Clinical trial results:
Efficacy and safety of bumetanide oral liquid formulation in children and adolescents aged from 7 to less than 18 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	2017-004419-38
Trial protocol	GB FR DE ES NL HU PT PL IT IE CZ SK
Global end of trial date	13 September 2021

Results information

Result version number	v1 (current)
This version publication date	20 March 2022
First version publication date	20 March 2022

Trial information

Trial identification

Sponsor protocol code	CL3-95008-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03715166
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
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Sponsor organisation address	Sefton House, Sefton Park, Bell Hill, Stoke Poges, Slough, Berkshire, United Kingdom, SL245S
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Scientific contact	Institut de Recherches Internationales Servier, Therapeutic Area in Neurology, +33 01 55 72 43 66, clinicaltrials@servier.com

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	13 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2021
Global end of trial reached?	Yes
Global end of trial date	13 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of bumetanide (0.5 mg b.i.d.) oral liquid formulation compared to placebo in the improvement of ASD core symptoms, as evaluated on Childhood Autism Rating Scale, second edition (CARS2), after 6 months of treatment in ASD children and adolescents aged from 7 to less than 18 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	21 September 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	Brazil: 27
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	United Kingdom: 29
Worldwide total number of subjects	211
EEA total number of subjects	155

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)	141
Adolescents (12-17 years)	70
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 7 to less than 18 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	Investigator, Subject

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	
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	89	93
Not completed	18	11
Non medical reason	10	7
Adverse event, non-fatal	7	3
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	90	86
Completed	74	76
Not completed	16	10
Non medical reason	2	4
Adverse event, non-fatal	13	4
Lack of efficacy	1	-
Protocol deviation	-	2

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	76
Not completed	10
Non medical reason	4
Adverse event, non-fatal	4
Protocol deviation	2

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	27
Completed	16
Not completed	11
Non medical reason	11

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)	68	73	141
Adolescents (12-17 years)	39	31	70
Age continuous Units: years			
arithmetic mean	10.5	10.4	
standard deviation	± 3.0	± 2.9	-
Gender categorical Units: Subjects			
Female	20	17	37
Male	87	87	174

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	90	93		
Units: No unit				
arithmetic mean (standard deviation)	-3.48 (± 4.31)	-2.96 (± 4.22)		

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 (Data amputation of missing data).

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	= 0.455
Method	Two-sided 95% CI of the Estimate
Parameter estimate	Estimate of the adjusted difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.61

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 + 1 day (included) 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	11 / 107 (10.28%)	5 / 104 (4.81%)	2 / 90 (2.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Blood potassium increased			

subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 90 (1.11%)
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			
Epilepsy			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Febrile convulsion			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 107 (0.93%)	1 / 104 (0.96%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 90 (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
Petit mal epilepsy			
subjects affected / exposed	2 / 107 (1.87%)	0 / 104 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Seizure			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 90 (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
Syncope			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Tonic convulsion			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Bronchospasm			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Sleep apnoea syndrome			

subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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			
Autism spectrum disorder			
subjects affected / exposed	1 / 107 (0.93%)	0 / 104 (0.00%)	0 / 90 (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
Intentional self-injury			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	0 / 90 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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
Hypokalaemia			
subjects affected / exposed	2 / 107 (1.87%)	0 / 104 (0.00%)	0 / 90 (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
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 107 (0.00%)	1 / 104 (0.96%)	0 / 90 (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

Serious adverse events	S95008/S95008 - Combined period	S95008 - Extension period	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 83 (12.05%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (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	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			

subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (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			
Asthma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Autism spectrum disorder			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	2 / 83 (2.41%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	97 / 107 (90.65%)	84 / 104 (80.77%)	77 / 90 (85.56%)
Investigations			
Urine calcium increased			
subjects affected / exposed	5 / 107 (4.67%)	0 / 104 (0.00%)	1 / 90 (1.11%)
occurrences (all)	5	0	1
Weight decreased			
subjects affected / exposed	10 / 107 (9.35%)	1 / 104 (0.96%)	5 / 90 (5.56%)
occurrences (all)	13	1	7
Weight increased			
subjects affected / exposed	9 / 107 (8.41%)	9 / 104 (8.65%)	2 / 90 (2.22%)
occurrences (all)	13	9	3
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	3 / 107 (2.80%)	4 / 104 (3.85%)	0 / 90 (0.00%)
occurrences (all)	3	4	0
Headache			
subjects affected / exposed	9 / 107 (8.41%)	12 / 104 (11.54%)	6 / 90 (6.67%)
occurrences (all)	14	17	8
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 107 (11.21%)	12 / 104 (11.54%)	6 / 90 (6.67%)
occurrences (all)	13	13	6
Pyrexia			

subjects affected / exposed	8 / 107 (7.48%)	7 / 104 (6.73%)	11 / 90 (12.22%)
occurrences (all)	9	10	13
Thirst			
subjects affected / exposed	50 / 107 (46.73%)	31 / 104 (29.81%)	36 / 90 (40.00%)
occurrences (all)	59	32	40
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 107 (5.61%)	8 / 104 (7.69%)	7 / 90 (7.78%)
occurrences (all)	7	8	10
Constipation			
subjects affected / exposed	6 / 107 (5.61%)	1 / 104 (0.96%)	2 / 90 (2.22%)
occurrences (all)	6	1	2
Diarrhoea			
subjects affected / exposed	13 / 107 (12.15%)	13 / 104 (12.50%)	4 / 90 (4.44%)
occurrences (all)	22	16	5
Dry mouth			
subjects affected / exposed	24 / 107 (22.43%)	14 / 104 (13.46%)	14 / 90 (15.56%)
occurrences (all)	24	15	15
Nausea			
subjects affected / exposed	5 / 107 (4.67%)	7 / 104 (6.73%)	4 / 90 (4.44%)
occurrences (all)	7	10	6
Vomiting			
subjects affected / exposed	8 / 107 (7.48%)	7 / 104 (6.73%)	10 / 90 (11.11%)
occurrences (all)	11	12	12
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 107 (3.74%)	7 / 104 (6.73%)	2 / 90 (2.22%)
occurrences (all)	4	7	3
Psychiatric disorders			
Affect lability			
subjects affected / exposed	5 / 107 (4.67%)	3 / 104 (2.88%)	1 / 90 (1.11%)
occurrences (all)	8	3	1
Aggression			
subjects affected / exposed	4 / 107 (3.74%)	5 / 104 (4.81%)	6 / 90 (6.67%)
occurrences (all)	6	6	7
Anger			

subjects affected / exposed	8 / 107 (7.48%)	3 / 104 (2.88%)	1 / 90 (1.11%)
occurrences (all)	9	4	2
Anxiety			
subjects affected / exposed	8 / 107 (7.48%)	7 / 104 (6.73%)	4 / 90 (4.44%)
occurrences (all)	10	7	4
Depressed mood			
subjects affected / exposed	4 / 107 (3.74%)	3 / 104 (2.88%)	1 / 90 (1.11%)
occurrences (all)	4	5	1
Insomnia			
subjects affected / exposed	5 / 107 (4.67%)	4 / 104 (3.85%)	0 / 90 (0.00%)
occurrences (all)	6	4	0
Irritability			
subjects affected / exposed	9 / 107 (8.41%)	10 / 104 (9.62%)	5 / 90 (5.56%)
occurrences (all)	10	12	7
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	12 / 107 (11.21%)	2 / 104 (1.92%)	7 / 90 (7.78%)
occurrences (all)	13	2	8
Polyuria			
subjects affected / exposed	29 / 107 (27.10%)	12 / 104 (11.54%)	19 / 90 (21.11%)
occurrences (all)	31	12	21
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 107 (0.00%)	0 / 104 (0.00%)	5 / 90 (5.56%)
occurrences (all)	0	0	5
Influenza			
subjects affected / exposed	6 / 107 (5.61%)	5 / 104 (4.81%)	1 / 90 (1.11%)
occurrences (all)	6	5	1
Nasopharyngitis			
subjects affected / exposed	13 / 107 (12.15%)	5 / 104 (4.81%)	8 / 90 (8.89%)
occurrences (all)	17	6	11
Rhinitis			
subjects affected / exposed	3 / 107 (2.80%)	2 / 104 (1.92%)	2 / 90 (2.22%)
occurrences (all)	3	2	4
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	21 / 107 (19.63%)	8 / 104 (7.69%)	3 / 90 (3.33%)
occurrences (all)	21	10	3
Hypokalaemia			
subjects affected / exposed	20 / 107 (18.69%)	4 / 104 (3.85%)	16 / 90 (17.78%)
occurrences (all)	27	5	23
Increased appetite			
subjects affected / exposed	17 / 107 (15.89%)	9 / 104 (8.65%)	4 / 90 (4.44%)
occurrences (all)	20	9	4

