A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF 52 WEEKS OF TREATMENT WITH BASMISANIL IN PARTICIPANTS AGED 2 TO 14 YEARS OLD WITH DUP15Q SYNDROME FOLLOWED BY A 2-YEAR OPTIONAL OPEN-LABEL EXTENSION

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Part 1:To evaluate the effects of 52 weeks of treatment with basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and dailyfunctioning. Part 2:• To evaluate the tolerability and safety of up to 3 years of treatment with...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53905

Source
ToetsingOnline

Brief title
Quindecim - BP42992

Condition

- Other condition
- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Dup15q Syndrome, neurodevelopment disorder

Health condition

Dup15q syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman la Roche / Genentech inc

Intervention

Keyword: 5 receptor modulator, Basmisanil, Dup15q syndrome, GABAA &alfa, Pediatric

Outcome measures

Primary outcome

PART 1

Primary:

• Vineland-3: Adaptive Behavior Composite

PART 2

Safety:

• Incidence, nature, and severity of AEs and SAEs

• Incidence of treatment discontinuations due to AEs

• Incidence of laboratory abnormalities based on hematology, clinical

chemistry, and urinalysis test results

• ECG changes from baseline; incidence of abnormal ECG assessments

• Change from baseline in all seizure frequency, duration, and type as reported

in a seizure diary by caregivers

• Abnormal changes in EEG recordings compared to baseline with a focus on

treatment emergent epileptiform abnormalities

• Systolic and diastolic blood pressure and heart rate measurements

• Suicidality as assessed through questions from selected items adapted from

the C CASA in participants aged 6 years and above

• Height, weight, head circumference

• Tanner staging over time (in participants aged 9 years and above)

For other endpoints, please see protocol section 3.

Secondary outcome

See protocol section 3

Study description

Background summary

Dup15q syndrome is a rare and severe neurodevelopmental disorder (NDD) with a high unmet medical need. It is caused by maternal duplication or triplication of the q11.2-q13.1 region of chromosome 15, which contains several genes and noncoding regions.

This multi-center, randomized, double-blind, placebo-controlled, parallel group study will evaluate the safety, efficacy, and pharmacodynamics of 52 weeks of basmisanil treatment in children with Dup15q syndrome aged 2 to 14 years. The study will test the hypothesis that negative allosteric modulation of GABAA α5R can address excessive GABAAR function driven by the additional GABR copy numbers, as indexed by EEG, and positively impact core neurodevelopmental

disease features in children with Dup15q syndrome.

Study objective

Part 1:
To evaluate the effects of 52 weeks of treatment with basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning.

Part 2:
• To evaluate the tolerability and safety of up to 3 years of treatment with basmisanil
• To evaluate the effects of up to 3 years of treatment with basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning
• To evaluate the effects of up to 3 years of treatment with basmisanil on motor function, cognition, language, social skills, clinician global impression of severity and change, challenging behaviours, health-related quality of life of the caregiver, caregiver global impression of severity and change

For further objectives, see protocol section 3.

Study design

See figure 1 of the protocol, page 23.

Intervention

Basmisanil is a clinically characterized, brain penetrant, and highly selective negative allosteric modulator (NAM) of the GABAA α5R. Basmisanil has been developed for its high selectivity and specificity for the α5 -containing receptors versus the α1-, α2-, and α3-containing receptors, and is devoid of the anxiogenic and pro-convulsant liabilities of non-selective GABAA NAMs and antagonists.

The child receives one of two study treatments: Basmisanil or placebo. Study treatment is taken three times a day (morning, afternoon and evening, at least 4 hours apart) from Day 2.

PART 1:
The doses depend on the age of the child on day 1:
- Doses: 240 mg for children 2- 5 years of age
- Doses: 320 mg for children aged 6-14 years

The doses depend on the age of the child from day 2 onwards:
- Doses: 360 mg for children 10 to 14 years of age

- Doses: 240 mg for children 6 to 9 years of age
- Doses: 120 mg for children 2 to 5 years of age.

PART 2: the same dose as for day 2 and onwards applies for part 2.

Placebo or basmisanil are packed in sticker packs. The granules should be taken with soft food such as yogurt, apple sauce or pudding.

Furthermore please refer to the Basmisanil Investigator's Brochure.

Study burden and risks

Section 2.3 of the Protocol presents a Benefit / Risk Assessment. The test taxes and risks are described in appendices C and D of informed consent for information to the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Children (2-11 years)

Inclusion criteria

PART 1
• Participants aged 2 to 14 years inclusive at the time the caregiver signs the
informed consent.
• Documented maternal duplication (3 copies) or triplication (4 copies) of the chromosome 15q11.2-q13.1 region that includes the Prader-Willi/Angelman critical region defined as [BP2-BP3] segment
• Dup15q syndrome Clinician Global Impression of Severity scale (Dup15q CGI-S) overall severity score >= 4 (at least moderately ill)
• Stage 1 specific inclusion criterion: Participants aged 6 to 14 years with epilepsy.
• Body weight equal to or above the third percentile for age
• Male and female participants: Some of the provisions that follow may have limited applicability based on the age range of study participants (i.e., up to the age of 14) and the nature of the disease under study
• Female Participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding
• Male Participants: Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse
• The participant has a parent, caregiver, or legally authorized representative (hereinafter *caregiver*) of at least 18 years of age, who is fluent in the local language at the site, and capable and willing to provide written informed consent for the participant according to International Council for Harmonisation and local regulations
• The participant*s caregiver must be living with the participant and, in the opinion of the Investigator, able and willing to reliably assess the participant*s ongoing condition, to accompany the participant to all clinic visits, and ensure compliance to study treatment throughout the study. The same caregiver is able and willing to complete the caregiver assessments and is available to the Investigational Site by telephone or email if needed
• The participant*s caregiver is able and willing to use electronic devices to record information on the participant*s condition and to complete assessments at home and agrees to home nursing visits, if local regulations allow for it and if home nursing service is available in the country/region.

PART 2:
All participants who complete the 52 weeks of study treatment in Part 1 will be offered the option to roll over into an OLE to receive basmisanil treatment for a duration of approximately 2 years (Part 2). Participants will be required to sign a separate ICF for participation in Part 2.

Exclusion criteria

PART 1
• Uncontrolled epilepsy at Screening as indicated by:
Use of rescue medication(s) to treat more than one seizure cluster per month on average in the past 6 months; OR
Concomitant chronic use of more than 4 anti-epileptic medications or status epilepticus within the past 6 months requiring hospitalization for treatment of the status epilepticus; OR
any implanted devices to treat drug-resistant epilepsy
• Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
• Clinically significant ECG abnormalities at Screening, including an average triplicate QTcF > 450 ms for participants > 10 years or QTcB > 450 ms for children up to and including age 10 years
• Clinically significant abnormalities in laboratory test results at screening (including positive results for HIV, hepatitis B and/or hepatitis C). ALT values > 1.5 × the upper limit of normal. GFR < 90 mL/min per 1.73 m2 (Grade 1 CKD) as estimated using Schwarz formula.
• Allowed prior existing medication should be on a stable regimen (or frequency of intervention) for at least 6 weeks, and at least 8 weeks for anti-epileptic treatment, prior to Screening
• Non-pharmacological / behavioral therapies should not be stopped or newly started at least 6 weeks prior to Screening and are expected to remain stable for the entire study duration (excluding changes related to standard age and educational interventional programs and minor interruptions such as illness or vacation
• Concomitant use of prohibited medications
• Participation in an investigational drug study within one month or within 6 × the elimination half-life, whichever is longer, prior to dosing in the study
• Significant risk for suicidal behavior, as assessed through the suicidal behavior question adapted from the Columbia Classification Algorithm for Suicide Assessment (C-CASA) (participants >= 6 years of age only)
• Known sensitivity to any of the study treatments or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study, including severe lactose intolerance
• Concomitant clinically relevant disease or condition or any clinically significant finding at screening that could interfere with, or for which, the treatment might interfere with, the conduct of the study or that would pose an unacceptable risk to the participants in this study
• Known active or uncontrolled bacterial, viral, or other infection or any major clinically significant episode of infection or hospitalization (relating to the completion of the course of antibiotics) within 6 weeks prior to the start of drug administration.

PART 2
A participant will not be eligible to receive study treatment after the end of Part 1 of the study if any of the following conditions are met:
• The study treatment is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or would not otherwise create a financial hardship for the participant).
• The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for Dup15q syndrome.
• The Sponsor has reasonable safety concerns with regards to the study treatment.
• Provision of study treatment is not permitted under the laws and regulations of the participant's country.
• The participant discontinued prematurely from study treatment or withdrew from the study before completing 52 weeks of treatment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2023
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Basmisanil
Generic name:	Basmisanil

Ethics review

Approved WMO Date:	16-01-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2021-003791-13-NL
ClinicalTrials.gov	NCT05307679
CCMO	NL83001.100.22