# Bumetanide in Autism Medication and Biomarker study

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Mental impairment disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44696

**Source**
ToetsingOnline

**Brief title**
BAMBI

### Condition

- Mental impairment disorders
- Developmental disorders NEC

**Synonym**
autism, autism spectrum disorders

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** Ministerie van OC&W,ZonMW subsidie "Goed Gebruik Geneesmiddelen",De Franse biotech company Neurochlore betaalt een gedeelte van de medicatiekosten.,Neurochlore

## Intervention

**Keyword:** autism spectrum disorder, bumetanide, chloride, treatment

## Outcome measures

### Primary outcome

Primary endpoints will be the change in score on Social Responsiveness Scale

(SRS).

### Secondary outcome

Secondary endpoints will involve adaptive skill assessments; behavioral

symptoms relating to rigidity; sensory modulation profiles , resting state EEG,

sensory evoked EEG paradigms (ERP) and genetic analysis to predict treatment

response.

# Study description

### Background summary

Currently no treatments exist for the core symptoms of Autism Spectrum Disorder (ASD). Recently an old drug, bumetanide, has been proposed as a novel treatment for ASD. Bumetanide has been used for decades as a diuretic drug and its safety has been firmly established also in newborns and children. Bumetanide has a secondary function; in the brain bumetanide blocks the NKCC1 cation-chloride co-transporter, and thus decreases internal chloride concentration in neurons. In turn, this concentration change enhances the inhibitory action of the neurotransmitter *-aminobutyric acid (GABA) and may thus improve functioning of brain networks with disturbed chloride homeostasis. Recent pilot study from our group as well as a first trial in the literature point towards a beneficial effect of bumetanide on ASD morbidity and confirmed that the drug is safe to use in children provided that diuretic effects are monitored. If bumetanide would indeed improve GABAergic signaling and reduce hyperexcitability, then this treatment is not only expected to improve behavioral symptoms, but also the notoriously difficult to treat symptoms of sensory overload and cognitive distraction. In this grant proposal, we aim to perform a placebo-controlled randomized clinical trial to test efficacy bumetanide on ASD symptomatology and to derive prognostic biomarkers using cognitive, genetic and EEG assessments

before and after treatment.These studies may lead to a breakthrough in finding a rational, safe treatment for core features of ASD by repositioning of an off-patent drug.

## Study objective

The primary objective of the proposed study is to investigate whether bumetanide therapy indeed reduces autistic symptomatology. Important secondary goals of this project are to determine whether bumetanide will improve specific behavioral, neurocognitive, resting state EEG and sensory processing features.

## Study design

We will conduct a 91 day, double blind, randomized, placebo- controlled trial with bumetanide followed by a 28 day wash-out period. Eligible patients will be randomly assigned (1:1) to either bumetanide or placebo according to a computer-generated randomization schedule using a permuted block design, with stratification for gender and developmental age. Healthy controls will be tested on EEG and neurocognitive measurements to generate adequate reference values for the monitoring of the trial.

## Intervention

Patients will be treated with bumetanide according to a titration period twice daily or placebo, in the form of syrup, for 91 days followed by a 28-day washout after each treatment period.
For patients with a body weight of *30 kg: The investigational products consist of bumetanide or placebo and will be given at a dosage between 0.5mg and 1.0mg twice a day (before breakfast and at the end of the afternoon, at least 2.5 hours before bedtime) for 91 days. The IP will be administered in the formulation of a solution (1 mL per intake = 0.5 mg bumetanide or placebo) will be administered directly into the mouth by means of a graduated dosing syringe. Starting dosage will be 0.5 mg once a day, then the dose will be escalated to 0.5 mg twice a day on D7, if blood electrolytes are normal and no signs of dehydration are present after the first checking of blood and urine.
For patients with a body weight of <30 kg: the Bumetanide (0.5 mg/mL solution) or placebo dose will be calculated on a body weight basis. For these children, the starting amount will be 0.03 mg/kg divided over 2 dosages per day and escalated to 0.06mg/day in 2 dosages per day under the same physical conditions as described above. Parents and patients (as applicable) will be provided with user instructions to favor the correct and full administration of the IP solution.

