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A phase II clinical trial to investigate the safety, tolerability and efficacy of TransCon CNP, weekly subcutaneous injections, compared with placebo, in infants with achondroplasia

Submission date
15/12/2023

Recruitment status
No longer recruiting

Registration date
28/02/2024

Overall study status
Ongoing

Last Edited
20/05/2025

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Achondroplasia (ACH) is the most common form of skeletal growth disorder and the most frequent form of disproportionately short stature, where the arms and legs are short in proportion to the body. It occurs with a frequency of 1 in 10,000 to 30,000 live births. A gene mutation causes ACH. Individuals with ACH have a distinct appearance, including short stature but with an average size trunk, a large head with a prominent forehead, and shortened limbs. Associated complications occur at various developmental stages. Newborns with ACH can be at high risk of problems related to growth of the skull and spine, such as a curvature of the spine or spinal cord compression causing weakness. Many infants with ACH may have sleep apnea and recurrent ear infections which may lead to hearing loss. C-type natriuretic peptide (CNP) is a chemical that plays a role in controlling the movement of blood around the body and bone growth. There is an approved treatment using CNP, which requires daily injections under the skin to promote bone growth in children with ACH. However, daily injections can be burdensome. The TransCon™ (Transient Conjugation) technology is designed to provide sustained release of CNP, decreasing injection frequency to once-weekly. TransCon CNP has been used in children aged 2-11 years in previous studies. International clinical recommendations are to investigate children with ACH from birth, and to initiate treatment as early as possible.

Who can participate?
Children aged up to 2 years old with ACH

What does the study involve?
This study will assess the safety and effectiveness of TransCon CNP compared to placebo in infants from birth up to 2 years of age. Participants will be randomised (allocated by chance, like a flip of the coin) into either the placebo or active treatment group for 52 weeks, followed by an optional open-label treatment phase for a further 52 weeks. The study aims to recruit approximately 72 infants worldwide, including North America, Asia-Pacific, Europe and the UK.

What are the possible benefits and risks of participating?
Although no direct health benefits are guaranteed, the treatment may have a positive impact on participants' ACH and may give information leading to better treatments for ACH in the future.

X-rays: X-rays of lower limbs are done to assess bone morphology and growth plate changes. X-rays of the hand and wrist are done to assess epiphyseal changes and bone age. Allowance is made for X-rays to be undertaken on children lying down if they are unable to stand yet. The number of x-rays has been kept to a minimum to minimise exposure to ionising radiation over the 2-year study period. A study specific x-ray manual has been produced to aid the study team on the x-ray procedures. The PISCF specifically asks the parent/caregiver to inform the study site of any other x-rays their child may have had, so that x-ray exposure can be monitored and minimised.
MRI: the number of MRI scans has been kept to a minimum. Participants may be sedated with /without a feed wrap for the procedure. The MRI procedure is explained in the PISCF.
Blood sampling: may cause some discomfort at the time of blood draw, with risk of bruising and irritation around the venepuncture site. There is also a risk of fainting associated with the blood sampling procedure. Only study team members experienced in taking blood samples from very young children will undertake the blood sampling procedures.
The anthropometric measurements require the participant to remain relatively still; this may cause some discomfort for the child to hold their limbs still for the measurements.
The injections may cause some local injection site reactions: parents/caregivers are trained in how to look out for these and record them during their training in administration of the study drug/placebo injections.
The study drug has some known side effects, seen in current TransCon CNP studies in patients aged 2-11 years, the most common being: cough, fever, upper respiratory tract infection, pain in extremity, vomiting, common cold, runny nose, nasal congestion, headache, pain in the joints, and injection site reactions (redness, pain, swelling); these are listed in the parent/caregiver PISCF so they are aware of them.
Other potential side effects (but not seen in the ongoing studies in 2-11 years old participants) include blood pressure changes and bone overgrowth. Bone growth is monitored by the x-ray and MRIs conducted during the study. The PISCF provides some guidance on how to deal with symptoms seen in blood pressure changes if they occur in the child during the study.
There is the risk of an allergic reaction to the study drug. The potential symptoms are listed in the PISCF for parent/caregiver, with instruction on how to report them and what to do in the event of an allergic reaction occurring.
The questionnaires may be a burden for parents/caregivers to complete. Training is provided and the questionnaires are provided on an electronic tablet rather than in paper form, for convenience.
Parents/caregivers will be responsible for administering the weekly injections at home; they can request assistance from homecare nurses if needed, but will be fully trained on the administration of injections in the clinic with the study team, and provided with instructions for use for the injections.
Data from the participant and parent/caregivers will be collected including some personal data and clinical data (e.g. confirmation of heterozygous genotype for ACH is an eligibility assessment criterion, and is collected from patient notes to confirm diagnosis, medical history). Personal data will be handled sensitively and in line with GDPR data protection laws. Participants will be assigned a unique trial ID to minimise use of identifiable personal data during the study. Data collected must be securely kept at study site, and securely transferred e.g. to the electronic data collection forms (which use the unique trial ID). The majority of data collected is pseudonymised, meaning it can be linked back to the individual. The investigator will hold the code securely at the study site.

