



Clinical trial results:

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 Patients with Chronic Kidney Disease with Estimated Glomerular Filtration Rate (eGFR) 20 mL/min/1.73 m²

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2020-004101-32 |
| Trial protocol | HU NL BG DK IT ES SK HR |
| Global end of trial date | 01 June 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 06 June 2024 |
| First version publication date | 06 June 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D4325C00001 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04724837 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 15185 |
| Public contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 July 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of zibotentan 1.5 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on urinary albumin to creatinine ratio (UACR).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 April 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 29 |
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Brazil: 32 |
| Country: Number of subjects enrolled | Bulgaria: 13 |
| Country: Number of subjects enrolled | Canada: 26 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | Georgia: 29 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Italy: 27 |
| Country: Number of subjects enrolled | Japan: 54 |
| Country: Number of subjects enrolled | Malaysia: 1 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | South Africa: 6 |
| Country: Number of subjects enrolled | Spain: 39 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Ukraine: 3 |
| Country: Number of subjects enrolled | United States: 170 |
| Worldwide total number of subjects | 447 |
| EEA total number of subjects | 93 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 210 |
| From 65 to 84 years | 233 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in approximately 170 sites in North America, South America, Africa, Asia/Pacific, and European countries.

Pre-assignment

Screening details:

The screening period was of 4 weeks. All the study assessments were performed as per the schedule of assessments. Participants who met the eligibility criteria were randomised to study intervention in addition to receiving background local standard of care therapy.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Carer, Investigator, Subject |

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Zibotentan 0.25 mg + Dapagliflozin |

Arm description:

Participants received once daily oral dose of 0.25 mg zibotentan and 10 mg dapagliflozin for 12 weeks.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily oral dose of 0.25 mg zibotentan with 10 mg dapagliflozin for 12 weeks.

| | |
|--|------------|
| Investigational medicinal product name | Zibotentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily oral dose of 0.25 mg zibotentan with 10 mg dapagliflozin for 12 weeks.

| | |
|------------------|-----------------------------------|
| Arm title | Zibotentan 1.5 mg + Dapagliflozin |
|------------------|-----------------------------------|

Arm description:

Participants received once daily oral dose of 1.5 mg zibotentan and 10 mg dapagliflozin for 12 weeks.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily oral dose of 1.5 mg zibotentan with 10 mg dapagliflozin for

12 weeks.

| | |
|--|------------|
| Investigational medicinal product name | Zibotentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with once daily oral dose of 1.5 mg zibotentan with 10 mg dapagliflozin for 12 weeks.

| | |
|------------------|-------------------------|
| Arm title | Placebo + Dapagliflozin |
|------------------|-------------------------|

Arm description:

Participants received once daily oral dose of dapagliflozin 10 mg and matching placebo for 12 weeks.

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received once daily oral dose of dapagliflozin 10 mg with matching placebo for 12 weeks.

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received once daily oral dose of dapagliflozin 10 mg with matching placebo for 12 weeks.

| Number of subjects in period 1 | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin |
|--|---|--|--------------------------------|
| Started | 91 | 179 | 177 |
| Completed | 82 | 142 | 157 |
| Not completed | 9 | 37 | 20 |
| Adverse event, serious fatal | - | - | 1 |
| Consent withdrawn by subject | 2 | 9 | 9 |
| Physician decision | 1 | 2 | - |
| Adverse event, non-fatal | 2 | 7 | 4 |
| Failure to Meet Randomization Criteria | - | 1 | 3 |
| Other | 4 | 16 | - |
| Study Terminated by Sponsor | - | 1 | - |
| Lost to follow-up | - | 1 | 3 |

Baseline characteristics

Reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Zibotentan 0.25 mg + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of 0.25 mg zibotentan and 10 mg dapagliflozin for 12 weeks. | |
| Reporting group title | Zibotentan 1.5 mg + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of 1.5 mg zibotentan and 10 mg dapagliflozin for 12 weeks. | |
| Reporting group title | Placebo + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of dapagliflozin 10 mg and matching placebo for 12 weeks. | |

| Reporting group values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin |
|--|------------------------------------|-----------------------------------|-------------------------|
| Number of subjects | 91 | 179 | 177 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 45 | 87 | 78 |
| From 65-84 years | 45 | 91 | 97 |
| 85 years and over | 1 | 1 | 2 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.3 | 62.7 | 63.6 |
| standard deviation | ± 12.72 | ± 12.33 | ± 11.60 |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 28 | 55 | 55 |
| Male | 63 | 124 | 122 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 18 | 26 | 26 |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | 0 |
| Black or African American | 7 | 17 | 22 |
| White | 56 | 124 | 125 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 10 | 10 | 4 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 23 | 58 | 46 |

| | | | |
|-------------------------|----|-----|-----|
| Not Hispanic or Latino | 68 | 121 | 131 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 447 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 210 | | |
| From 65-84 years | 233 | | |
| 85 years and over | 4 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 138 | | |
| Male | 309 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 70 | | |
| Native Hawaiian or Other Pacific Islander | 2 | | |
| Black or African American | 46 | | |
| White | 305 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 24 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 127 | | |
| Not Hispanic or Latino | 320 | | |
| Unknown or Not Reported | 0 | | |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Zibotentan 0.25 mg + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of 0.25 mg zibotentan and 10 mg dapagliflozin for 12 weeks. | |
| Reporting group title | Zibotentan 1.5 mg + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of 1.5 mg zibotentan and 10 mg dapagliflozin for 12 weeks. | |
| Reporting group title | Placebo + Dapagliflozin |
| Reporting group description: | |
| Participants received once daily oral dose of dapagliflozin 10 mg and matching placebo for 12 weeks. | |

Primary: Change in UACR from baseline to Week 12

| | |
|--|--|
| End point title | Change in UACR from baseline to Week 12 ^[1] |
| End point description: | |
| The effect of zibotentan 1.5/dapagliflozin 10 mg versus dapagliflozin 10 mg on UACR was assessed in the full analysis set. | |
| The full analysis set included all participants who were randomised and received any study intervention. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline (Week 0 [Day 1]) until Week 12 (Day 84) | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint description is specific to the arms which are presented. Separate outcome measures for Change in UACR are presented according to arm specificity. Hence, only the arms which are referenced in the description are presented per outcome measure.

| End point values | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | | |
|---------------------------------|-----------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 132 | | |
| Units: milligram/gram (mg/g) | | | | |
| geometric mean (standard error) | 0.48 (± 1.094) | 0.72 (± 1.090) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in UACR |
| Statistical analysis description: | |
| Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + Placebo (PBO) | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 237 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted % mean change from baseline |
| Point estimate | -33.7 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -42.5 |
| upper limit | -23.5 |

Notes:

[2] - Two-sided p-value is presented. A p-value <0.10 indicates statistical significance, which is consistent with a one-sided test at the 5% level.

Secondary: Change in UACR from baseline to Week 12

| | |
|--|--|
| End point title | Change in UACR from baseline to Week 12 ^[3] |
| End point description: | |
| The effect of zibotentan 0.25 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy on UACR was assessed in the full analysis set. | |
| The full analysis set included all participants who were randomised and received any study intervention. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline (Week 0 [Day 1]) until Week 12 | |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint description is specific to the arms which are presented. Separate outcome measures for Change in UACR are presented according to arm specificity. Hence, only the arms which are referenced in the description are presented per outcome measure.

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Placebo + Dapagliflozin | | |
|---------------------------------|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 132 | | |
| Units: mg/g | | | | |
| geometric mean (standard error) | 0.52 (± 1.106) | 0.72 (± 1.090) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in UACR |
| Statistical analysis description: | |
| Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 194 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.002 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted % mean change from baseline |
| Point estimate | -27 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -38.4 |
| upper limit | -13.6 |

Notes:

[4] - Two-sided p-value is presented. A p-value <0.10 indicates statistical significance, which is consistent with a one-sided test at the 5% level.