## Study burden and risks

The burden and risks are acceptable while the benefits are expected to be

considerable. Since the 1970s, no serious adverse events were described after short or prolonged treatment with bumetanide as a diuretic drug in children or adults. The main adverse events are related to the diuretic activity of the molecule leading to a decrease in electrolytes, notably hypokalemia are frequently reported. The burden and risks are acceptable while the benefits are expected to be considerable. To monitor diuretic effects, physical examination and blood/urine tests will be performed 8 times with negligible and known risks. To monitor treatment effect, questionnaires, cognitive testing sessions and EEG investigations will be conducted 3 times. These tests are generally well tolerated and are non-invasive .
Bumetanide could be the first pharmacological treatment for the core symptoms of ASD acting on a key component of the pathophysiology of the disease. Bumetanide may not only improve behavioral symptoms but may also enhance cognitive functions and sensory processing. Since these phenomena are notoriously difficult to treat in ASD, this rational treatment may be very promising. The symptoms related to ASD and hyperexcitation in particular are important factors for the inability of patients to fully integrate in society, the potential benefits are enormous: the treatment is not only relatively safe and cheap (bumetanide is off-patent), but if successful, will also substantially reduce the (financial) burden on society. Patients, who otherwise have no medical treatment option and depend on extensive behavioral treatment and guidance, could now become integrated in society again. If successful, our studies may lead to bumetanide to become incorporated in the near future as the first rational treatment in the clinical guideline for ASD.

## Contacts

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## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

1. Males or females aged *7 years to *15 years;
2. Criteria met for autism spectrum disorder and on DSM-V Social Responsiveness Scale (SRS) (24).
3. Written informed consent.

## Exclusion criteria

1. Total IQ < 55 (WISC) and/or inability to comply with the protocol-specified procedures for the duration of the study, including treatment and blood sampling to control diuretic effects.
2. Serious, unstable illnesses including, gastroenterologic, respiratory, cardiovascular (arythmias, QT interval lengthening), endocrinologic, immunologic, hematologic disease, dehydration or hypotension;
3. Renal insufficiency (CKD st2-5; estimated glomerular filtration rate < 90 ml/min/1.73m2), congential or acquired renal disease with decreased concentration capacity (tubulopathy, diabetes insipidus) and liverinsufficiency interfering with excretion or metabolism of Bumetanide;
4. Neurological disorders such as epilepsy, seizures and microcephaly;
5. Start of behavioral treatment during study
6. Treatment with psychoactive medications (antipsychotics, antidepressants, anxiolytic drugs, psychostimulant drugs or other medication with effect on the central nervous system, including anti-epileptic drugs) in the last 8 weeks prior to start of the study, except melatonin; no use of other psychoactive substances is allowed from 8 weeks prior to the pre-study evaluation until the endpoint measurements at the end of the washout period. If clinically feasible and desired by the patients and/or parents, then it is allowed to stop psychoactive medication to allow enrollment in the study after a 8 week washout period of their psychoactive medication.
7. Treatment with NSAIDS, aminoglycosides, digitals, antihypertensive agents, indomethacin, probenecid, Lithium, other diuretics (e.g. furosemide, hydrochlorothiazide), drugs known to have a nephrotoxic potential

8. Documented history of hypersensitivity reaction to sulfonamide derivatives.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Basic science |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-06-2016 |
| Enrollment: | 90 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Bumetanide |
| Generic name: | Bumetanide |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 13-01-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

Approved WMO

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|---|---|
| Date: | 07-04-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 04-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 01-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 28-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 27-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2014-001560-35-NL |
| CCMO | NL49210.041.15 |