1.5 mg, zibotentan 0.25 mg or placebo.

Participants were stratified by diabetes (diabetic kidney disease (DKD) versus non-diabetes mellitus [DM] CKD) and baseline eGFR (below or equal versus above 45 mL/min/1.73 m^2) at the time of randomisation to ensure an approximate balance between treatment groups within each sub-population. The number of randomised participants in each stratum were monitored to ensure the non-DM CKD sub-population is approximately a minimum of 30% and a maximum of 50% of the total number of participants randomised.

The first dose was taken after randomisation at the baseline visit on Day 1. In addition to the baseline visit, the participant visited the clinic 5 times during the following 12 weeks of treatment. Approximately 2 weeks after the last dose, the participant visited the clinic again for a follow-up assessment.

Target population and sample size

Participants were 18 years of age or older and diagnosed with CKD defined as eGFR (CKD-EPI) ≥ 20 mL/min/1.73 m^2 AND with urine albumin to creatinine ratio ≥ 150 and ≤ 5000 mg albumin/g creatinine.

A total of 495 participants were planned to be randomised into this study, including participants randomised under the earlier design.

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

Participants who met the eligibility criteria were randomised to either of the following treatments, taken orally, in addition to receiving background local SoC therapy:

- Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily.
- Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily.
- Dapagliflozin 10 mg + Placebo once daily.

To ensure blinding to treatment and zibotentan dose, daily dosing consisted of one dapagliflozin tablet, containing dapagliflozin 10 mg and one zibotentan capsule containing zibotentan 1.5 mg, zibotentan 0.25 mg or placebo.

Duration of treatment

For each participant, the total duration of participation including the 4 weeks screening period, was approximately 17 to 19 weeks.

Statistical methods

The primary efficacy endpoint for this study is the change in log-transformed UACR from baseline to Week 12 for zibotentan 1.5 mg combined with dapagliflozin 10 mg and for dapagliflozin 10 mg monotherapy.

Urinary albumin to creatinine ratio were log-transformed and analysed using a mixed model repeated measures (MMRM) method. The values were back-transformed onto the original scale to give the geometric mean relative change from baseline to Week 12. The analysis model included the fixed categorical effects of stratification factor (diabetes [DKD participants versus non-DM CKD participants] and eGFR [$\leq$ or $>$ 45 mL/min/1.73 m^2]), clinical study protocol version (Amendment 2 versus pre-Amendment 2), treatment, visit, and treatment-by-visit interaction, plus the continuous covariates of baseline log (UACR) and baseline log (UACR)-by-visit interaction.

The secondary efficacy endpoint of change in log-transformed UACR from baseline to Week 12 for zibotentan 0.25 mg combined with dapagliflozin 10 mg and for dapagliflozin 10 mg monotherapy was assessed in a similar manner to the primary endpoint.

These secondary variables of blood pressure (BP) and eGFR were analysed using MMRM for consistency with the primary efficacy variable analysis, with an option for analysis of covariance (ANCOVA) if none of the covariance structures converge.

Safety analyses were performed using the safety analysis set. Safety data were presented using summary statistics unless otherwise specified.

Change from baseline were calculated as the difference between the post-dose value at each time point and the last non-missing value prior to or on the same date as administration of the first dose of study intervention.

Study population

Overall, in total, 1492 participants were screened of whom 525 participants were randomised and 522 (99.4%) participants received study intervention (main analysis and descriptive analysis sets). For the main analysis, 449 participants were randomised and 447 (99.6%) participants received study intervention. Overall, 112 (25.1%) participants discontinued study intervention.

The participants' demographic and baseline characteristics generally resembled those in the target population. There were no imbalances between the treatment groups.

Summary of efficacy results

- Zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg statistically significantly reduced UACR compared with dapagliflozin 10 mg monotherapy at Week 12 (-27.0 [90% CI: -38.4, -13.6; p-value = 0.002] and -33.7 [90% CI: -42.5, -23.5; p-value <0.001], respectively).
- Zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg statistically significantly reduced office systolic and diastolic BP compared with dapagliflozin 10 mg monotherapy at Week 12.
- There was no significant difference in eGFR reduction for both zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg compared with dapagliflozin 10 mg monotherapy.
- There were no clinically meaningful changes in body weight, total body water volume, extracellular water volume, and intracellular water volume.
- There were no clinically meaningful changes in exploratory pharmacodynamic endpoints or cardiovascular biomarkers over time.

Summary of pharmacodynamic results

There were no clinically meaningful changes from baseline in K^+, Na^+, urea nitrogen, glucose, and haematocrit for zibotentan 0.25 mg/dapagliflozin 10 mg, zibotentan 1.5 mg/dapagliflozin 10 mg, or dapagliflozin 10 mg monotherapy.

Summary of safety results

- Zibotentan/dapagliflozin was well tolerated in the study population. No new safety concern was identified.
- The most commonly reported adverse events (AEs) were headache, metabolic acidosis, brain natriuretic peptide increased, and hypertension. These AEs are not unexpected in a CKD population.
- A total of 15.4% and 18.4% participants treated with zibotentan (0.25 mg/1.5 mg)/dapagliflozin 10 mg and 9.0% participants treated with dapagliflozin 10 mg monotherapy had AEs considered to be possibly related to study intervention.
- Most of the AEs were considered mild or moderate in intensity, 2.2% and 3.4% participants treated with zibotentan (0.25 mg/1.5 mg)/dapagliflozin 10 mg and 2.3%

participants treated with dapagliflozin 10 mg monotherapy had AEs considered severe in intensity.

- One participant treated with dapagliflozin 10 mg monotherapy PPD The event was assessed by investigator as not possibly related to study intervention.
- Serious AEs were reported in 2.2% and 5.6% participants treated with zibotentan (0.25 mg/1.5 mg)/dapagliflozin 10 mg and in 2.3% participants treated with dapagliflozin 10 mg monotherapy.
- Discontinuation of zibotentan (0.25 mg/1.5 mg)/dapagliflozin 10 mg due to AEs was reported in 12.7% and 12.3% of participants, respectively. Discontinuation of dapagliflozin 10 mg monotherapy was reported in 4.0% of participants.
- There was a lower risk of fluid retention for the zibotentan 0.25 mg/dapagliflozin 10 mg treatment group compared with the zibotentan 1.5 mg/dapagliflozin 10 mg treatment group.
- There were no clinically meaningful changes in vital signs, clinical laboratory tests, electrocardiogram assessments. There were no clinically significant changes in liver function tests, no participants fulfilled potential Hy's Law criteria.

Conclusion(s)

- Zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg statistically significantly reduced UACR compared with dapagliflozin 10 mg monotherapy at Week 12.
- Zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg statistically significantly reduced office systolic and diastolic BP compared with dapagliflozin 10 mg monotherapy at Week 12.
- There was no significant difference in eGFR reduction for both zibotentan 0.25 mg/dapagliflozin 10 mg and zibotentan 1.5 mg/dapagliflozin 10 mg compared with dapagliflozin 10 mg monotherapy.
- Zibotentan/dapagliflozin was well tolerated in the study population. No new safety concern was identified.