post-trial access cohort BUmetanide for Developmental DIsorders

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1. Provide post-trial access to bumetanide treatment for NDD participants.2. To test how bumetanide cohort data compare to the existing RCT data in terms of treatment effectiveness by using randomization tests. 3. To further develop EEG biomarker...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON55058

Source
ToetsingOnline

Brief title
BUDDI

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Mental impairment disorders
- Developmental disorders NEC

Synonym
Neurodevelopmental disorders

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,NWA

Intervention

Keyword: Autism, Bumetanide, Developmental disorders, Treatment

Outcome measures

Primary outcome

PROMIS proxy questionnaires:

• Physical stress experiences

• Psychological stress experience

• Sleep disturbances

• Sleep-related impairment

• Cognitive function

• Anxiety

• Fatigue

• Peer relationships

• Life satisfaction

• Depressive symptoms

Secondary outcome

- Conventional questionnaires: Repetitive behavior scale - revised (RBS-R),

Social Responsiveness Scale (SRS), aberrant behavior checklist (ABC), Sensory

profile (SP-NL)

- resting-state electroencephalogram (rsEEG)

- neurocognitive test battery.

- cellular assays (if consent is obtained)

- genetic analysis (WES) (if consent is obtained)

Study description

Background summary

Child psychiatric neurodevelopmental disorders (Attention Deficit Hyperactivity Disorder (ADHD), autism spectrum disorder (ASD), intellectual disability and learning disorders) are highly heterogeneous conditions affecting the daily lives of about 1 in 10 children worldwide. Especially the more severe case require medical intervention but current medicinal interventions are at best symptomatic and do not target pathophysiological mechanisms.
Despite extensive clinical variability, experimental research has indicated common pathways and treatment targets across neurodevelopmental disorders. For example, bumetanide, used for decades as a diuretic drug, has recently been put forward as a rational, safe off-patent intervention to improve GABAergic inhibition across neurodevelopmental disorders (NDDs). Several successful trials in the field have led to the approval of an EMA pediatric investigation plan for bumetanide for ASD and a phase III trial is underway (https://clinicaltrials.gov/ct2/show/NCT03715153).
Recently, we have conducted three independent trial studies testing bumetanide across the spectrum of NDDs. Our overall hypothesis was that bumetanide improves the balance between excitation and inhibition (E/I) with effects on sensory and cognitive information processing that in turn may improve core behavioral symptoms. Indeed, neural excitability and sensory processing is increasingly being marked as one of the fundamental processes underlying NDDs.

Consistent with our hypotheses, we found that bumetanide and not placebo alters the E/I balance (EEG biomarkers) and improves core symptomatology of NDDs in a substantial subset of patients. However, the extent and type of response was variable between individuals also within the same diagnostic subcategory. Another important lesson was that some of the effects reported by participants were not represented by the clinical endpoint questionnaires.

As a result, many patients and caregivers that participated in our trials are very eager to make use of the post-trial access to bumetanide treatment as described in the original protocols. Indeed, if we do not administer bumetanide under well-controlled circumstances, parents will seek alternative providers with the risk that random *one-size-fits-all* off-label prescription will become standard for bumetanide. In addition, we want to collect biobank samples (blood and skin biopsies) to be able to perform genetic and cellular analyses to develop additional stratification markers for future more personalized application of the drug.

Thus, we propose a protocol for off-label bumetanide treatment to participants of the previous trials. The duration of treatment will be a minimum a six-months period and a maximum a two-year period. Reasons to mark this

post-trial access cohort (i.e. delayed open-label extension phase) as research, for which we seek this IRB approval, and not as regular evidence-based clinical care, are:
• off-label bumetanide treatment is still considered experimental
• no rational alternatives exist for any NDDs
• benefit of bumetanide has been suggested in multiple state-of-the-art RCTs
• Patients and caregivers will seek other prescribers of bumetanide if post-trial access is not arranged by us.

Our aim is to confirm previous found effects of bumetanide on NDDs and to identify markers allowing us to estimate individual treatment response. Given that the end points previously used appeared non-representative of the effects observed by participants* caregivers we will use a different primary endpoint. This is also why we allow all participants of our previous trials access to this open label extension cohort, even if previous data suggests there might not be an effect. Furthermore, it is not yet known whether a longer treatment duration might have added effects, which can also be a reason for participants labeled as *non-responders* to participate in this trial. Patients and their caregivers have received an information letter about the group they were allocated in and whether they were grouped as responders/non-responders allowing them to make an informed decision whether to, or not to participate in this open-label trial.

Many trials focus on a one-size fits all treatment, leading to individual comparison to the mean. However, the large heterogeneity of NDDs suggests this might not be sufficient. A notion that is supported by our BAMBI data, where subgroups of responders and non-responders could be identified. Accordingly, we propose to use a more individualized study design, where the patient serves as its own control.

We aim to estimate individual treatment response by using single-case experimental designs (SCEDs). A SCED is an N-of-1 design in which a baseline period is compared to an intervention period, evidence of treatment effect is based on demonstrating that the change in behavior only occurs during intervention. As the individual serves as his or her own control in this design, the response per individual can be analyzed. To assess treatment-effect a frequent measurement of target behavior is required. Therefore, we use a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children: *Patient-Reported Outcomes Measurement Information System* (PROMIS).

By simultaneously performing rsEEGs, neurocognitive testing and collect blood- and skin biopsies with these 'patient reported outcome measures* (PROMs) we aim to develop prognostic markers for treatment effect. To gain inside how PROMs relate to the conventional endpoint measurements we also incorporate the conventional questionnaires as secondary outcome measures.