Secondary: Change in office systolic blood pressure from baseline to Week 12

| | |
|-----------------|---|
| End point title | Change in office systolic blood pressure from baseline to Week 12 |
|-----------------|---|

End point description:

The change in office systolic blood pressure for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy was assessed in the full analysis set.

The full analysis set included all participants who were randomised and received any study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Week 0 [Day 1]) until Week 12 (Day 84)

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---|------------------------------------|-----------------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 65 | 108 | 137 | |
| Units: Millimeters of mercury (mmHg) | | | | |
| arithmetic mean (confidence interval 90%) | -7.1 (-10.0 to -4.1) | -11.0 (-13.5 to -8.4) | -3.4 (-5.8 to -1.0) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change in office systolic blood pressure |
|----------------------------|--|

Statistical analysis description:

Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO

| | |
|---|--|
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted Least Square (LS) mean CFB |
| Point estimate | -3.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -6.8 |
| upper limit | -0.5 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Change in office systolic blood pressure |
|-----------------------------------|--|

Statistical analysis description:

Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO

| | |
|---|---|
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | -7.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.3 |
| upper limit | -4.9 |

Secondary: Change in office diastolic blood pressure from baseline to Week 12

| | |
|-----------------|--|
| End point title | Change in office diastolic blood pressure from baseline to Week 12 |
|-----------------|--|

End point description:

The change in office diastolic blood pressure for doses of zibotentan combined with dapagliflozin 10 mg versus dapagliflozin 10 mg monotherapy was assessed in the full analysis set.

The full analysis set included all participants who were randomised and received any study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Week 0 [Day 1]) until Week 12 (Day 84)

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---|------------------------------------|-----------------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 65 | 108 | 137 | |
| Units: mmHg | | | | |
| arithmetic mean (confidence interval 90%) | -4.3 (-6.2 to -2.5) | -6.8 (-8.4 to -5.2) | -1.4 (-2.9 to 0.1) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in office diastolic blood pressure |
| Statistical analysis description: | |
| Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 245 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS Mean CFB |
| Point estimate | -5.4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | -3.7 |

| | |
|---|--|
| Statistical analysis title | Change in office diastolic blood pressure |
| Statistical analysis description: | |
| Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS Mean CFB |
| Point estimate | -3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | -1 |

| | |
|--|--|
| Secondary: Change in UACR from baseline to Week 12 (all arms) | |
| End point title | Change in UACR from baseline to Week 12 (all arms) |
| End point description: | |
| The assessment of dose-response and relationship across different dose of zibotentan/dapagliflozin and dapagliflozin alone on UACR reduction in the full analysis set. | |
| The full analysis set included all participants who were randomised and received any study intervention. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline (Week 0 [Day 1]) until Week 12 (Day 84) | |

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---------------------------------|--|---|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 62 | 105 | 132 | |
| Units: mg/g | | | | |
| geometric mean (standard error) | 0.52 (± 1.106) | 0.48 (± 1.094) | 0.72 (± 1.090) | |

Statistical analyses

| Statistical analysis title | Change in UACR |
|--|---|
| Statistical analysis description: | |
| Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 237 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted % mean change from baseline |
| Point estimate | -33.7 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -42.5 |
| upper limit | -23.5 |

| Statistical analysis title | Change in UACR |
|---|--|
| Statistical analysis description: | |
| Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 194 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted % mean change from baseline |
| Point estimate | -27 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -38.4 |
| upper limit | -13.6 |

Secondary: Change in eGFR from baseline to Week 1, Week 12, and Week 14

| | |
|-----------------|--|
| End point title | Change in eGFR from baseline to Week 1, Week 12, and Week 14 |
|-----------------|--|

End point description:

The effect of different doses of zibotentan and dapagliflozin 10 mg in combination versus dapagliflozin

10 mg monotherapy on eGFR was assessed in the full analysis set.
The full analysis set included all participants who were randomised and received any study intervention.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline (Week 0 [Day 1]) until Week 1 (Day 8), Week 12 (Day 84), and Week 14 (Day 98) | |

