AN OPEN-LABEL, MULTICENTER STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7248824 IN PARTICIPANTS WITH ANGELMAN SYNDROME

Published: 06-05-2020
Last updated: 09-11-2024

This study has been transitioned to CTIS with ID 2024-514797-45-00 check the CTIS register for the current data. PRIMARY OBJECTIVE: - To assess the (long-term) safety and tolerability profile of RO7248824.SECONDARY OBJECTIVE: - To investigate the...

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

Summary

ID

NL-OMON54298

Source
ToetsingOnline

Brief title
BP41674 - Tangelo

Condition

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

Synonym
Angelman syndrome, developmental disorder

Health condition

ontwikkelingsstoornis door een chromosoomdeletie

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman - La Roche Ltd.

Intervention

Keyword: Angelman syndrome, antisense-oligonucleotide, Phase- 1, UBE3a

Outcome measures

Primary outcome

- Frequency and severity of adverse events, serious adverse events, treatment discontinuations due to adverse events.

- Frequency of abnormal laboratory findings (blood and cerebrospinal fluid [CSF]).

- Frequency of abnormal vital signs and ECG values.

- Mean changes from baseline in vital signs (temperature, systolic and diastolic blood pressure, heartrate, respiratory rate) over time.

Endpoints measured in OOE part:

• Frequency and severity of adverse events, serious adverse events, treatment discontinuations due to adverse events.

• Frequency of abnormal laboratory findings (blood and cerebrospinal fluid [CSF]).

Secondary outcome

- Time to maximum concentration (Tmax)

- Maximum plasma concentration observed (Cmax)

- AUC from Time 0 to time of last sampling point or last quantifiable sample,

whichever comes first (AUClast), AUC from Time 0 to infinity (AUCinf)

Study description

Background summary

Angelman syndrome (AS) is a rare genetic neurodevelopmental disorder with a prevalence of 1 in 12,000 to 20,000 births. Individuals with AS have many features such as global developmental delay, intellectual disability, epilepsy (90% before age 3 years) with atypical underlying electroencephalography (EEG), ataxia, tremor, hyperactivity, limited speech, and sleep dysregulation. Anxiety, aggression, and self-injurious behavior may also be present. There is a high unmet medical need and societal impact in many dimensions; affected individuals require life-long care and cannot live independently.

In individuals with AS, the maternal UBE3A allele is not functional, thus, UBE3A is not generally expressed in neurons. In non-neuronal cells in AS, although expression of UBE3A from the maternal allele is lacking, the paternal allele is active and therefore a lack of expression from the maternal allele results in haploinsufficiency rather than complete absence of UBE3A protein in neurons.

There is a high unmet medical need in AS patients as there are no approved treatments for AS and no clear guidelines for symptom-based interventions in this population.Currently available treatments are symptomatic and largely limited to improvement ofseizures and reduction of sleep disturbances. Insight into the mechanism of action (MoA) of the disease, however, has suggested a path forward for disease-modifying therapies RO7248824 is an ASO that is chemically modified with locked nucleic acids (LNA) and targets a sequence on the 3* end of the UBE3A-ATS. An LNA is a bicyclic nucleic acid where a ribonucleoside is linked between the 2*-oxygen and the 4*-carbon atoms with a methylene unit to enable high affinity binding to the target RNA sequence.

RO7248824 is hereafter refered to as an LNA. It aims to unsilence expression of the paternal Ube3a allele and enable UBE3A protein production in neurons in AS according to the mechanism described above.

This Phase I study BP41674 is planned as a multicenter, open label, non-randomized, adaptive, multiple ascending, intra-participant dose-escalation study with intrathecal (IT) administration of RO7248824 in participants with Angelman Syndrome (AS) aged 1-12 years. The primary objective of this study is to investigate the safety and tolerability of RO7248824.
PAv6: The LTE part of the study aims to investigate long-term safety and tolerability of RO7248824, it presents an opportunity of continued prospect for direct clinical benefit for the participants enrolled in this Phase I trial and will be used to inform the dosing regimen selection for future clinical studies.

Study objective

This study has been transitioned to CTIS with ID 2024-514797-45-00 check the CTIS register for the current data.

PRIMARY OBJECTIVE:
- To assess the (long-term) safety and tolerability profile of RO7248824.

SECONDARY OBJECTIVE:
- To investigate the plasma pharmacokinetics (PK) of RO7248824.

Study design

This is a Phase I, multicenter, non-randomized, adaptive, open label, multiple ascending,
intra-participant, dose-escalation study with a LTE part to investigate the safety,
tolerability, PK and PD of RO7248824 administered IT in participants with AS.

Two linked sets of dose escalation cohorts are planned based on two different age
groups, namely participants with AS aged from 5 to 12 years in cohorts A1 to A5 (with at
least 2 participants from 8 years old in each cohort) and AS participants aged 1 to 4
years in cohorts B1 to B5. The two sets of cohorts will be run in parallel, with each cohort
A1-A5 preceding and gating the linked cohort B1-B5 (e.g., A1 precedes B1).

Each participant will receive up to three IT injections of varying dose levels over a period

of 8 weeks, with a minimum of approximately 4 weeks between each dose administration. It is planned to test a dose range from 15 mg to 240 mg of RO7248824
for cohorts A and 6 mg to 240mg of RO7248824 for cohorts B, over multiple staggered
cohorts as shown in Figure 1 of Section 1.2.1

NEW PAv6/8: Long-term Extension Part (see figure 2 of section 1.2.1 of the protocol)
Participants whose caregivers agree to the continuation of treatment after the MAD treatment period will transition to the LTE part during the follow-up period of the main (MAD) part.
New participants can also be included only in the LTE
The LTE will consist of 8 cohorts (i.e., 4 dosing regimens in each age group) with 2 dosing frequencies (every 16 weeks [Q16W], and every 24 weeks [Q24W]

Participants transitioning to an LTE cohort with Q16W dosing will receive their first dose in the LTE part not earlier than 16 weeks after their last dose in the main part (including bridging dose).
Participants transitioning to an LTE cohort with Q24W dosing, will receive their first dose in the LTE part not earlier than 24 weeks after their last dose in the main part (including bridging dose).

Protocol V9: The 240 mg dose level has not been tested as part of the MAD part of this study, therefore Cohorts A5, B5, EA4, and EB4, have not been initiated.

Protocol V10:
Optional Open-label Extension Part
An optional OOE part will evaluate the long-term safety and tolerability of RO7248824 for up to 48 weeks. The objective of the OOE part is to provide an option for open-label access to RO7248824 within the context of a clinical trial to ensure that comprehensive safety assessments and monitoring are conducted while reducing the burden of exploratory assessments. The OOE part is open to participants who are currently or were previously enrolled in Study BP41674. The recommended dose and dosing interval for treatment in the OOE part will be the same dose and dosing interval the participant last received in the LTE part. Nonetheless, dose levels and dosing frequencies in the OOE part may be adjusted by the Investigator and endorsed by the Dose Decision Committee (DDC) following review of safety and tolerability data of previous doses.

Intervention

RO7248824 is a selective synthetic 20-mer oligonucleotide (see RO7248824 Investigator*s Brochure). IT injection of RO7248824 is considered to be a potential disease modifying approach for AS.

It is planned to test a dose range from 15 mg to 240 mg of RO7248824 for

cohorts A and 6 mg to 240 mg of RO7248824 for cohorts B, over multiple staggered cohorts as shown in Figure 1 of section 1.2.1 of the protocol.

For cohorts A, participants with planned doses of 120 mg or less will receive up to three IT injections of varying dose levels over a period of approximately 8 weeks, with approximately 4 weeks between each dose administration. Participants with planned doses of > 120 mg and < 240mg will receive up to two IT injections of varying dose levels with approximately 8 weeks between each dose administration. For the dose of 240 mg, only a single IT injection is planned. For cohorts B, the same dosing strategy will be followed as a minimum requirement; however, administration of two injections 8 weeks apart may be implemented at a lower dose level than 120 mg based on emerging data.

There is currently no clinical experience with RO7248824. The evaluation of the potential risks of RO7248824 in humans is based primarily on available data from non-clinical toxicology, safety pharmacology studies and documented drug class-related risk from ASO class drug candidates and approved drugs that are administered intrathecally.

NEW PAv8:
Age 5 to 12 years (*A* cohorts):
• EA1 (60 mg Q16W): for new participants enrolling directly in the LTE part
• EA2 (120 mg Q16W): for participants continuing from cohorts A1 and A2 main study
• EA3 (180 mg Q24W): for participants continuing from Cohort A3 and A4 main study
• EA4 (240 mg Q24W): for participants continuing from Cohort A5 main study

Age 1 to 4 years (*B* cohorts):
• EB1 (60 mg Q16W): for new participants enrolling directly into the LTE part
• EB2 (120 mg Q16W): for participants continuing from cohorts B1 and B2 main study
• EB3 (180 mg Q24W): for participants continuing from Cohort B3 and B4 main study
• EB4 (240 mg Q24W): participants continuing from Cohort B3 and B4 main study

As part of the procedure and immediately after the drug is injected, a small volume of salt solution (called a flush) may also be injected using the same needle. The drug administration procedure (including the amount of flush), might be modified during the study. The study doctor will inform the participants about the drug administration procedure that your child will be receiving.

PAv9:
With the implementation of Protocol Version 9, post-dose flush solution will not be administered anymore as IT administration without post-dose flush has been tested as described in the Protocol v9 and has been found safe and

well-tolerated for the 3 dose levels and in both age groups by the DDC.
The 240 mg dose level has not been tested as part of the MAD part of this study, therefore Cohorts A5, B5, EA4, and EB4, have not been initiated.

PAv10: De dosisregimes die tijdens het OOE-gedeelte zijn toegestaan, moeten dezelfde dosisregimes zijn die worden toegediend in het LTE-gedeelte.

Study burden and risks

Please see "aanvullende opmerkingen" for an overview of the procedures that are done in the context of the study and which are not, or partially overlap with the standard of care. This includes lumbal punctures, CSF sampling, venapunctures, MRI, EEG, pregnancy testing, performance scales and fundoscopy.

Risks related to treatment with the study drug:
- Allergical reactions
- Side effects that might be related to RO7248824

Safety data have become available from this study (BP41674) for 20 participants that received RO7248824 at doses of 6 mg to 120 mg. The most common clinical side effects (seen in 2 or more participants) were vomiting, decreased appetite, fever, fatigue, and ataxia (a temporary reduction in coordination and/or balance). These side effects were generally of short duration (1 to 3 days). In addition, there was a laboratory finding of increased numbers of white blood cells in the CSF samples of 2 participants.

Potential side effects are described in more detail in the subject information sheet.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

• The participant has a parent, caregiver or legal representative (hereinafter *caregiver*) who is reliable, competent and at least 18 years of age. The caregiver is willing and able to accompany the participant to clinic visits and to be available to the Investigational Site by phone or email if needed and who (in the opinion of the investigator) is and will remain sufficiently knowledgeable of participant*s ongoing condition to respond to any inquiries about the participant from personnel from the Study Site.
• A caregiver must be able to consent for the participant according to International Council on Harmonisation (ICH) and local regulations.
• Ability to comply with all study requirements.
• Have adequate supportive psychosocial circumstances.
• Able to undergo MRI scans (e.g., no metal implants including MRI incompatible intrauterine devices (IUDs), or any condition that renders testing intolerable for the participant), under sedation or anesthesia if needed and as determined appropriate by the Investigator.
• Able to tolerate blood draws.
• Able to undergo LP and IT injection, under sedation or anesthesia if needed and as determined appropriate by the Investigator.
• Stable medical status for at least 4 weeks prior to Screening and at the time of enrollment.
• Bodyweight of >= 7 kg.
• Participant must be >= 1 and <= 12 years of age at the time of signing of the informed consent by the caregiver.
• Clinical diagnosis of AS confirmed by a molecular diagnosis with genotypic classification of either:
o UBE3A truncation mutation of maternal allele
o 15q11-15 deletion of maternal allele
o Deletion on the maternally inherited chromosome 15q11q13 that includes the

UBE3A gene and is less than 7 Mb in size.
• Female Participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: Women of non-childbearing potential or Women of childbearing potential who agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 6 months after the final dose of RO7248824
• Male Participants: During the treatment period and for at least 6 months after the final dose of RO7248824, consent has to be provided to remain abstinent or use contraceptive measures with a female partner of childbearing potential, or pregnant female partner.

Inclusion Criteria for Optional Open-label Extension Part:
If a participant continues directly from the LTE part, only OOE informed consent is required, and eligibility reassessments are not required. If a participant has completed the LTE part of the BP41674 study or has discontinued participation in the BP41674 study for reasons not related to safety, reassessment of eligibility will be required along with the OOE informed consent.
11. Current or prior participations in the LTE part of Study BP41674.
12. Signed OOE Informed Consent Form
13. Continue to meet the inclusion criteria 1 to 8 and reproductive status as stated in the protocol at the time of entry into the OOE and met the inclusion criteria 9 (age) and 10 (disease characteristics) at the time of enrollment into the MAD part of the study.

Exclusion criteria

• Clinically-significant laboratory, vital sign or electrocardiography (ECG) abnormalities at Screening.
• Molecular diagnosis of AS with genotypic classification of:
o UBE3A missense mutation of maternal allele
o Paternal UPD of 15q11-13
o UBE3A ID
o A partial molecular diagnosis of AS that cannot exclude UPD or ID despite appropriate genetic testing.
• Clinically relevant hematological, hepatic, cardiac, renal disease event or laboratory abnormality, in the judgement of the Investigator.
• Any concomitant condition that might interfere with the clinical evaluation of AS and that is not related to AS.
• Known history of human immunodeficiency virus (HIV) or hepatitis B virus (HBV) or hepatitis C virus (HCV).
• Any condition that increases risk of meningitis.
• History of bleeding diathesis or coagulopathy.
• A medical history of brain or spinal disease that would interfere with the

lumbar puncture process, CSF circulation or safety assessment.
• History of post-lumbar-puncture headache of moderate or severe intensity and/or blood patch.
• Malignancy within 5 years of Screening.
• Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study.
• Have any other conditions which, in the opinion of the Investigator, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study, including any contraindication to administration of intrathecal therapy.
• Premature birth with gestational age at birth below 34 weeks.
• History of hypersensitivity to the investigational medicinal product (IMP), antisense oligonucleotides, or any excipients.
• Allowed sleep medications have not been stable for 4 weeks prior to screening and at the time of enrollment.
• Allowed medications for treatment of epilepsy have not been stable for 12 weeks prior to screening and at the time of enrollment.
• Use of antiplatelet or anticoagulant therapy for 2 weeks prior to screening and at the time of enrollment.
• Concurrent psychotropic medications have not been stable for 4 weeks prior to screening and at the time of enrollment.
• Received an investigational drug within 90 days or 5 times the halflife of the investigational drug (whichever is longer) or participation in a study testing an investigational medical device within 90 days prior to first dosing or if the device is still active.
• Concurrent or planned concurrent participation in any clinical study (including observational, non-drug and non-interventional studies) without a signed data sharing agreement covering the participant in place between other clinical study and the Sponsor.
• Previous participation in a cellular therapy, or gene therapy or gene editing, or any other gene expression modulating clinical study.

Exclusion Criteria for Optional Open-label Extension Part:
22. The participants re-entering the study to participate in the OOE must continue to comply with exclusion criteria 1 to 21 as stated in the protocol at the time of enrollment in the OOE.
a. ECG will be waived for participants who are re-entering the study.
23. Participants who never enrolled in Study BP41674, or who discontinued participation due to safety reasons, are not eligible for the OOE part.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-01-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	06-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2020
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	08-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	26-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-07-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EU-CTR	CTIS2024-514797-45-00
EudraCT	EUCTR2019-003787-48-NL
CCMO	NL73321.000.20