Where is the study run from?
Ascendis Pharma Growth Disorders A/S

When is the study starting and how long is it expected to run for?
December 2023 to December 2027

Who is funding the study?
Ascendis Pharma Growth Disorders A/S

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2023-506091-27-00

Integrated Research Application System (IRAS)
1008877

ClinicalTrials.gov (NCT)
NCT06079398

Protocol serial number
ASND0030, IRAS 1008877, CPMS 59694

Study information

Scientific Title
A phase II, multicenter, double-blind, randomized, placebo-controlled trial, evaluating safety, tolerability, and efficacy of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in infants (0 to <2 years of age) with achondroplasia followed by an open-label extension (OLE) period

Acronym
reACHin

Study objectives
1. To evaluate the safety and tolerability of TransCon CNP
2. To evaluate the effect of TransCon CNP on growth

1. To evaluate the effect of TransCon CNP on annualized growth velocity (AGV)
2. To evaluate the effect of TransCon CNP on long-term growth
3. To evaluate the effect of TransCon CNP on developmental milestones
4. To evaluate the effect of TransCon CNP on morphology and growth of bones and spine
5. To evaluate the effect of TransCon CNP on foramen magnum morphology and growth
6. To evaluate the treatment impact of TransCon CNP on non-linear growth manifestations and complications in children with achondroplasia
7. To evaluate safety and tolerability of treatment with TransCon CNP
8. To evaluate the pharmacokinetic properties of TransCon CNP
9. To assess the potential immunogenic response to TransCon CNP

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/02/2024, West Midlands - Edgbaston Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; None available; edgbaston.rec@hra.nhs.uk), ref: 24/WM/0006

Study design
Phase II multicenter double-blind randomized placebo-controlled trial with an open-label extension period

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Achondroplasia in infants

Interventions
Blinded phase: Once-weekly subcutaneous injection of 100 µg/kg TransCon CNP for 52 weeks or once-weekly subcutaneous injection of 100 µg/kg placebo for TransCon CNP for 52 weeks. Participants will be randomised in 2:1 ratio (TransCon CNP:Placebo). To balance the treatment groups, participants will be stratified by age and sex for randomization. An internet-based Interactive Response Technology (IRT) is used for randomisation.
Open-Label phase: All participants receive once-weekly subcutaneous injection of 100 µg/kg TransCon CNP.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
TransCon CNP 3.9 mg CNP-38/vial [C-Type natriuretic peptide conjugated to multi-arm polyethylene glycol carrier through a cleavable linker]

Primary outcome(s)
1. Incidence of treatment-emergent adverse events (TEAEs) over 52 weeks, including Grade ≥ 3 TEAEs; serious adverse events (SAEs); TEAEs leading to discontinuation; deaths due to TEAEs, and all deaths. Adverse events will be reported to the Investigator by the participant's parent(s) /caregiver(s) throughout the study.
2. Change from baseline to 52 weeks in length/height Z-score. Length/height will be measured by trained site staff using a standardized and calibrated device at Visit 1, Visits 4 (week 12) through 7 (week 52).