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---|--|---|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 83 | 152 | 151 | |
| Units: milliliters/minutes/1.73 square metres | | | | |
| arithmetic mean (confidence interval 90%) | | | | |
| Week 1 (n= 83, 152, 151) | -2.0 (-3.5 to -0.5) | -3.9 (-5.2 to -2.6) | -3.1 (-4.4 to -1.8) | |
| Week 12 (n= 64, 108, 135) | -3.1 (-4.7 to -1.5) | -3.0 (-4.4 to -1.6) | -1.9 (-3.3 to -0.6) | |
| Week 14 (n= 63, 105, 131) | 0.2 (-1.4 to 1.8) | -2.0 (-3.4 to -0.6) | 0.1 (-1.2 to 1.5) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 1 - Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 2.6 |

| | |
|--|---|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 14 - Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |

| | |
|---|----------------------|
| Number of subjects included in analysis | 303 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | -0.7 |

| | |
|--|---|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 12 - Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 303 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 0.3 |

| | |
|---|--|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 14 - Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 1.8 |

| | |
|---|----------------|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 1 - Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |

| | |
|---|---|
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 303 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 0.5 |

| | |
|---|--|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 12 - Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean CFB |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 0.5 |

Secondary: Number of participants with Adverse Events (AE) and Serious Adverse Events (SAE)

| | |
|---|--|
| End point title | Number of participants with Adverse Events (AE) and Serious Adverse Events (SAE) |
| End point description: | |
| The safety and tolerability of all doses of zibotentan combined with dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy was assessed in the safety analysis set. | |
| The safety analysis set included all participants that were randomised and received any study intervention. | |
| End point type | Secondary |
| End point timeframe: | |
| From Screening (Day -28) until Follow-up visit (Day 98) | |

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---|--|---|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 91 | 179 | 177 | |
| Units: Participants | | | | |
| Any AE | 45 | 86 | 66 | |
| AE with outcome of death | 0 | 0 | 1 | |
| Any SAE | 2 | 10 | 4 | |
| Any AE leading to discontinuation of IP | 11 | 22 | 7 | |
| Any AE leading to dose interruption | 3 | 7 | 10 | |
| Any AE leading to withdrawal from study | 2 | 7 | 4 | |
| Any AE related to IP | 14 | 33 | 16 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in eGFR from Week 1 to Week 12

| | |
|--|---------------------------------------|
| End point title | Change in eGFR from Week 1 to Week 12 |
| End point description: | |
| The effect of different doses of zibotentan and dapagliflozin 10 mg in combination versus dapagliflozin 10 mg monotherapy on eGFR was assessed in the full analysis set. | |
| The full analysis set included all participants who were randomised and received any study intervention. | |
| End point type | Secondary |
| End point timeframe: | |
| From Week 1 (Day 8) to Week 12 (Day 84) | |

| End point values | Zibotentan 0.25 mg + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin | Placebo + Dapagliflozin | |
|---|--|---|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 108 | 135 | |
| Units: milliliters/minutes/1.73 square metres | | | | |
| arithmetic mean (confidence interval 90%) | -1.1 (-2.5 to 0.4) | 0.9 (-0.2 to 2.0) | 1.2 (0.1 to 2.2) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: | |
| Week 1 and 12 - Comparison between Zibotentan 1.5 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 1.5 mg + Dapagliflozin v Placebo + Dapagliflozin |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 243 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean change |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 1.3 |

| | |
|---|--|
| Statistical analysis title | Change in eGFR |
| Statistical analysis description: Week 1 and Week 12 - Comparison between Zibotentan 0.25 mg + Dapagliflozin and Dapagliflozin 10 mg + PBO | |
| Comparison groups | Zibotentan 0.25 mg + Dapagliflozin v Placebo + Dapagliflozin |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Adjusted LS mean change |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | -0.4 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: From screening (Day -28) to Final Follow-up (Day 98)

AEs: From Day 1 to Final Follow-up (Day 98)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Zibotentan 0.25 mg + Dapagliflozin |
|-----------------------|------------------------------------|

Reporting group description:

Participants received once daily oral dose of 0.25 mg zibotentan and 10 mg dapagliflozin for 12 weeks.

| | |
|-----------------------|-------------------------|
| Reporting group title | Placebo + Dapagliflozin |
|-----------------------|-------------------------|

Reporting group description:

Participants received once daily oral dose of dapagliflozin 10 mg and matching placebo for 12 weeks.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Zibotentan 1.5 mg + Dapagliflozin |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received once daily oral dose of 1.5 mg zibotentan and 10 mg dapagliflozin for 12 weeks.

| Serious adverse events | Zibotentan 0.25 mg + Dapagliflozin | Placebo + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin |
|---|------------------------------------|-------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 4 / 177 (2.26%) | 10 / 179 (5.59%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 177 (0.00%) | 0 / 179 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic left ventricular failure | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 177 (0.56%) | 0 / 179 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 91 (1.10%) | 0 / 177 (0.00%) | 0 / 179 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 177 (0.56%) | 0 / 179 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 177 (0.56%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 1 / 177 (0.56%) | 0 / 179 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 91 (0.00%) | 0 / 177 (0.00%) | 1 / 179 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Zibotentan 0.25 mg + Dapagliflozin | Placebo + Dapagliflozin | Zibotentan 1.5 mg + Dapagliflozin |
|---|---|--------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 91 (15.38%) | 6 / 177 (3.39%) | 24 / 179 (13.41%) |
| Investigations | | | |
| Brain natriuretic peptide increased | | | |
| subjects affected / exposed | 2 / 91 (2.20%) | 1 / 177 (0.56%) | 9 / 179 (5.03%) |
| occurrences (all) | 2 | 1 | 9 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 1 / 177 (0.56%) | 0 / 179 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 91 (6.59%) | 2 / 177 (1.13%) | 8 / 179 (4.47%) |
| occurrences (all) | 6 | 2 | 9 |
| Metabolism and nutrition disorders | | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 5 / 91 (5.49%) | 2 / 177 (1.13%) | 7 / 179 (3.91%) |
| occurrences (all) | 5 | 2 | 8 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 03 December 2021 | Lower eGFR limit decreased to eGFR \geq 20 mL/min/1.73 m ² , upper limit of \leq 60 mL/min/1.73 m ² removed, and lower UACR limit decreased to \geq 150 mg/g to align study population with target population in Phase 3; removed local B-type natriuretic peptide (BNP) testing after screening, added local N-terminal pro-BNP (NT-proBNP) as an option at the screening visit; removed home-based ambulatory blood pressure monitoring (ABPM); updated study schema to clarify that data contributing to interim analyses and data to be reviewed was combined from Part A and Part B; updated sample size determination to reduce number of Part B participants while maintaining statistical power for primary endpoint; updated inclusion criteria; updated exclusion criteria to allow for participants with epilepsy syndrome, add ejection fraction < 50% at screening exclusion, and clarify reproduction exclusion. |
| 05 April 2022 | Update of study design with randomisation of participants closed to zibotentan 5 mg monotherapy arm, zibotentan 5 mg/dapagliflozin 10 mg arm, and placebo arm, with dapagliflozin 10 mg used as primary active comparator instead of placebo: title page, study schema and schedule of activities updated to reflect new study design; end of treatment visit removed; updated mitigation strategy for potential fluid retention risk from zibotentan; updated number of study sites; added clarification of inclusion criteria; updated doses, dose range, and IP information for remaining treatment arms; added that participants on a stable dose of mineralocorticoid receptor antagonists (MRA) may be included in the study; added clarification of discontinuation criteria for study intervention; updated statistical hypothesis and sample size determination; updated populations for analyses; updated primary, secondary, and exploratory endpoints; updated number and timing of interim analyses to reflect new study design. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No multiple testing correction was considered in this early phase study.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37632201>

<http://www.ncbi.nlm.nih.gov/pubmed/37931629>