Study objective

1. Provide post-trial access to bumetanide treatment for NDD participants.
2. To test how bumetanide cohort data compare to the existing RCT data in terms of treatment effectiveness by using randomization tests.
3. To further develop EEG biomarker treatment-effect predictions.
4. To establish a biobank of blood and skin biopsies for future additional predictive biomarker development.

Study design

Post-trial access cohort (i.e. delayed open-label extension phase) over a time-period for a minimum of a six-months period and a maximum of a two-year period. Executed in a moncenter study of multiple n-of1 trials using Single-Case Experimental Designs (SCEDs) testing bumetanide treatment during six months with the primary end point of change in PROMs at Day 180 in approximately 75 children with NDDs between 8 and 20 years of age. The effects on PROMs will be compared to the main conventional endpoints used in the original trials as well as accompanying measurements of EEG and neurocognition to further establish effects on brain activity and functioning and to validate predictive markers of treatment response.

Intervention

Bumetanide 2dd1.0-2.0mg daily.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The burden and risk of the application of this off-label drug for children with NDD are acceptable while the benefits are expected to be considerable especially when taking into account the lack of treatments for these highly prevalent and often devastating disorders.

Risks
Bumetanide has been used as a diuretic drug for decades. In patients with conditions of fluid overload, its safety and tolerability after short and prolonged treatment has been established in all ages apart from neonates. Experience and safety of bumetanide in patients with NDD is based upon recent studies, including three randomized controlled trials in a sample of 56, 92 and 83 children7. These data indicate that bumetanide significantly alleviates behavioral morbidity at dosages ranging from 1 to 2 mg daily. The main observed adverse events were related to the diuretic activity of the molecule leading to a decrease in electrolytes, notably mild hypokalemia, are frequently reported.

Skin biopsy is a safe, commonly performed procedure, carried out by a healthcare professional. The risk of this procedure includes transient bleeding, which usually subsides within minutes. There is a minimal risk of wound infection and/or prolonged discomfort to the patient. If technological advances will make it possible to use in the future alternative sources of patient cells, such as hair, buccal or blood cells, this will be implemented in the study to minimize the risk and discomfort of the patients further.

Burden
The main burden of this study is posed by the outpatient clinic visits to follow up the safety of the diuretic effects. This requires physical examination and blood tests, which are of negligible and known risks. Additional burden is posed by the measurement of cognitive and EEG tests. These tests are deemed necessary to further develop the prognostic markers to select the most responsive patients out of the NDD population.

Skin biopsies are not commonly carried out as part of the diagnostic or treatment procedures and will optionally be performed specifically for the purpose of this study (unless a sample of fibroblast cells is available already). By obtaining a skin biopsy from patients it will be possible to create a cellular model, without interference of unknown modulating factors in the patient*s genome, to perform cellular analyses in order to develop additional stratification markers.

Benefit and group-relatedness
The promising results of our previous bumetanide trial studies are here followed up in order to confirm and specify efficacy on symptomatology important for the individual patient and to establish prognostic EEG markers that can predict favorable effects in patients with NDD.

Contacts

Public
Vrije Universiteit Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Vrije Universiteit Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Inclusion in BAMBI, BASCET or BATSCH trial;
2. Written informed consent
Or
1. Males or females aged >=7 years to <=15 years;
2. One of the following:
a. Above clinical cut-off scores of altered sensory reactivity on the Sensory Profile and either a clinical ASD or ADHD diagnosis based on DSM-5 (or DSM-IV) or an epilepsy diagnosis,
b. Criteria met for autism on DSM-IV or V and Social Responsiveness Scale (SRS)
c. A history of behavioral problems combined with a definite diagnosis of TSC: either meeting criteria for clinical definite TSC, or a mutation identified in the TSC1 or
TSC2 gene;
3. Written informed consent

Exclusion criteria

Inability to comply with the protocol
specified procedures for the duration of the study, including treatment anblood sampling to control diuretic effects;
2. Presence of a severe medical or genetic disorder other than related to TSC or epilepsy;
3. Serious, unstable illnesses including, gastroenterological, respiratory, card iovascular (arrhythmias, QT

interval lengthening), endocrinologic, immunologic, hematologic disease, dehydra
tion or hypotension, electrolyte disturbances (Na <133 mmol/L, K <3.5 mmol/
L or Ca <2.17 mmol/L <13y] or <2.2 mmol/L [>13y]); 4.
Renal insufficiency (CKD st25; estimated glomerular filtration rate < 90 ml/
min/1.73m2), congenital or acquired
renal disease with decreased concentration capacity (tubulopathy, diabetes insip
idus) and liver insufficiency
interfering with excretion or metabolism of bumetanide; 5. Start of behavioral t
reatment during study; 6.
Treatment with psychoactive medications, including antipsychotics and AEDs, exce
pt methylphenidate s
allowed albeit on a stable regime in terms of types and dosage from 2 months pri
or to the study to the end of the
study; 7. Treatment with NSAIDS, aminoglycosides, digitals, antihypertensive age
nts, indomethacin, probenecid,
acetazolamide, Lithium, other diuretics (e.g., furosemide, hydrochlorothiazide),
 drugs known to have a
nephrotoxic potential; 8. Documented history of hypersensitivity reaction to sul
fonamide derivatives; 9. Body weight < 30 kg

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-12-2020
Enrollment:	115
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bumetanide

Generic name:	Bumetanide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-04-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2020-002196-35-NL
CCMO	NL73520.041.20