Clinical trial results:
A Phase II dose ranging study of Bumetanide solution in children and adolescents with autism spectrum disorders.

Summary

EudraCT number	2013-003259-39
Trial protocol	ES FR
Global end of trial date	06 July 2016

Results information

Result version number	v1 (current)
This version publication date	18 August 2021
First version publication date	18 August 2021

Trial information

Trial identification

Sponsor protocol code	NeuroClin02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Neurochlore
Sponsor organisation address	Parc Scientifique et Technologique de Luminy Bâtiment Beret Delaage Zone Luminy Biotec, Marseille, France, 13288
Public contact	director of drug development, Neurochlore, denis.ravel@initial-rd.fr
Scientific contact	director of drug development, Neurochlore , denis.ravel@initial-rd.fr

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	10 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2016
Global end of trial reached?	Yes
Global end of trial date	06 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the optimal dose strength of Bumetanide for the pivotal Phase III studies.

Age and gender characteristics as well as type of developmental disorder were not available for the completer's subject analysis set. Approximate values have therefore been entered in order to ensure the technical validation of the file.

Protection of trial subjects:

The Investigator was responsible for ensuring that the investigation was conducted according to the signed Investigator agreement, the protocol, good clinical practice guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator’s care; and for the control of investigational products under investigation. The Investigator at each study center was responsible for the management of the study, which consisted of maintaining the study file and patient records, corresponding with the IRB/IEC, and completing the electronic case report forms (eCRFs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	72
Adolescents (12-17 years)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 91 patients signed informed consent from January 2014 to July 2015. Three were found not to meet inclusion or exclusion criteria. A total of 88 subjects were included in the study at 7 clinical sites located in France. A total of 72 patients has completed the study.

Pre-assignment

Screening details:

Main inclusion criteria: male or female, children and adolescents, 2-18 years old, with ASD according to ICD-10 [F84.0 (Childhood Autism) or F84.5 (Asperger's Syndrome)], CARS (Childhood Autism Rating Scale) score > 34, criteria for Autism on ADOS-G (Autism Diagnosis Observation Schedule-General) and ADI-R (Autism Diagnosis Interview-Revised).

Pre-assignment period milestones

Number of subjects started	91[1]
Number of subjects completed	88

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period is considered as the screening phase. 91 patients were screened, 3 were screen failures, hence the worldwide number of patients actually enrolled in the trial is 88.

Period 1

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

Blinding implementation details:

The study team at site including investigators, nurses and pharmacists, patients and patient's parent[s]. They remained blinded until database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bumetanide low dose

Arm description:

oral administration, liquid formulation, 0.5 mg BID for 3 months, for patients below 25 kg (0.02 mg/kg BID)

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

Dosage and administration details:

Double-blind placebo-controlled study:
Patients received Bumetanide (0.5, 1.0 or 2.0 mg BID) for 3 months. Dose was calculated on a body weight basis for patients below 25 kg (0.02, 0.04 or 0.08 mg/kg, BID).

Arm title	Bumetanide medium dose

Arm description:	
oral administration, liquid formulation, 1.0 mg BID for 3 months, for patients below 25 kg (0.04 mg/kg, BID)	
Arm type	Experimental
Investigational medicinal product name	Bumetanide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
Double-blind placebo-controlled study: Patients received Bumetanide (0.5, 1.0 or 2.0 mg BID) for 3 months. Dose was calculated on a body weight basis for patients below 25 kg (0.02, 0.04 or 0.08 mg/kg, BID).	
Arm title	Bumetanide high dose
Arm description:	
oral administration, liquid formulation, 2.0 mg BID for 3 months, for patients below 25 kg (0.08mg/kg,BID)	
Arm type	Experimental
Investigational medicinal product name	Bumetanide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
Double-blind placebo-controlled study: Patients received Bumetanide (0.5, 1.0 or 2.0 mg BID) for 3 months. Dose was calculated on a body weight basis for patients below 25 kg (0.02, 0.04 or 0.08 mg/kg, BID).	
Arm title	Placebo
Arm description:	
oral administration, liquid formulation, Placebo for 3 months	
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:	
Double-blind placebo-controlled study: Patients received placebo for 3 months.	

Number of subjects in period 1	Bumetanide low dose	Bumetanide medium dose	Bumetanide high dose
Started	20	23	22
Completed	20	19	13
Not completed	0	4	9
Adverse event, not serious	-	2	5
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Protocol violation	-	1	1

Adverse event, serious non-fatal	-	1	1
Lost to follow-up	-	-	1

Number of subjects in period 1	Placebo
Started	23
Completed	20
Not completed	3
Adverse event, not serious	1
Consent withdrawn by subject	-
Physician decision	1
Protocol violation	1
Adverse event, serious non-fatal	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Bumetanide low dose
Reporting group description:	
oral administration, liquid formulation, 0.5 mg BID for 3 months, for patients below 25 kg (0.02 mg/kg BID)	
Reporting group title	Bumetanide medium dose
Reporting group description:	
oral administration, liquid formulation, 1.0 mg BID for 3 months, for patients below 25 kg (0.04 mg/kg, BID)	
Reporting group title	Bumetanide high dose
Reporting group description:	
oral administration, liquid formulation, 2.0 mg BID for 3 months, for patients below 25 kg (0.08mg/kg,BID)	
Reporting group title	Placebo
Reporting group description:	
oral administration, liquid formulation, Placebo for 3 months	

Reporting group values	Bumetanide low dose	Bumetanide medium dose	Bumetanide high dose
Number of subjects	20	23	22
Age categorical			
Children and adolescents (2-18 years)			
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)	16	18	16
Adolescents (12-17 years)	4	5	6
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	4	1	1
Male	16	22	21
Type of developmental disorder			
Demographic characteristics were comparable between the Bumetanide and placebo treated groups. Patients in the FAS had a mean age of 8.26 years (SD=4.53) and the majority of patients were male (78 patients, 88.6%). The majority of patients had an initial diagnosis of F84.0 (Childhood Autism), (82 patients, 93.2%). Six patients (6.8%) had an initial diagnosis of F84.5 (Asperger's Syndrome).			
Units: Subjects			
F84.0 (Childhood Autism)	18	23	21
F84.5 (Asperger's Syndrome)	2	0	1

Reporting group values	Placebo	Total	
Number of subjects	23	88	

Age categorical			
Children and adolescents (2-18 years)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	16	66	
Adolescents (12-17 years)	7	22	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	4	10	
Male	19	78	
Type of developmental disorder			
Demographic characteristics were comparable between the Bumetanide and placebo treated groups. Patients in the FAS had a mean age of 8.26 years (SD=4.53) and the majority of patients were male (78 patients, 88.6%). The majority of patients had an initial diagnosis of F84.0 (Childhood Autism), (82 patients, 93.2%). Six patients (6.8%) had an initial diagnosis of F84.5 (Asperger's Syndrome).			
Units: Subjects			
F84.0 (Childhood Autism)	20	82	
F84.5 (Asperger's Syndrome)	3	6	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS) - Bumetanide low dose
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Bumetanide medium dose
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Bumetanide high dose
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomised patients.	
Subject analysis set title	Completer's analysis - Bumetanide low dose
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients from the FAS who completed the study with CARS evaluation at Day 90.	
Subject analysis set title	Completer's analysis - Bumetanide medium dose
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients from the FAS who completed the study with CARS evaluation at Day 90.	

Subject analysis set title	Completer's analysis - Bumetanide high dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	
Subject analysis set title	Completer's analysis - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	

Reporting group values	Full Analysis Set (FAS) - Bumetanide low dose	Full Analysis Set (FAS) - Bumetanide medium dose	Full Analysis Set (FAS) - Bumetanide high dose
Number of subjects	20	23	22
Age categorical			
Children and adolescents (2-18 years)			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	16	18	16
Adolescents (12-17 years)	4	5	6
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical			
Units: Subjects			
Female	4	1	1
Male	16	22	21
Type of developmental disorder			
Demographic characteristics were comparable between the Bumetanide and placebo treated groups. Patients in the FAS had a mean age of 8.26 years (SD=4.53) and the majority of patients were male (78 patients, 88.6%). The majority of patients had an initial diagnosis of F84.0 (Childhood Autism), (82 patients, 93.2%). Six patients (6.8%) had an initial diagnosis of F84.5 (Asperger's Syndrome).			
Units: Subjects			
F84.0 (Childhood Autism)	18	23	21
F84.5 (Asperger's Syndrome)	2	0	1

Reporting group values	Full Analysis Set (FAS) - Placebo	Completer's analysis - Bumetanide low dose	Completer's analysis - Bumetanide medium dose
Number of subjects	23	20	19
Age categorical			
Children and adolescents (2-18 years)			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	16	16	16
Adolescents (12-17 years)	7	4	3

Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female	4	4	1
Male	19	16	18
Type of developmental disorder			
Demographic characteristics were comparable between the Bumetanide and placebo treated groups. Patients in the FAS had a mean age of 8.26 years (SD=4.53) and the majority of patients were male (78 patients, 88.6%). The majority of patients had an initial diagnosis of F84.0 (Childhood Autism), (82 patients, 93.2%). Six patients (6.8%) had an initial diagnosis of F84.5 (Asperger's Syndrome).			
Units: Subjects			
F84.0 (Childhood Autism)	20	18	19
F84.5 (Asperger's Syndrome)	3	2	0

Reporting group values	Completer's analysis - Bumetanide high dose	Completer's analysis - Placebo	
Number of subjects	13	21	
Age categorical			
Children and adolescents (2-18 years)			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	11 2	15 6	
Gender categorical Units: Subjects			
Female	1	3	
Male	12	18	
Type of developmental disorder			
Demographic characteristics were comparable between the Bumetanide and placebo treated groups. Patients in the FAS had a mean age of 8.26 years (SD=4.53) and the majority of patients were male (78 patients, 88.6%). The majority of patients had an initial diagnosis of F84.0 (Childhood Autism), (82 patients, 93.2%). Six patients (6.8%) had an initial diagnosis of F84.5 (Asperger's Syndrome).			
Units: Subjects			
F84.0 (Childhood Autism)	12	19	
F84.5 (Asperger's Syndrome)	1	2	

End points

End points reporting groups

Reporting group title	Bumetanide low dose
Reporting group description:	
oral administration, liquid formulation, 0.5 mg BID for 3 months, for patients below 25 kg (0.02 mg/kg BID)	
Reporting group title	Bumetanide medium dose
Reporting group description:	
oral administration, liquid formulation, 1.0 mg BID for 3 months, for patients below 25 kg (0.04 mg/kg, BID)	
Reporting group title	Bumetanide high dose
Reporting group description:	
oral administration, liquid formulation, 2.0 mg BID for 3 months, for patients below 25 kg (0.08mg/kg,BID)	
Reporting group title	Placebo
Reporting group description:	
oral administration, liquid formulation, Placebo for 3 months	
Subject analysis set title	Full Analysis Set (FAS) - Bumetanide low dose
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Bumetanide medium dose
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Bumetanide high dose
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was defined as all randomised patients.	
Subject analysis set title	Full Analysis Set (FAS) - Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS was defined as all randomised patients.	
Subject analysis set title	Completer's analysis - Bumetanide low dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	
Subject analysis set title	Completer's analysis - Bumetanide medium dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	
Subject analysis set title	Completer's analysis - Bumetanide high dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	
Subject analysis set title	Completer's analysis - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the FAS who completed the study with CARS evaluation at Day 90.	

Primary: Childhood Autism Rating Scale (CARS)

End point title	Childhood Autism Rating Scale (CARS)

End point description:

The CARS is a tool used to diagnose Autism for children and adolescents, and to measure the intensity of ASD. The scale contains 15 items. The first 14 ones represents different domains of child functioning and the last one is a global rating of Autism. Each item is a 4-point scale from 1, normal functioning to 4, severely disrupted functioning. Results of each item are summed up for a final score between 15 and 60. The CARS classification allows to distinguish several categories: autistic features, mild, moderate and severe autism. A reduction in CARS corresponds to an improvement.

End point type	Primary

End point timeframe:

Change in CARS from screening to Day 90 (LOCF)

End point values	Full Analysis Set (FAS) - Bumetanide low dose	Full Analysis Set (FAS) - Bumetanide medium dose	Full Analysis Set (FAS) - Bumetanide high dose	Full Analysis Set (FAS) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	23	22	23
Units: score				
arithmetic mean (standard deviation)				
Change from screening to Day 90 (LOCF)	-4.98 (± 4.33)	-3.09 (± 3.3)	-3.16 (± 3.98)	-1.63 (± 2.34)

End point values	Completer's analysis - Bumetanide low dose	Completer's analysis - Bumetanide medium dose	Completer's analysis - Bumetanide high dose	Completer's analysis - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	19	13	21
Units: score				
arithmetic mean (standard deviation)				
Change from screening to Day 90 (LOCF)	-4.98 (± 4.33)	-3.74 (± 3.28)	-5.35 (± 3.88)	-1.79 (± 2.39)

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary analysis of the primary endpoint was an intent-to-treat analysis, performed using the Full Analysis Set (FAS) with imputation of no change when the result for Day 90 was missing, provided the patient received at least one dose of treatment. The treatment groups were compared using the Kruskal-Wallis test with Steel-Dwass adjusted pair-wise comparisons.

Comparison groups	Full Analysis Set (FAS) - Bumetanide low dose v Full Analysis Set (FAS) - Bumetanide medium dose v Full Analysis Set (FAS) - Bumetanide high dose v Full Analysis Set (FAS) - Placebo v Completer's analysis - Bumetanide low dose v Completer's analysis - Bumetanide medium dose v Completer's analysis - Bumetanide high dose v Completer's analysis - Placebo

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0689
Method	Kruskal-wallis

Statistical analysis title	Change in CARS from Screening to Day 90

Statistical analysis description:

Full Analysis Set (FAS)
The FAS was defined as all patients who are randomised. The FAS was used for all efficacy analyses..
Change in CARS from Screening to Day 90
If total CARS score was missing at Day 90 the screening score was imputed for Day 90 (Last Observation Carried Forward [LOCF] imputation).
The treatment groups are compared using the Kruskal-Wallis test
The analyses are repeated without the imputation as a completers analysis.

Comparison groups	Completer's analysis - Bumetanide low dose v Completer's analysis - Bumetanide medium dose v Completer's analysis - Bumetanide high dose v Completer's analysis - Placebo v Full Analysis Set (FAS) - Placebo v Full Analysis Set (FAS) - Bumetanide high dose v Full Analysis Set (FAS) - Bumetanide medium dose v Full Analysis Set (FAS) - Bumetanide low dose
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0689
Method	Kruskal-wallis
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: Social Responsiveness Scale (SRS)

End point title	Social Responsiveness Scale (SRS)

End point description:

SRS, a brief quantitative 65-item rating scale of autistic behaviours designed to be completed by an adult who is familiar with the child's current behaviour and developmental history was administered and scores were obtained for five treatment subscales: Social awareness, social cognition, social communication, social motivation and autistic mannerisms.

End point type	Secondary

End point timeframe:

Score change from screening to Day 90

End point values	Completer's analysis - Bumetanide low dose	Completer's analysis - Bumetanide medium dose	Completer's analysis - Bumetanide high dose	Completer's analysis - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	19	13	21
Units: score				
arithmetic mean (standard deviation)				

Change from screening to Day 90 (LOCF)	-12.36 (± 23.57)	-13.17 (± 20.45)	-21.83 (± 19.78)	-1.55 (± 20.38)

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

The same analysis as the primary analysis was repeated on the completers set. The treatment groups were compared using the Kruskal-Wallis test with Steel-Dwass adjusted pair-wise comparisons.

Comparison groups	Completer's analysis - Bumetanide low dose v Completer's analysis - Bumetanide high dose v Completer's analysis - Placebo v Completer's analysis - Bumetanide medium dose
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0202
Method	Kruskal-wallis

Statistical analysis title	Secondary analysis

Statistical analysis description:

The same analysis as the primary analysis was repeated on the completers set. The treatment groups were compared using the Kruskal-Wallis test with Steel-Dwass adjusted pair-wise comparisons.

Comparison groups	Completer's analysis - Bumetanide high dose v Completer's analysis - Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [1]
Method	Steel-Dwass test

Notes:

[1] - Pair-wise comparison 2 mg Bumetanide group vs Placebo

Secondary: Clinical Global Impression-Improvement (CGI-I)

End point title	Clinical Global Impression-Improvement (CGI-I)

End point description:

The child psychiatric compared the patient’s overall clinical condition to the baseline visit using a seven-point scale, ranging from very much improved (1) to very much worse (7).

Very much improved
Much improved
Minimally improved
No change
Minimally worse
Much worse
Very much worse
Not assessed/missing

End point type	Secondary

End point timeframe:

CGI-I improvement was assessed at baseline, at the end of the treatment phase

End point values	Full Analysis Set (FAS) - Bumetanide low dose	Full Analysis Set (FAS) - Bumetanide medium dose	Full Analysis Set (FAS) - Bumetanide high dose	Full Analysis Set (FAS) - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	23	22	23
Units: score				
Very much improved	0	0	1	0
Much improved	7	5	5	1
Minimally improved	7	10	7	10
No change	4	4	0	9
Minimally worse	1	0	0	1
Much worse	0	0	0	0
Very much worse	0	0	0	0
Not assessed/missing	1	4	9	2

Statistical analyses

Statistical analysis title	kruskal wallis
Comparison groups	Full Analysis Set (FAS) - Bumetanide low dose v Full Analysis Set (FAS) - Bumetanide medium dose v Full Analysis Set (FAS) - Bumetanide high dose v Full Analysis Set (FAS) - Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0043
Method	Kruskal-wallis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of signing informed consent to the last study visit

Adverse event reporting additional description:

The safety population included all randomly assigned participants who received at least 1 dose of double-blind study drug. A total of 64 participants in the 3 Bumetanide groups and 22 participants in the placebo group received at least 1 dose of double-blind study medication and were included in the safety analysis set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	Lay language
Dictionary version	1

Reporting groups

Reporting group title	Bumetanide low dose

Reporting group description:

Patients received 0.5 mg BID Bumetanide for 3 months.
Dose was calculated on a body weight basis for patients below 25 kg (0.02 mg/kg, BID).

