Clinical trial results:
Efficacy and safety of bumetanide oral liquid formulation in children aged from 2 to less than 7 years old with Autism Spectrum Disorder. A 6-month randomised, double-blind, placebo controlled multicentre parallel group study to evaluate efficacy and safety of bumetanide 0.5mg twice a day followed by an open label active 6-month treatment period with bumetanide (0.5mg twice a day) and a 6 weeks discontinuation period after treatment stop.

Summary

EudraCT number	2017-004420-30
Trial protocol	GB FR ES NL HU PT PL IE CZ SK IT
Global end of trial date	26 October 2021

Results information

Result version number	v1 (current)
This version publication date	11 May 2022
First version publication date	11 May 2022

Trial information

Trial identification

Sponsor protocol code	CL3-95008-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03715153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Laboratorios Servier SL
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001303-PIP01-12
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	26 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2021
Global end of trial reached?	Yes
Global end of trial date	26 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of bumetanide (0.5mg BID) oral liquid formulation compared to placebo in the improvement of ASD core symptoms after 6 months of treatment in ASD children aged from 2 to less than 7 years old

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2018
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	Australia: 4
Country: Number of subjects enrolled	Brazil: 30

Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	211
EEA total number of subjects	152

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)	211
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male and female patients from 2 to less than 7 years old.
Primary diagnosis of ASD as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) , confirmed by Autism Diagnostic Observation Schedule-Generic (ADOS-2) and Autism Diagnosis Interview Revised, Clinical Global Impression Severity (CGI-S) Score ≥ 4, CARS2 total raw score ≥ 34.

Period 1

Period 1 title	Double-blind period (From W000 to W026)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	S95008 - Double-blind period

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S95008
Investigational medicinal product code	S95008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The IMP dispensed was an oral solution of 0.5 mg/mL of S95008 (bumetanide).
All the patients took orally the study treatment twice a day:
- in the morning at wake up.
- in the afternoon, 3 hours before going to bed at the latest.
The volume of the oral solution was adapted according to a body-weight basis for patients with a weight lower than 25 kg.

Arm title	Placebo - Double-blind period

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The IMP dispensed was an oral solution.
All the patients took orally the study treatment twice a day:
- in the morning at wake up.
- in the afternoon, 3 hours before going to bed at the latest.
The volume of the oral solution was adapted according to a body-weight basis for patients with a weight lower than 25 kg.

Number of subjects in period 1	S95008 - Double-blind period	Placebo - Double-blind period
Started	107	104
Completed	90	95
Not completed	17	9
Non medical reason	8	2
Adverse event, non-fatal	8	6
Protocol deviation	1	1

Period 2

Period 2 title	Open-label period (From W026 to W052)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Placebo/S95008 - Open-label period

Arm description:

Patients assigned to Placebo group at W0 and treated by S95008 in the open-label period.

Arm type	Experimental
Investigational medicinal product name	S95008
Investigational medicinal product code	S95008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

All patients received bumetanide b.i.d. between month 6 (W026) and month 12 (W052).
This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

Arm title	S95008/S95008 - Open label period

Arm description:

Patients assigned to S95008 group at W0 and treated by S95008 in the open-label period.

Arm type	Experimental
Investigational medicinal product name	S95008
Investigational medicinal product code	S95008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

All patients received bumetanide b.i.d. between month 6 (W026) and month 12 (W052).
This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

Number of subjects in period 2	Placebo/S95008 - Open-label period	S95008/S95008 - Open label period
Started	92	86
Completed	50	46
Not completed	42	40
Non medical reason	38	31
Adverse event, non-fatal	3	8
Protocol deviation	1	1

Period 3

Period 3 title	Combined period (From W000 to W052)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	S95008/S95008 - Combined period

Arm description:

For the Combined period (Double-blind + Open label periods), treatment group was defined as S95008/S95008 arm: patients assigned to S95008 group at W0 and treated with S95008 in the open label period.

Arm type	Experimental
Investigational medicinal product name	S95008
Investigational medicinal product code	S95008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

All patients received bumetanide b.i.d. between W000 and month 12 (W052).
This was followed by a period from W052 to WEND. During this follow-up period, the patients were not treated with IMP.

Number of subjects in period 3	S95008/S95008 - Combined period
Started	86
Completed	46
Not completed	40
Non medical reason	31
Adverse event, non-fatal	8
Protocol deviation	1

Period 4

Period 4 title	Extension period (From M000 to M006)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	S95008 - Extension period

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S95008
Investigational medicinal product code	S95008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

During the 6-month extension period in open label (from M000 to M006), all patients were treated by bumetanide as done in the open label treatment period.

Number of subjects in period 4[1]	S95008 - Extension period
Started	6
Completed	5
Not completed	1
Non medical reason	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The extension period was not mandatory.

Baseline characteristics

Reporting groups	
Reporting group title	S95008 - Double-blind period
Reporting group description: -	
Reporting group title	Placebo - Double-blind period
Reporting group description: -	

Reporting group values	S95008 - Double-blind period	Placebo - Double-blind period	Total
Number of subjects	107	104	211
Age categorical Units: Subjects			
Children (2-11 years)	107	104	211
Age continuous Units: years			
arithmetic mean	4.4	4.6	
standard deviation	± 1.2	± 1.1	-
Gender categorical Units: Subjects			
Female	18	17	35
Male	89	87	176

End points

End points reporting groups

Reporting group title	S95008 - Double-blind period
Reporting group description: -	
Reporting group title	Placebo - Double-blind period
Reporting group description: -	
Reporting group title	Placebo/S95008 - Open-label period
Reporting group description:	
Patients assigned to Placebo group at W0 and treated by S95008 in the open-label period.	
Reporting group title	S95008/S95008 - Open label period
Reporting group description:	
Patients assigned to S95008 group at W0 and treated by S95008 in the open-label period.	
Reporting group title	S95008/S95008 - Combined period
Reporting group description:	
For the Combined period (Double-blind + Open label periods), treatment group was defined as S95008/S95008 arm: patients assigned to S95008 group at W0 and treated with S95008 in the open label period.	
Reporting group title	S95008 - Extension period
Reporting group description: -	

Primary: CARS2 total raw score: change from baseline to 6 months.

End point title	CARS2 total raw score: change from baseline to 6 months.
End point description:	
Its main expression was the change from baseline to 6 months. The primary analysis consisted in the difference between bumetanide and placebo using a general linear model with baseline CARS2 total raw score and stratification factors as covariates.	
End point type	Primary
End point timeframe:	
CARS2 was completed by an independent rater, who performed a mandatory training before his/her involvement in the study, at W000, W004, W012, W026.	

End point values	S95008 - Double-blind period	Placebo - Double-blind period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: No unit				
arithmetic mean (standard deviation)	-3.66 (± 4.52)	-3.88 (± 5.06)		

Statistical analyses

Statistical analysis title	S95008 minus Placebo
Statistical analysis description:	
Bumetanide was compared to placebo on the primary efficacy endpoint (change from baseline to W026	

of the CARS2 total score) in the RS, using a General Linear Model including the fixed, categorical effect of treatment, gender and country as well as the continuous fixed covariate of baseline value. The Estimate of the adjusted difference was based on 211 patients (Missing data were imputed).

Comparison groups	S95008 - Double-blind period v Placebo - Double-blind period
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.617
Method	Two-sided 95% CI of the Estimate
Parameter estimate	Estimate of the adjusted difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	1.75
Variability estimate	Standard error of the mean
Dispersion value	0.71

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred or worsen or became serious according to the investigator, or upgraded by the Sponsor, between the first IMP intake date (included) and the last IMP intake date + 2 days of the considered period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	S95008 - Double-blind period
Reporting group description: -	
Reporting group title	Placebo - Double-blind period
Reporting group description: -	
Reporting group title	Placebo/S95008 - Open-label period
Reporting group description: -	
Reporting group title	S95008/S95008 - Combined period
Reporting group description: -	
Reporting group title	S95008 - Extension period
Reporting group description: -	

Serious adverse events	S95008 - Double-blind period	Placebo - Double-blind period	Placebo/S95008 - Open-label period
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 107 (6.54%)	3 / 104 (2.88%)	2 / 92 (2.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (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
Multisystem inflammatory syndrome in children			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 92 (1.09%)
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			
Cardiac arrest			

subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Atonic seizures			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (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
Brain oedema			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	1 / 107 (0.93%)	1 / 104 (0.96%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Hyperacusis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (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
Vomiting			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (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
Urticaria			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 92 (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
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyuria			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (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
Dehydration			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 92 (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
Hypokalaemia			
subjects affected / exposed	2 / 107 (1.87%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			

subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	S95008/S95008 - Combined period	S95008 - Extension period	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multisystem inflammatory syndrome in children			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis allergic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Atonic seizures			

subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyuria			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rhinitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	S95008 - Double-blind period	Placebo - Double-blind period	Placebo/S95008 - Open-label period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 107 (96.26%)	96 / 104 (92.31%)	81 / 92 (88.04%)
Investigations			
Blood creatinine increased			

subjects affected / exposed	6 / 107 (5.61%)	3 / 104 (2.88%)	5 / 92 (5.43%)
occurrences (all)	6	3	5
Blood uric acid increased			
subjects affected / exposed	5 / 107 (4.67%)	0 / 104 (0.00%)	2 / 92 (2.17%)
occurrences (all)	6	0	2
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 107 (1.87%)	4 / 104 (3.85%)	5 / 92 (5.43%)
occurrences (all)	2	4	5
Creatinine urine decreased			
subjects affected / exposed	4 / 107 (3.74%)	0 / 104 (0.00%)	2 / 92 (2.17%)
occurrences (all)	4	0	2
Weight decreased			
subjects affected / exposed	13 / 107 (12.15%)	2 / 104 (1.92%)	10 / 92 (10.87%)
occurrences (all)	13	2	10
Urine calcium increased			
subjects affected / exposed	4 / 107 (3.74%)	1 / 104 (0.96%)	6 / 92 (6.52%)
occurrences (all)	4	1	6
Nervous system disorders			
Akathisia			
subjects affected / exposed	8 / 107 (7.48%)	4 / 104 (3.85%)	4 / 92 (4.35%)
occurrences (all)	8	5	4
Headache			
subjects affected / exposed	0 / 107 (0.00%)	6 / 104 (5.77%)	2 / 92 (2.17%)
occurrences (all)	0	10	2
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	62 / 107 (57.94%)	36 / 104 (34.62%)	30 / 92 (32.61%)
occurrences (all)	76	40	36
Fatigue			
subjects affected / exposed	10 / 107 (9.35%)	2 / 104 (1.92%)	4 / 92 (4.35%)
occurrences (all)	11	2	4
Pyrexia			
subjects affected / exposed	10 / 107 (9.35%)	8 / 104 (7.69%)	12 / 92 (13.04%)
occurrences (all)	11	13	13
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	10 / 107 (9.35%)	5 / 104 (4.81%)	4 / 92 (4.35%)
occurrences (all)	13	5	4
Abdominal pain			
subjects affected / exposed	8 / 107 (7.48%)	5 / 104 (4.81%)	3 / 92 (3.26%)
occurrences (all)	9	5	3
Diarrhoea			
subjects affected / exposed	9 / 107 (8.41%)	11 / 104 (10.58%)	10 / 92 (10.87%)
occurrences (all)	9	16	10
Dry mouth			
subjects affected / exposed	20 / 107 (18.69%)	11 / 104 (10.58%)	9 / 92 (9.78%)
occurrences (all)	27	15	9
Vomiting			
subjects affected / exposed	16 / 107 (14.95%)	15 / 104 (14.42%)	9 / 92 (9.78%)
occurrences (all)	23	19	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 107 (3.74%)	7 / 104 (6.73%)	6 / 92 (6.52%)
occurrences (all)	4	8	7
Dysphonia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 92 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 107 (4.67%)	2 / 104 (1.92%)	1 / 92 (1.09%)
occurrences (all)	5	2	1
Psychiatric disorders			
Aggression			
subjects affected / exposed	7 / 107 (6.54%)	9 / 104 (8.65%)	7 / 92 (7.61%)
occurrences (all)	8	9	7
Affect lability			
subjects affected / exposed	6 / 107 (5.61%)	8 / 104 (7.69%)	6 / 92 (6.52%)
occurrences (all)	6	11	7
Anger			
subjects affected / exposed	7 / 107 (6.54%)	7 / 104 (6.73%)	4 / 92 (4.35%)
occurrences (all)	8	9	4

Agitation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	5 / 92 (5.43%)
occurrences (all)	0	0	9
Anxiety			
subjects affected / exposed	5 / 107 (4.67%)	2 / 104 (1.92%)	5 / 92 (5.43%)
occurrences (all)	5	3	5
Impulsive behaviour			
subjects affected / exposed	3 / 107 (2.80%)	9 / 104 (8.65%)	5 / 92 (5.43%)
occurrences (all)	3	12	6
Initial insomnia			
subjects affected / exposed	6 / 107 (5.61%)	6 / 104 (5.77%)	0 / 92 (0.00%)
occurrences (all)	6	6	0
Irritability			
subjects affected / exposed	16 / 107 (14.95%)	16 / 104 (15.38%)	9 / 92 (9.78%)
occurrences (all)	17	19	11
Insomnia			
subjects affected / exposed	9 / 107 (8.41%)	6 / 104 (5.77%)	3 / 92 (3.26%)
occurrences (all)	10	6	3
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	10 / 107 (9.35%)	5 / 104 (4.81%)	2 / 92 (2.17%)
occurrences (all)	10	5	2
Polyuria			
subjects affected / exposed	39 / 107 (36.45%)	23 / 104 (22.12%)	25 / 92 (27.17%)
occurrences (all)	46	25	26
Hypercalciuria			
subjects affected / exposed	4 / 107 (3.74%)	1 / 104 (0.96%)	2 / 92 (2.17%)
occurrences (all)	4	1	3
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 107 (2.80%)	5 / 104 (4.81%)	0 / 92 (0.00%)
occurrences (all)	3	6	0
Gastroenteritis viral			
subjects affected / exposed	9 / 107 (8.41%)	5 / 104 (4.81%)	1 / 92 (1.09%)
occurrences (all)	9	5	1
Rhinitis			

subjects affected / exposed	1 / 107 (0.93%)	7 / 104 (6.73%)	5 / 92 (5.43%)
occurrences (all)	1	7	5
Upper respiratory tract infection			
subjects affected / exposed	6 / 107 (5.61%)	4 / 104 (3.85%)	0 / 92 (0.00%)
occurrences (all)	9	5	0
Nasopharyngitis			
subjects affected / exposed	12 / 107 (11.21%)	11 / 104 (10.58%)	10 / 92 (10.87%)
occurrences (all)	17	14	13
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 107 (5.61%)	7 / 104 (6.73%)	5 / 92 (5.43%)
occurrences (all)	7	10	6
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 107 (15.89%)	16 / 104 (15.38%)	10 / 92 (10.87%)
occurrences (all)	17	18	12
Hyperkalaemia			
subjects affected / exposed	1 / 107 (0.93%)	6 / 104 (5.77%)	4 / 92 (4.35%)
occurrences (all)	3	6	9
Hypokalaemia			
subjects affected / exposed	16 / 107 (14.95%)	2 / 104 (1.92%)	21 / 92 (22.83%)
occurrences (all)	29	2	35
Increased appetite			
subjects affected / exposed	14 / 107 (13.08%)	10 / 104 (9.62%)	3 / 92 (3.26%)
occurrences (all)	14	15	3
Polydipsia			
subjects affected / exposed	8 / 107 (7.48%)	4 / 104 (3.85%)	2 / 92 (2.17%)
occurrences (all)	8	4	2

Non-serious adverse events	S95008/S95008 - Combined period	S95008 - Extension period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 84 (100.00%)	4 / 6 (66.67%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	11 / 84 (13.10%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Blood uric acid increased			

subjects affected / exposed	5 / 84 (5.95%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Glomerular filtration rate decreased			
subjects affected / exposed	10 / 84 (11.90%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Creatinine urine decreased			
subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Weight decreased			
subjects affected / exposed	12 / 84 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	13	0	
Urine calcium increased			
subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Nervous system disorders			
Akathisia			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Headache			
subjects affected / exposed	2 / 84 (2.38%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	50 / 84 (59.52%)	0 / 6 (0.00%)	
occurrences (all)	66	0	
Fatigue			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Pyrexia			
subjects affected / exposed	13 / 84 (15.48%)	0 / 6 (0.00%)	
occurrences (all)	19	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	15 / 84 (17.86%)	0 / 6 (0.00%)	
occurrences (all)	18	0	
Abdominal pain			

subjects affected / exposed	8 / 84 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Diarrhoea			
subjects affected / exposed	11 / 84 (13.10%)	0 / 6 (0.00%)	
occurrences (all)	14	0	
Dry mouth			
subjects affected / exposed	19 / 84 (22.62%)	0 / 6 (0.00%)	
occurrences (all)	29	0	
Vomiting			
subjects affected / exposed	15 / 84 (17.86%)	0 / 6 (0.00%)	
occurrences (all)	27	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Dysphonia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 84 (5.95%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	5 / 84 (5.95%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Affect lability			
subjects affected / exposed	5 / 84 (5.95%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Anger			
subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Agitation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Anxiety			

subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Impulsive behaviour			
subjects affected / exposed	3 / 84 (3.57%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Initial insomnia			
subjects affected / exposed	6 / 84 (7.14%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Irritability			
subjects affected / exposed	16 / 84 (19.05%)	0 / 6 (0.00%)	
occurrences (all)	19	0	
Insomnia			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	9 / 84 (10.71%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Polyuria			
subjects affected / exposed	33 / 84 (39.29%)	0 / 6 (0.00%)	
occurrences (all)	43	0	
Hypercalciuria			
subjects affected / exposed	5 / 84 (5.95%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	5 / 84 (5.95%)	1 / 6 (16.67%)	
occurrences (all)	5	2	
Gastroenteritis viral			
subjects affected / exposed	8 / 84 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Rhinitis			
subjects affected / exposed	2 / 84 (2.38%)	1 / 6 (16.67%)	
occurrences (all)	2	2	
Upper respiratory tract infection			

subjects affected / exposed	7 / 84 (8.33%)	1 / 6 (16.67%)	
occurrences (all)	10	1	
Nasopharyngitis			
subjects affected / exposed	16 / 84 (19.05%)	1 / 6 (16.67%)	
occurrences (all)	27	1	
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 84 (17.86%)	0 / 6 (0.00%)	
occurrences (all)	18	0	
Hyperkalaemia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	18 / 84 (21.43%)	0 / 6 (0.00%)	
occurrences (all)	37	0	
Increased appetite			
subjects affected / exposed	15 / 84 (17.86%)	0 / 6 (0.00%)	
occurrences (all)	16	0	
Polydipsia			
subjects affected / exposed	7 / 84 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2018	Amendment No. 1, applicable in all countries, concerned the update of the potassium supplementation recommendations in case of hypokalaemia.
12 December 2018	Amendment No. 2, applicable in all countries, mainly aimed to increase the planned number of countries (from 10 to 12), to correct safety measurements, to clarify the investigation schedule and to update some non-selection, exclusion and withdrawal criteria.
12 August 2019	Amendment No. 3, applicable in all countries, aimed to update the exclusion and the withdrawal criteria, about abnormal urinary calcium/creatinine ratio and calciuria.
30 November 2020	-Amendment No.8, applicable in all countries, aimed to update the definition of the end of the trial as a 6-month extension period in open-label was performed in some countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 September 2021	The superiority of bumetanide compared to placebo in ASD was not demonstrated in this phase III study. As none of the efficacy endpoints were reached and due to the identified risk of hypokalaemia and associated effects linked to the drug's diuretic activity, the Benefit/Risk ratio of the study treatment in ASD was considered negative. Consequently, the sponsor decided to stop the S95008 development and prematurely discontinue the extension period. This decision was not related to unexpected safety concerns.	-

Notes:

Limitations and caveats

None reported