Key secondary outcome(s))
1. Annualized growth velocity (AGV) (cm/year) at 52 weeks and 104 weeks. Length/height will be measured by trained site staff using a standardized and calibrated device at Visit 1, Visits 4 (week 12) through 7 (week 52) and Visits 10 (week 64) through 13 (week 104). AGV is calculated from the measurements of length/height.
2. Change from baseline to 104 weeks in length/height Z-score. Length/height will be measured by trained site staff using a standardized and calibrated device at Visit 1, Visits 4 (week 12) through 7 (week 52) and Visits 10 (week 64) through 13 (week 104).
3. Change from baseline to 52 weeks and 104 weeks in developmental milestones. Assessment of developmental milestones will be performed by trained and certified site staff using the Bayley Scales of Infant and Toddler Development, motor and language domains (Fourth Edition) at Visit 1, Visits 5 (week 26), 7 (week 52),11 (week 78) and 13 (week 104).
4.1. Change from baseline to 52 weeks and 104 weeks in evaluation (X-ray) of long bones and angles in lower limbs (e.g., femur, tibia, fibula, and tibia/fibula and femur/tibia ratio, mechanical axis deviations). X-rays of one hand and lower limbs will be performed at Visit 1, Visit 7 (week 52) and Visit 13 (week 104).
4.2. Change from baseline to 52 weeks and 104 weeks in evaluation of Magnetic Resonance Imaging (MRI) of spine (e.g., spine interpedicular distance (IPD), spine pedicle width (PW), spinal cord volume, and ratio of area of spinal cord to spinal canal). MRI assessments of head and spine will be performed at Screening, Visit 7 (week 52) and Visit 13 (week 104).

5. Change from baseline to 52 weeks and 104 weeks in evaluation of MRI of foramen magnum (e. g., sagittal and transverse diameters, surface area (cm2) of foramen magnum, ratio of spinal cord to foramen magnum area, and Achondroplasia Foramen Magnum Score (AFMS). MRI assessments of head and spine will be performed at Screening, Visit 7 (week 52) and Visit 13 (week 104).
6. Incidence of complications and manifestations of ACH, for example, breathing related sleep disorder, otitis media, hearing loss, musculoskeletal (MS) pain and MS deformities, ACH-related TEAEs reported by investigators. Adverse events will be reported to the Investigator by the participant's parent(s)/caregiver(s) throughout the study.
7. Safety endpoints to be evaluated throughout the trial:
7.1. TEAEs
7.2. Laboratory results of safety blood parameters. Blood samples will be taken for safety assessments at all study visits.
7.3. Vital signs (blood pressure, heart rate, body temperature). Vital signs will be measured at all study visits.
7.4 12-lead electrocardiogram (ECG). ECG will be performed at Screening, Visit 1, Visit 2 (week 4), 3 (week 8), 4 (week 12), 7 (week 52), 9 (week 60), 10 (week 64) and 13 (week 104).
7.5. Abnormal physical examination finding. A physical examination will be performed at all study visits.
7.6. Imaging assessments of bone age, epiphyseal change, bone growth, bone morphology, and foramen magnum. X-rays of one hand and lower limbs will be performed at Visit 1, Visit 7 (week 52) and Visit 13 (week 104). MRI assessments of head and spine will be performed at Screening, Visit 7 (week 52) and Visit 13 (week 104). 8. Plasma concentration of Total CNP, Free CNP, and mPEG. Blood samples will be taken for pharmacokinetic assessments at Visit 1, Visits 2 (week 4), 4 (week 12), 5 (week 26), 7 (week 52), 10 (week 64), 11 (week 78) and 13 (week 104).
9. Detection and characterization of anti-TransCon CNP and anti-CNP antibodies. Blood samples will be taken for anti-drug antibody assessments at Visit 1, Visit 2 (week 4), 4 (week 12), 5 (week 26), 6 (week 39), 7 (week 52), 8 (week 56), 10 (week 64), 11 (week 78), 12 (week 91) and 13 (week 104).