Non-serious adverse events	S95008/S95008 - Combined period	S95008 - Extension period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 83 (98.80%)	10 / 27 (37.04%)	
Investigations			
Urine calcium increased			
subjects affected / exposed	5 / 83 (6.02%)	0 / 27 (0.00%)	
occurrences (all)	7	0	
Weight decreased			
subjects affected / exposed	9 / 83 (10.84%)	0 / 27 (0.00%)	
occurrences (all)	14	0	
Weight increased			
subjects affected / exposed	12 / 83 (14.46%)	0 / 27 (0.00%)	
occurrences (all)	21	0	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	5 / 83 (6.02%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Headache			
subjects affected / exposed	9 / 83 (10.84%)	2 / 27 (7.41%)	
occurrences (all)	19	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 83 (10.84%)	1 / 27 (3.70%)	
occurrences (all)	11	1	
Pyrexia			

subjects affected / exposed	12 / 83 (14.46%)	0 / 27 (0.00%)	
occurrences (all)	14	0	
Thirst			
subjects affected / exposed	47 / 83 (56.63%)	0 / 27 (0.00%)	
occurrences (all)	69	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 83 (13.25%)	1 / 27 (3.70%)	
occurrences (all)	17	1	
Constipation			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Diarrhoea			
subjects affected / exposed	11 / 83 (13.25%)	1 / 27 (3.70%)	
occurrences (all)	22	1	
Dry mouth			
subjects affected / exposed	22 / 83 (26.51%)	0 / 27 (0.00%)	
occurrences (all)	29	0	
Nausea			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	8	0	
Vomiting			
subjects affected / exposed	8 / 83 (9.64%)	0 / 27 (0.00%)	
occurrences (all)	13	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	10	0	
Aggression			
subjects affected / exposed	2 / 83 (2.41%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Anger			

subjects affected / exposed	7 / 83 (8.43%)	0 / 27 (0.00%)	
occurrences (all)	8	0	
Anxiety			
subjects affected / exposed	7 / 83 (8.43%)	0 / 27 (0.00%)	
occurrences (all)	13	0	
Depressed mood			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Insomnia			
subjects affected / exposed	9 / 83 (10.84%)	0 / 27 (0.00%)	
occurrences (all)	11	0	
Irritability			
subjects affected / exposed	10 / 83 (12.05%)	0 / 27 (0.00%)	
occurrences (all)	13	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	9 / 83 (10.84%)	0 / 27 (0.00%)	
occurrences (all)	11	0	
Polyuria			
subjects affected / exposed	28 / 83 (33.73%)	1 / 27 (3.70%)	
occurrences (all)	32	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 83 (4.82%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Influenza			
subjects affected / exposed	7 / 83 (8.43%)	0 / 27 (0.00%)	
occurrences (all)	7	0	
Nasopharyngitis			
subjects affected / exposed	17 / 83 (20.48%)	1 / 27 (3.70%)	
occurrences (all)	25	1	
Rhinitis			
subjects affected / exposed	6 / 83 (7.23%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	18 / 83 (21.69%)	0 / 27 (0.00%)	
occurrences (all)	18	0	
Hypokalaemia			
subjects affected / exposed	22 / 83 (26.51%)	3 / 27 (11.11%)	
occurrences (all)	34	7	
Increased appetite			
subjects affected / exposed	16 / 83 (19.28%)	0 / 27 (0.00%)	
occurrences (all)	20	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 addition of the mention that additional pregnancy tests could be performed during the study according to local regulations and/or if the medical doctor deemed them as necessary and the update of the potassium supplementation recommendations in case of hypokalaemia.
12 December 2018	-Amendment No. 2 applicable in all countries, mainly aimed 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. 9, 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 3 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