Reporting group title	Bumetanide medium dose

Reporting group description:

Patients received 1.0 mg BID Bumetanide for 3 months.
Dose was calculated on a body weight basis for patients below 25 kg (0.04 mg/kg, BID).

Reporting group title	Bumetanide high dose

Reporting group description:

Patients received 2.0 mg BID Bumetanide for 3 months.
Dose was calculated on a body weight basis for patients below 25 kg (0.08 mg/kg, BID).

Reporting group title	Placebo

Reporting group description:

Patients received placebo for 3 months.

Serious adverse events	Bumetanide low dose	Bumetanide medium dose	Bumetanide high dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Social circumstances			
Right broken leg			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Accidental overdose due to parent's inattentiveness			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 22 (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
Metabolism and nutrition disorders			
Hypokalaemia			
alternative dictionary used: Lay language 1			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Social circumstances			
Right broken leg			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Accidental overdose due to parent's inattentiveness			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
alternative dictionary used: Lay language 1			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bumetanide low dose	Bumetanide medium dose	Bumetanide high dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	22 / 23 (95.65%)	21 / 22 (95.45%)
Nervous system disorders			
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	3 / 22 (13.64%)
occurrences (all)	0	1	3
Irritability	Additional description: irritable and anxious behavior,		
subjects affected / exposed	2 / 20 (10.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Sleep disorder			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Agitation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	3 / 22 (13.64%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Diuresis, enuresis, polyuria pollakiuria			
subjects affected / exposed	2 / 20 (10.00%)	8 / 23 (34.78%)	11 / 22 (50.00%)
occurrences (all)	4	12	13
Loss of appetite, anorexia			
subjects affected / exposed	0 / 20 (0.00%)	7 / 23 (30.43%)	9 / 22 (40.91%)
occurrences (all)	0	7	9
Asthenia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 23 (8.70%)	3 / 22 (13.64%)
occurrences (all)	2	2	4
Hyperuricemia			
subjects affected / exposed	1 / 20 (5.00%)	3 / 23 (13.04%)	1 / 22 (4.55%)
occurrences (all)	2	3	1
Hypochloremia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	4 / 22 (18.18%)
occurrences (all)	0	1	4
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	5 / 22 (22.73%)
occurrences (all)	0	1	5
Diarrhea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	0	4	0
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	2	1	2
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Sweating			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	1	2
Endocrine disorders			
Polydipsia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 23 (8.70%)	2 / 22 (9.09%)
occurrences (all)	1	2	2
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 20 (30.00%)	14 / 23 (60.87%)	16 / 22 (72.73%)
occurrences (all)	6	20	22
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	3 / 23 (13.04%)	6 / 22 (27.27%)
occurrences (all)	0	3	6
Weight loss			
subjects affected / exposed	0 / 20 (0.00%)	3 / 23 (13.04%)	3 / 22 (13.64%)
occurrences (all)	0	3	3

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)		
Nervous system disorders			
Nausea			

subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Irritability	Additional description: irritable and anxious behavior,		
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Diuresis, enuresis, polyuria pollakiuria			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Loss of appetite, anorexia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Hyperuricemia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Hypochloremia			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Diarrhea			

subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0		
Skin and subcutaneous tissue disorders Sweating subjects affected / exposed occurrences (all)	 0 / 23 (0.00%) 0		
Endocrine disorders Polydipsia subjects affected / exposed occurrences (all)	 0 / 23 (0.00%) 0		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all)	 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2015	Amendment 01: Open label extension. A 6-month extension study of Bumetanide 0.5 mg/mL solution. The proposed continued use of Bumetanide was for compassionate purposes and was not considered within the development framework of Bumetanide in ASD patients. Participation in the extension phase was on a voluntary basis. Nineteen patients were enrolled in the extension phase. Bumetanide was given at 0.5 or 1 mg BID. The primary objective was to provide Bumetanide to patients who were enrolled in the NeuroClin02 study. The secondary objective was to collect additional safety data. No specific ASD outcomes were included. The extension was conducted in 3 clinical centres in France, 19 patients entered the extension.

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.

Only the drug-related adverse events have been listed in line with the information presented in the Clinical Study Report.

Notes: