Clinical Trial Summary

Efficacy and safety of bumetanide oral liquid formulation in children aged from 2 to less than 7 years old with Autism Spectrum Disorder.

Full scientific title: 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.

We thank all the participants who took part in the study. Clinical study participants are very important for making progress in science, for the benefit of patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for patients. For medical science to progress, many studies involving patients are running all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results. You should not change your current treatment or that of your children based on the results of this single study. If you have any questions about this study, please talk to your doctor.

Therapeutic area: Psychiatry

Disease: Autism Spectrum Disorder (ASD)

Study phase: Phase 3

CL3-95008-002

Final version: 25th April 2022

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1 Why was this study done?

This study was done to test if a drug called bumetanide could help children with Autism Spectrum Disorder (ASD).

ASD has many different symptoms. For example, difficulties in communication and relationships with others.

Bumetanide is a well-known drug which helps remove water, salt and chloride from the body. Too much chloride in the brain cells could affect how the brain develops and works in people with ASD. Bumetanide helps reduce the amount of chloride in the brain cells.
In a previous study, bumetanide was linked to an improvement in some of the symptoms of children with ASD. Researchers needed to confirm this in a study with a larger number of patients called a Phase 3 study.

The main goal of this Phase 3 study was to confirm if bumetanide improves ASD symptoms in children. To do this, it was compared with a placebo.

A placebo looks like a medicine but does not contain any real medicine.

2 When and where did this study take place?

When did the study take place?

- This study started in October 2018.
- It ended in October 2021.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
Spain	33
Brazil	30
Italy	30
Poland	27
France	23
United Kingdom	22
Hungary	16
Czech Republic	12
Portugal	6
Slovakia	5
Australia	4
USA	3

3 Who participated in the study?

Which participants were included in the study?

To take part, participants had to:

- Be a child (from 2 to under 7 years old)
- Have a moderate to severe Autism Spectrum Disorder before the study.

How many participants took part in the study?

A total of 211 participants joined the study.
About 5 participants out of 6 were boys.

How old were the participants?

The average age of the participants was 4 years and half. The youngest participant was 2 years old and the oldest was 6 years old.

4 Which treatments did the participants receive?

During the first part of the study (which lasted for 6 months), the participants received either:

- The study drug or
- A placebo.

During the second part of the study (which also lasted for 6 months), the participants all received the study drug.

The study drug is called bumetanide. It is an oral solution of 0.5 milligrams (mg) of bumetanide per millilitre (mL).
The placebo looked like bumetanide (oral solution) but did not contain any real medicine.

The participants took the solution orally in the morning after waking up and in the afternoon, 3 hours before going to bed.

5 How was the study carried out?

The study was split into different periods:

Before starting the treatment, there was a 4-week period called a **run-in period**, in which no drug were taken. This was done to check if the participants could join the study.

Then, there were **2 treatment periods**. Each lasted for 6 months.

- First part of the study:

The study was called a randomised study. This means that the participants were put by chance into one of the 2 following groups of treatment:

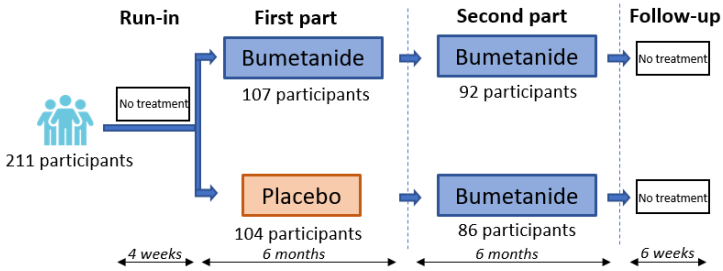
- Bumetanide (107 participants),
- Placebo (104 participants).

This part was double-blind. This means that neither the participants nor their parents nor the doctors knew which treatment was taken. This was to avoid any influence on the results.

- Second part of the study:

Out of the 211 participants who were included in the first part, 178 participants entered the second part. They all received bumetanide. This part was open-label. This means that the participants, the parents, and the doctors knew that only bumetanide was taken.

At the end of this period, there was a 6-week **follow-up period** in which no drug was taken.



The participants visited the doctors regularly. During the visits, the doctors collected information about the participants' health.

6 What were the side effects?

Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.

In this summary, we describe unwanted medical events thought to be potentially caused by either bumetanide or placebo.

The results may be presented differently in other documents related to the study.

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The table below shows the number of participants who had side effects:

	First part of the study		Second part of the study in participants who started with placebo	Participants treated with bumetanide during the whole study
	Bumetanide (out of 107 participants)	Placebo (out of 104 participants)	Bumetanide (out of 92 participants)	Bumetanide (out of 84 participants)
Participants who had side effect(s)	90 (84.1%)	58 (55.8%)	63 (68.5%)	74 (88.1%)
Participants who had serious* side effect(s)	4 (3.7%)	1 (1.0%)	0	3 (3.6%)
Participants who stopped the treatment because of side effect(s)	9 (8.4%)	7 (6.7%)	2 (2.2%)	5 (6.0%)

**See definition of serious side effects below*

= Participants

What were the side effects?

The table below shows the most common side effects reported in the study (reported by more than 10 participants who took bumetanide during the first part of the study).

The most frequent side effects were related to the known diuretic activity of bumetanide.

	First part of the study		Second part of the study in participants who started with placebo	Participants treated with bumetanide during the whole study
	Bumetanide (out of 107 participants)	Placebo (out of 104 participants)	Bumetanide (out of 92 participants)	Bumetanide (out of 84 participants)
Thirst	60 (56.1%)	31 (29.8%)	30 (32.6%)	49 (58.3%)
Increase in urine production	39 (36.4%)	22 (21.2%)	25 (27.2%)	33 (39.3%)
Dry mouth	20 (18.7%)	9 (8.7%)	7 (7.6%)	19 (22.6%)
Low blood potassium level	18 (16.8%)	2 (1.9%)	21 (22.8%)	17 (20.2%)
Irritability	11 (10.3%)	2 (1.9%)	3 (3.3%)	12 (14.3%)

= Participants

= Most frequent side effects reported in the first and second parts of the study, and in the whole study.

What were the serious side effects?

A side effect is considered serious when:

- it causes lasting damage or death or,
- the participant's life is in danger or,
- the participant needs to be hospitalised or,
- it is medically important in the doctor's opinion.

In the first part of the study:

5 participants had serious side effects:

- With bumetanide:
  - Two participants had low blood potassium level.
  - One participant had stuffy and runny nose, diarrhoea and vomiting caused by a virus, and nosebleed.
  - One participant had hearing disorder.
- With placebo:
  - One participant had rapid swelling under the skin, inflammation of the eye caused by an allergic reaction, drug allergic reaction and hives.

In the second part of the study in participants who were previously taking placebo:
None of the participants had serious side effects with bumetanide.

In participants treated with bumetanide during the whole study:
3 participants had serious side effects:

- One participant had stuffy and runny nose, diarrhoea and vomiting caused by a virus, and nosebleed.
- One participant had hearing disorder
- One participant had sudden kidney failure

In the study, none of the participants died because of an unwanted event thought to be caused by bumetanide.

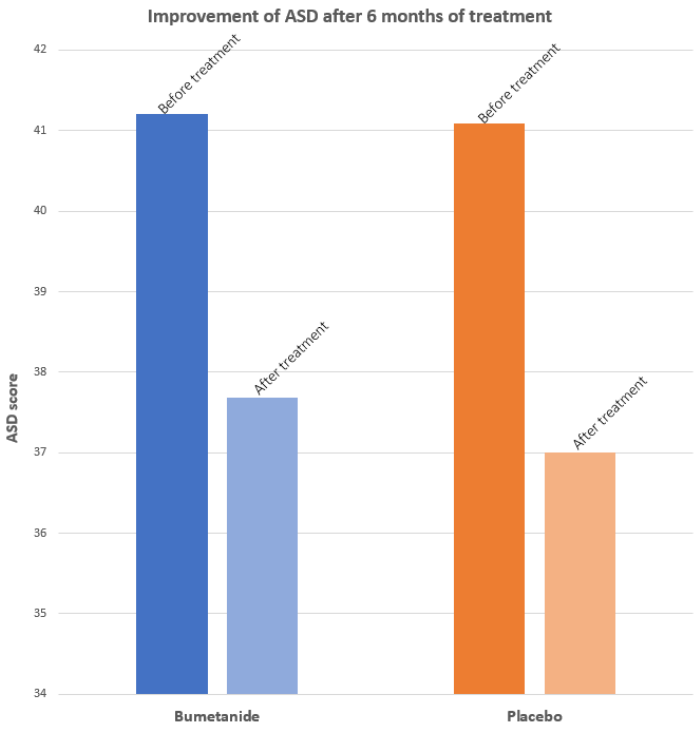
7 What were the study results?

The first part of the study was completed as planned. This document presents only the results for the main goal of the study. Other results are available in other documents listed in Section 10.

The doctors evaluated the symptoms of Autism Spectrum Disorder (ASD) at each visit. For that, they used a questionnaire called CARS2 (Childhood Autism Rating Scale-2). CARS2 was filled in by trained doctors after observing the participant. Where possible, the participant was evaluated by the same doctor throughout the study. At each visit, a CARS-2 score was obtained. The lower the score, the less severe the ASD symptoms.

After 6 months of treatment, the CARS2 score was lower in both the bumetanide and placebo groups. However, the difference between bumetanide and placebo was not in favour of an improvement of ASD with bumetanide.

The graph below shows how much the CARS2 score decreased in all participants over 6 months of treatment. The lower the light-coloured bar, the more the ASD improved.



Because of these results, the second part of the study was stopped early.

8 How has this study helped research?

Unfortunately, the study did not show that bumetanide works better than placebo in children with Autism Spectrum Disorder (ASD).

However, the study helped researchers get more information on ASD and how symptoms progress in children with ASD.

9 Are there plans for further studies?

No other studies with bumetanide are planned by Servier. Due to the study results, the sponsor decided to stop the development of bumetanide in ASD.

10 Further information

What are the identification numbers of the study?

- Protocol code: CL3-95008-002
- EudraCT number: 2017-004420-30
- US NCT number: NCT03715153

Who did the study?

The company that organised and funded the research, called the 'sponsor', is the Institut de Recherches Internationales Servier based in Suresnes, France.

How can you contact the sponsor?

Contact us on the Servier website: https://servier.com/en/

Where can you learn more about this study?

You can find more information about this study on these websites:

- https://clinicaltrials.servier.com
- https://www.clinicaltrialsregister.eu/ctr-search
- https://clinicaltrials.gov

In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary at https://clinicaltrials.servier.com/glossary/

You can find general information about clinical trials at https://clinicaltrials.servier.com/