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Written, signed informed consent by the parent(s)/caregiver(s) of the participant, and as required by the institutional review board/human research ethics committee/independent ethics committee (IRB/HREC/IEC).
2. Male or female younger than 2 years of age at the time of randomization; or for open-label sentinel participants, at the time of first administration of IMP.
3. Clinical diagnosis of achondroplasia (ACH) with genetic confirmation of heterozygous genotype present during screening.
4. Parent(s)/caregiver(s) willing to follow the protocol and instructions provided, including being able to administer weekly subcutaneous injections of trial treatment.
5. Compliance with daily Vitamin D supplementation for infants aged 14 days to 1 year. All participants older than 1 year of age with serum 25-hydroxyvitamin D (25OHD) measured below the lower limit of reference range at screening should start daily Vitamin D supplementation before randomization.
6. Considered eligible based on the medical history, physical examination, and the results of vital signs, ECG, imaging, and clinical laboratory tests performed during the screening period.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
0 years

Upper age limit
2 years

Sex
All

Key exclusion criteria
1. Known or suspected hypersensitivity to the investigational product or related products (trehalose, tris[hydroxymethyl]aminomethane, succinate, and polyethylene glycol [PEG]).
2. Genetic confirmation of ACH homozygous genotype.
3. Premature birth with gestational age < 32 weeks.
4. Premature birth with gestational age 32 to 37 weeks, unless time from birth is > 6 months at the time of screening and the child is in good nutritional status, defined as gain in body weight expected for age and diagnosis of ACH, as determined by the Investigator and confirmed with the Medical Monitor.
5. Anticipated, as assessed by the Investigator and confirmed with Medical Monitor, to undergo surgical intervention during trial participation, including cervicomedullary decompression. Evaluation of the immediate risk of requiring cervicomedullary decompression surgery will rely on the following assessments:
5.1. Physical examination (e.g., neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
5.2. Evidence of uncontrolled sleep apnea as confirmed by local standard of care assessment (e.g. polysomnography or simple sleep test) performed within 6 months before screening.
5.3. MRI performed at screening indicating the presence of severe cervicomedullary compression (CMC) or spinal cord damage. The presence of abnormal MRI T2 signal intensity at and immediately above and below the cervicomedullary junction should be considered high risk for requiring surgery and the participant is not eligible for trial participation.
Common surgeries, such as insertion of grommets, adenoidectomy, tonsillectomy, or myringotomy tube placement are permitted during trial participation.
6. Have a growth disorder or medical condition, other than ACH, resulting in short stature or abnormal growth as determined by the Investigator and confirmed with the Medical Monitor.
7. Have received any dose of prescription medications and/or investigational medicinal product or device intended to affect stature, growth, or body proportionality (including human growth hormone or vosoritide) at any time.
8. Requires or anticipated to require chronic (> 4 weeks) or repeated treatment (more than twice /year) with oral corticosteroids, or high-dose inhaled corticosteroids during trial participation.
9. History or presence of injury or disease of the growth plate(s), other than ACH, affecting growth potential of long bones, including Salter-Harris fracture and recent bone-related surgery,

as determined by Investigator and confirmed with the Medical Monitor.
10. Have a clinically significant finding indicating abnormal cardiac function, including but not limited to:
10.1. Repaired or unrepaired coarctation.
10.2. Moderate or greater complexity congenital heart disease including tetralogy of Fallot, atrioventricular septal defects, truncus arteriosus, total anomalous pulmonary venous return, double outlet right ventricle, or single ventricle heart disease.
10.3. QTcF ≥ 450 msec on screening 12-lead ECG.
11. History or presence of a condition impacting hemodynamic stability (such as autonomic dysfunction and orthostatic intolerance).
12. History or presence of the following:
12.1. Chronic anemia.
12.2. Chronic renal insufficiency.
12.3. Chronic or recurrent illness that can affect hydration or volume status, including conditions associated with decreased nutritional intake or increased volume loss.
13. History or presence of malignant disease.
14. Any disease or condition that, in the opinion of the Investigator, may make the participant unlikely to fully complete the trial, not adhering to trial procedures, may confound the interpretation of trial results or may present undue risk from receiving trial treatment. This could include family situations, comorbid conditions, or medications that might impact safety or be considered confounding.

Date of first enrolment
22/01/2024

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
United Kingdom

England

Australia

Austria

Denmark

France

Germany

Ireland

Italy

New Zealand

Norway

Spain

Sweden

United States of America

Study participating centre
Guys and St Thomas' NHS Foundation Trust
Trust Offices Guy's Hospital, Great Maze Pond
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SE1 9RT

Sponsor information

Organisation
Ascendis Pharma (Denmark)

ROR
https://ror.org/022pvsb81

Funder(s)

Funder type
Industry

Funder Name
Ascendis Pharma Denmark

Alternative Name(s)
Ascendis Pharma A/S

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Denmark

Results and Publications

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes