



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	v2 (current)
This version publication date	30 October 2024
First version publication date	06 June 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D4325C00001
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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	Subject, Investigator, Carer

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
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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
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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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.	
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	Placebo + Dapagliflozin v Zibotentan 1.5 mg + 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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.	
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
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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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.

End point type	Secondary
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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
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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
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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

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

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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.	
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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.

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 (\pm 1.106)	0.48 (\pm 1.094)	0.72 (\pm 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
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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. Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.

End point type	Secondary
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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
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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 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 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 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 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 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
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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.

Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.

End point type	Secondary
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End point timeframe:

From Screening (Day -28) until Follow-up visit (Day 98), up to 126 days

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
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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.

Here, N = number of participants analyzed refers to n = number analyzed for this outcome measure at specific timepoints.

End point type	Secondary
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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:

From screening (Day -28) to Final Follow-up (Day 98), up to 126 days

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Zibotentan 0.25 mg + Dapagliflozin
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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
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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
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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
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

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
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
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 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
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
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>