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.

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

Ethical review	Not approved
Status	Will not start
Health condition type	Communication disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON45966

Source
ToetsingOnline

Brief title
Efficacy +safety of bumetanide in children from 2 to less than 7 with ASD.

Condition

- Communication disorders and disturbances

Synonym
autism spectrum disorder

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: Institut de Recherches Internationales Servier

Intervention

Keyword: autism spectrum disorder, bumetanide

Outcome measures

Primary outcome

Childhood Autism Rating Scale, Second Edition (CARS2) total raw score. Main

expression will be change from baseline to 6 month.

Secondary outcome

To assess the effect of bumetanide on the other efficacy endpoints

To assess the safety of bumetanide

To confirm the acceptability and palatability of the oral liquid formulation

To describe the bumetanide effects on patients quality of life

To improve existing pharmacokinetic model of bumetanide in this population.

Study description

Background summary

Recent studies suggest that GABAergic neurons and circuits may be altered in ASD. The conversion of GABA-mediated neuronal excitation into inhibition during maturation of specific neuronal populations has been reported to be altered in neurodevelopmental diseases such as autism. This lack of *GABA switch* is due to persistent high level of expression of Na+/K+/2Cl- co-transporter (NKCC1) vs K-Cl co- transporters (KCC2). This in turn may lead to abnormal cell migration and differentiation, immature and imbalanced neuronal network development and thus to clinically diagnosed deficits observed in this pathology.
Levels of intracellular chloride determine the levels of neuronal inhibition and have been shown to be elevated in immature neurons and being progressively reduced within neuronal development. These observations suggest that drugs reducing intracellular chloride levels may be helpful in normalising chloride levels and thereby restore inhibitory GABAergic function and neuronal network maturation.
Bumetanide (Burinex®) is a sulfonamide-derived loop diuretic used for the management in adult patients of oedema associated with congestive heart failure, hepatic cirrhosis and renal disease including nephropatic syndrome. Acting centrally as a NKCC1 inhibitor, bumetanide provokes reduction of intracellular chloride, switching the aberrant excitatory action of GABA into an inhibitory action.

Study objective

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

Study design

This study is divided into the following periods:
1. Run-in period up to 4 weeks between selection (ASSE) and inclusion (week 0) visits: without Investigational Medicinal Product (IMP) treatment to evaluate eligibility.
2. Double-blind treatment period of 6 months between inclusion (week 0) and month 6 (week 26): at inclusion patients will be randomised to one of the two parallel groups: bumetanide 0.5mg BID or placebo BID- balanced randomisation (ratio 1:1).
3. Open label active treatment period of 6 months between month 6 (week 26) and month 12 (week 52): patients randomised in the bumetanide arm during the double blind period will continue to be treated by bumetanide up to 0.5mg BID

during the whole open label period. Patients randomised in the placebo arm during the double blind period will receive bumetanide up to 0.5mg BID.
4. Safety follow-up visit (Wend), 6 weeks after treatment discontinuation:
This period is without any IMP and it will be completed at the end of the study

Intervention

Blood and urine samples, renal echographies, ecgs, specific scales for the evaluation of the disease

Study burden and risks

Cfr adverse events of medication and procedures described in information and consent form.

Contacts

Public
Servier R&D Benelux

Internationalelaan 57
Brussel 1070
BE
Scientific
Servier R&D Benelux

Internationalelaan 57
Brussel 1070
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Male and female patients from 2 to less than 7 years
- Out patients
- Primary diagnosis of ASD as per DSM-5 criteria
- Criteria met for ASD on Autism Diagnostic Observation Schedule (ADOS-2) and Autism Diagnosis Interview Revised (ADI-R)
- CGI (Clinical Global Impression) * Severity rating Score * 4
- Childhood Autism Rating Scale second edition (CARS2-ST or HF) total raw score * 34
- Social Responsiveness Scale second edition total score (SRS-2 T-Score) * 66
- Absence of known monogenic syndrome (Fragile X, Rett syndrome ...)
- Absence of any clinically significant abnormality likely to interfere with the conduct of the study according to the judgment of the investigator
-Absence of electrolyte imbalance that is likely to interfere with the study conduct or evaluation

Exclusion criteria

- Patients not able to follow the study assessments defined by the protocol, with the exception of self-rating questionnaires which will be assessed by parent/legal representative/caregiver for those patients unable to complete them
- Patients having a high suicidal risk according to the investigator judgement
- Chronic renal dysfunction
- Chronic cardiac dysfunction
- Patient with unstable psychotherapy, behavioural, cognitive or cognitive-behavioural therapy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	20-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Not approved

Date:	04-02-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-004420-30-NL
CCMO	NL66258.091.18