Once-weekly TransCon CNP (navepegritide) in children with achondroplasia (ACcomplisH): a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial

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Summary

Background TransCon CNP (navepegritide) is an investigational prodrug of C-type natriuretic peptide (CNP) designed to allow for continuous CNP exposure with once-weekly dosing. This 52-week phase 2 (ACcomplisH) trial assessed the safety and efficacy of TransCon CNP in children with achondroplasia.

Methods ACcomplisH is a global, randomised, double-blind, placebo-controlled, dose-escalation trial. Study participants were recruited between June 10, 2020, and September 24, 2021. Eligible participants were prepubertal, aged 2–10 years, with genetically confirmed achondroplasia, and randomised 3:1 to once-weekly subcutaneous injections of TransCon CNP (6, 20, 50, or 100 µg CNP/kg/week) or placebo for 52 weeks. Primary objectives were safety and annualised growth velocity (AGV). ACcomplisH is registered with ClinicalTrials.gov (NCT04085523) and Eudra (CT 2019-002754-22).

Findings Forty-two participants received TransCon CNP at doses of 6 µg (n = 10; 7 female), 20 µg (n = 11; 3 female), 50 µg (n = 10; 3 female), or 100 µg (n = 11; 6 female) CNP/kg/week, with 15 receiving placebo (5 female). Treatment-emergent adverse events (TEAEs) were mild or moderate with no grade 3/4 events reported. There were 2 serious TEAEs that were assessed as not related to TransCon CNP. Eleven injection site reactions occurred in 8 participants receiving TransCon CNP and no symptomatic hypotension occurred. TransCon CNP demonstrated a dose-dependent improvement in AGV. At 52 weeks, TransCon CNP 100 µg CNP/kg/week significantly improved AGV vs placebo (least squares mean [95% CI] 5.42 [4.74–6.11] vs 4.35 [3.75–4.94] cm/year; p = 0.0218), and improved achondroplasia-specific height SDS from baseline (least squares mean [95% CI] 0.22 [0.02–0·41]

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vs −0·08 [−0.25 to 0.10]; p = 0.0283). All participants completed the randomised period and continued in the ongoing open-label extension period receiving TransCon CNP 100 µg CNP/kg/week.

Interpretation This phase 2 trial suggests that TransCon CNP is effective, safe, with low injection site reaction frequency, and may provide a novel, once-weekly treatment option for children with achondroplasia. These results support TransCon CNP at 100 µg CNP/kg/week in the ongoing pivotal trial.

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Keywords: Achondroplasia; C-type natriuretic peptide; Growth; TransCon CNP; Paediatric

Research in context

Evidence before this study

A PubMed literature search conducted on March 9, 2023, for articles published in English in the last 10 years using the terms "achondroplasia" and "treatment" showed that treatment of achondroplasia has historically aimed to manage symptoms. Novel treatment options are emerging for patients with achondroplasia, with newly available or investigational products targeting chondrocytes, including vosoritide and TransCon CNP (C-type natriuretic peptide), both of which bind NPR-B to inhibit downstream signaling of the constitutively activated FGFR3 variants, restoring differentiation of chondrocytes and promoting bone growth. Results from a phase 1 trial showed that TransCon CNP was well tolerated in healthy adult volunteers, and subsequently led to the design of a phase 2, global dose-escalation trial of once-weekly TransCon CNP in prepubertal children (aged 2–10 years), ACcomplisH.

Added value of this study

To our knowledge, ACcomplisH is the first randomised, double-blind, placebo-controlled, dose-escalation trial of CNP in children with achondroplasia aged 2–10 years. TransCon CNP resulted in a low frequency of injection site reactions with no incidence of symptomatic hypotension, which has been a potential concern with the development of CNP therapeutics based on the role of CNP in regulating vascular homeostasis, including systemic blood pressure. At the 100 µg CNP/kg/week dose, TransCon CNP demonstrated significantly improved annualised growth velocity compared to placebo. This trial provides the first evidence that TransCon CNP significantly increased annualised growth velocity in children with achondroplasia with a favourable safety profile, thus supporting the continued investigation of its safety and efficacy together with its impact on achondroplasia-related health complications.

Implications of all the available evidence

Results from this randomised placebo-controlled trial demonstrate that once-weekly TransCon CNP had a significant effect on growth in children with achondroplasia aged 2–10 years. In addition to significantly improved annualised growth velocity vs placebo, TransCon CNP was well tolerated, with very few occurrences of injection site reactions, and no incidence of symptomatic hypotension. Additionally, the frequency of achondroplasia-related adverse events within each TransCon CNP cohort was lower than in the pooled placebo group. We consider that the trial results suggest TransCon CNP to be a promising once-weekly treatment option for children with achondroplasia through continuous exposure of unmodified CNP and low Cmax, which may offer a holistic benefit and reduced burden of care on children and caregivers. Investigations are ongoing in an open-label extension period in which participants will be followed for 2 years, as well as in a pivotal trial, to further evaluate the balance of harms and benefits of the 100 µg/kg/week dose of TransCon CNP.

Introduction

Achondroplasia is one of the most common genetic forms of skeletal dysplasia, affecting over 250,000 people globally, and presents with disproportionate short stature and a well-delineated profile of medical complications and psychosocial challenges throughout the lifespan.[1–3] Some of the clinical manifestations are shortening of all limb segments, macrocephaly with frontal bossing, midface hypoplasia and nasal anteversion, thoracolumbar kyphosis, hypermobility of the hips and knees, and tibial bowing.[4,5] Medical complications in individuals with achondroplasia include hypotonia with weakness, otitis media, hearing deficit, upper airway obstruction, sleep-disordered breathing, kyphosis, foramen magnum stenosis, cervicomedullary compression, spinal stenosis, and sudden death.[4]

Achondroplasia is caused by variants of the *FGFR3* gene; these variants lead to the ligand-independent overactivation of the tyrosine kinase receptor FGFR3, which is a negative regulator of endochondral bone growth.[6–8] C-type natriuretic peptide (CNP) is an

endogenous positive regulator of endochondral bone growth that promotes chondrocyte differentiation by inhibiting the FGFR3 signalling pathway.[2,9,10] CNP, therefore, has the potential to inhibit downstream signalling of the constitutively activated FGFR3, consequently restoring chondrocyte differentiation and promoting bone growth.[10–12]

CNP has been validated as a therapeutic target by vosoritide, a recombinant human CNP analogue with a modified N-terminal domain that was shown to increase annualised growth velocity (AGV) in children compared with placebo.[13,14] The side effect profile of vosoritide was generally mild with injection site reactions being the most commonly reported adverse events. Hypotension, predominantly asymptomatic, also occurred frequently. This led to the approval of vosoritide to improve linear growth in children with achondroplasia, with open epiphyses, in several regions including the United States, European Union, Australia, and Japan.[14–17] However, an unmet need remains for a treatment that improves the additional medical complications arising from achondroplasia.

TransCon CNP (navepegritide) is an investigational prodrug of CNP designed to provide sustained release of CNP supporting continuous exposure with a once-weekly dosing regimen. TransCon refers to "transient conjugation," a proprietary drug delivery platform that transiently links an inert carrier to a parent drug with known biology to achieve sustained release.[18] In TransCon CNP, CNP (1–38), which is identical to the corresponding amino acid sequence of the C-terminus of endogenous CNP, is transiently bound (via a proprietary linker) to an inert polyethylene glycol carrier in order to prolong its half-life via shielding from proteolytic degradation and CNP clearance mechanisms until cleavage of the linker under physiologic pH and temperature. This results in the sustained release of active unmodified CNP (1–38) while maintaining a low systemic plasma concentration (C_{max}).[18] Proof-of-principle safety and efficacy of TransCon CNP were established in preclinical studies. Subsequent phase 1 data obtained from 45 healthy adult males administered TransCon CNP or placebo (4:1) showed that TransCon CNP was well tolerated with a pharmacokinetic profile supporting a once-weekly dosing regimen, including a half-life of approximately 120 h.[19] Combined results from these studies support the hypothesis that TransCon CNP, with its unmodified amino acid sequence and delivery method, might offer a novel and effective treatment option for children with achondroplasia with a favourable safety profile and potentially improved patient tolerability and compliance due to its weekly formulation vs daily injection. These results guided the design of ACcomplisH, a phase 2 dose-escalation trial of once-weekly TransCon CNP in prepubertal children (aged 2–10 years). The primary objectives of this 52-week trial were to assess the safety (as assessed by the incidence of treatment-emergent adverse events [TEAEs]) and efficacy (as assessed by AGV) of escalating doses of weekly subcutaneous administration of TransCon CNP (with doses increasing from 6 μg CNP/kg to 100 μg CNP/kg per week) in children with achondroplasia (ClinicalTrials.gov Identifier: NCT04085523).

Methods

Trial design

This phase 2, global, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial investigated four different dose levels of once-weekly, subcutaneously administered TransCon CNP with placebo in prepubertal children (stage 1 breasts for girls or testicular volume <4 mL for boys) with achondroplasia (see Appendix Figure S1 for trial design schematic). This trial was registered in the National Institutes of Health ClinicalTrials.gov database (NCT04085523) on September 11, 2019, and in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT 2019-002754-22) on November 1, 2019. The trial was conducted at 16 academic hospitals and research institutes in eight countries (Australia, Austria, Denmark, Germany, Ireland, New Zealand, Portugal, and the United States) over 52 weeks. A 2-year open-label extension period to evaluate long-term safety and efficacy is underway. An independent Data Monitoring Committee (DMC) was established to oversee the safety data during the trial.

Participants

Eligible children were prepubertal, aged 2–10 years. The clinical diagnosis of achondroplasia was confirmed by genetic testing in all participants. Participants must have been able to stand without assistance and have a caregiver willing and able to administer subcutaneous injections of TransCon CNP or placebo. Exclusion criteria included clinically significant findings that were expected to require surgical intervention during the trial, were musculoskeletal in nature, or were otherwise considered to make a participant unsuitable to undergo trial-related procedures. The protocol (available in the Appendix) contains the complete list of inclusion and exclusion criteria.

Ethics statement

The trial was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice as outlined by the International Conference on Harmonization E6 (R2) and regional regulations. The trial protocol was approved by the relevant ethics boards at each site. Before enrolment, written informed consent was obtained from the parent or legal guardian of each participant and written assent, if feasible given the participant's age, from the participant.

Randomisation and masking

In this double-blind trial, participants were randomly assigned in a 3:1 ratio within each dosing cohort to receive either TransCon CNP or matched, identical placebo for 52 weeks. Participants were randomised with the use of an Interactive Web Response System. No stratification factors were used for randomisation of participants in this trial. Participants, investigators, and caregivers administering injections were all blinded to group assignment.

Procedures

Participants received either TransCon CNP (6, 20, 50, 100 μg CNP/kg) or placebo as assigned, onsite (first dose at week 0) or by their caregiver, administered as weekly subcutaneous injections. Caregivers received training on administering injections onsite at week 0. For the first 4 weeks of the trial, home healthcare service was offered to provide support to the caregiver on administration. For this dose-escalation trial, a gated sequential-cohort procedure was implemented. After 12 weeks of treatment at the 6 μg CNP/kg/week dose, the DMC reviewed the safety data to determine if the next cohort could proceed. Initiation of each cohort was gated by the safety review from the DMC. Participants had scheduled visits at screening, and at weeks 0, 4, 8, 12, 26, 39, and 52. Physical examination, including visual inspection of injection sites, vital sign assessment, and blood chemistry/haematology were performed at all visits. The Clinical Global Impression of Severity (CGI-S) scale, which assesses the clinician's interpretation of each participant's disease severity, was employed at weeks 8, 12, 26, and 39. A full participant-reported outcome/observer-reported outcome validation battery was completed by the caregiver at week 52, and a subset of the validation battery was completed at weeks 0, 8, 12, 26, and 39. The battery included Achondroplasia Experience Measures (AEMs; a child impact measure [ACEM-Impact], a child symptom measure [ACEM-Symptom], and a parent experience measure [APEM]) plus a range of other questionnaires, including Paediatric Quality of Life Inventory, SF-10 Health Survey for Children, Sheehan Disability Scale, the Quality of Life Short Stature Youth [QoLISSY], and Parent Global Impression Items [PGI-S]. Additional trial assessments can be found in the Appendix. Electronic case report forms were used to capture trial-specific data and were kept current to reflect participant status during the trial. An internet-based remote data entry system was used to collect clinical trial data at the investigational sites, and the system was compliant with all applicable regulatory requirements for record keeping and record retention in clinical trials.

Outcomes

The primary objectives were to determine the safety and efficacy of once-weekly subcutaneous doses of TransCon CNP. The safety endpoint included incidence of TEAEs and the primary efficacy endpoint was AGV at 52 weeks. Secondary objectives were to evaluate change in body proportionality (upper to lower body segment ratio) at 52 weeks and pharmacokinetic properties and immunogenic response of once-weekly subcutaneous doses of TransCon CNP. The objectives were centrally evaluated by the Sponsor.

Statistical analysis

A sample size of nine in the active groups (per cohort) and 12 in the placebo group (combined across cohorts) was determined to provide a high (97%) power to detect a treatment difference of 2 cm/year in 12-month AGV at a two-sided significance level of 5%, assuming a standard deviation of 1.1 cm/year.

The full analysis set included all randomly assigned participants who received at least one dose of TransCon CNP or placebo and had a baseline height recorded plus at least one post-baseline height measurement. The safety analysis set included all randomly assigned participants who received at least one dose of TransCon CNP or placebo. There were no missing efficacy data during the randomised period; for safety endpoints, all analyses were based on the observed data, with no imputation of missing data unless otherwise stated. Analyses were conducted by dose level, and results from participants who received placebo were pooled. Data from clinical assessments were summarised using descriptive statistics. Categorical data were presented using counts and percentages of participants. Continuous variables were presented using the number of participants, mean, standard deviation, standard error, median, minimum, and maximum. Statistical significance was defined as $p < 0.05$ (two-sided). For the primary efficacy endpoint (AGV at week 52, calculated as [height (week 52)–height (baseline)] × 365.25/[date (week 52) - date (baseline) + 1]), the primary analysis was an ANCOVA model with AGV at week 52 as the response variable, treatment (dose groups and placebo) and sex as factors, and baseline age and baseline height standard deviation score (SDS) as covariates. A similar ANCOVA model was applied to secondary and exploratory efficacy endpoints with treatment (dose groups and placebo) and sex as factors, and baseline age and the baseline of the corresponding parameter as a covariate. Once the highest investigated dose was established, a sequential testing procedure was used for the comparison between the dose group and pooled placebo group. Descriptive analysis for safety mainly included incidence and type of TEAEs, laboratory values, vital signs, radiographic findings, electrocardiogram parameters, and incidence of anti-drug antibodies. SAS version 9.4 was used for statistical analyses.

Role of the funding source

The funder, Ascendis Pharma, designed the trial and was involved in the collection, analysis, and

interpretation of the trial data. MM, AS, MC, AG, BW, BV, ADS of Ascendis Pharma are coauthors on the report. The corresponding author had accessed and verified the trial data, and made the final decisions regarding the content of the submitted manuscript. All authors reviewed and revised a draft of the manuscript and approved the final submitted manuscript.

Results

Between June 10, 2020, and September 24, 2021, 60 participants were recruited to participate in this trial. After screening, 57 participants (24 females and 33 males) were enrolled and randomly assigned in a 3:1 ratio to receive TransCon CNP or placebo in each of the four cohorts (Fig. 1). Across the dose cohorts, 42 participants received TransCon CNP at weekly doses of 6 µg CNP/kg (n = 10, 70% female, 70% ≥ 5 years), 20 µg CNP/kg (n = 11, 27% female, 55% ≥ 5 years), 50 µg CNP/kg (n = 10, 30% female, 50% ≥ 5 years), or 100 µg CNP/kg (n = 11, 55% female, 73% ≥ 5 years); 15 participants received placebo (33% female, 47% ≥ 5 years) (Table 1). Baseline characteristics were generally similar between treatment groups except for median age, though mean ages were similar, and achondroplasia-specific height SDS. For TransCon CNP and placebo, respectively, 62% (26 of 42) and 47% (7 of 15) were ≥5 years old, and median achondroplasia-specific height SDS was 0.02 vs 0.65. High compliance rates were observed across all study cohorts with minimum rates of 98%, 98%, 96%, 100%, and 92% for participants who received TransCon CNP dosed at 6, 20, 50, and 100 µg CNP/kg/week and placebo, respectively. There were no discontinuations or interruptions of trial treatment during the 52-week randomised double-blind treatment period, which was completed as of September 27, 2022, and no participants were lost to follow-up. All 57 participants have continued into the 2-year open-label extension period.

All randomly assigned participants were included in the safety analyses. An overview of TEAEs is shown in Table 2 and all TEAEs are listed in the Appendix (Table S1). Overall, TEAEs were reported in 95% of participants receiving TransCon CNP across the four dose cohorts and 93% of participants receiving placebo. The most common TEAEs occurring in ≥15% of participants were cough, pyrexia, upper respiratory tract infection, pain in extremity, vomiting, and nasopharyngitis in the TransCon CNP group and pyrexia, cough, vomiting, nasal congestion, otitis media, and snoring in the placebo group (Appendix Table S1). TEAEs were grade 1 or 2 across TransCon CNP dose cohorts and with placebo, with no occurrences of grade ≥3 TEAEs. Serious TEAEs were uncommon (n = 2) with a viral infection occurring in 10% of participants (1 of 10) in the 6 µg CNP/kg/week cohort and febrile convulsion occurring in 10% of participants (1 of 10) in the 50 µg CNP/kg/week cohort; both events resolved with medication.

Treatment-related AEs occurred in 24% of participants (10 of 42) receiving TransCon CNP and 33% (5 of 15) receiving placebo and incidence did not increase with increasing dose (Table 2). Injection site reactions, which included preferred terms of injection site

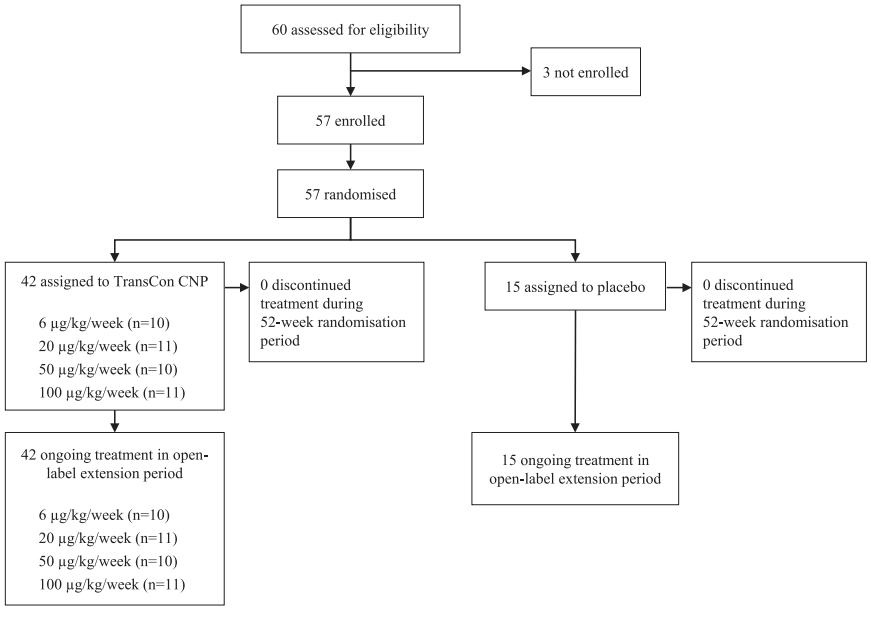

***Fig. 1:* Trial profile**. CNP = C-type natriuretic peptide.

	TransCon CNP					Total placebo (n = 15)
	6 µg CNP/kg/week (n = 10)	20 µg CNP/kg/week (n = 11)	50 µg CNP/kg/week (n = 10)	100 µg CNP/kg/week (n = 11)	Total (n = 42)	
Age, years						
Mean (SD)	6.5 (2.6)	6.3 (2.9)	5.2 (3.0)	5.8 (2.6)	6.0 (2.7)	5.9 (3.1)
Median (IQR)	6.8 (4.3, 8.1)	7.3 (3.7, 8.0)	4.7 (2.7, 6.8)	5.4 (3.6, 7.4)	5.6 (3.7, 7.6)	4.9 (2.8, 8.3)
<5 years	3 (30%)	5 (45%)	5 (50%)	3 (27%)	16 (38%)	8 (53%)
≥5 years	7 (70%)	6 (55%)	5 (50%)	8 (73%)	26 (62%)	7 (47%)
Sex						
Female	7 (70%)	3 (27%)	3 (30%)	6 (55%)	19 (45%)	5 (33%)
Male	3 (30%)	8 (73%)	7 (70%)	5 (45%)	23 (55%)	10 (67%)
Race						
White	8 (80%)	10 (91%)	8 (80%)	10 (91%)	36 (86%)	12 (80%)
Other	2 (20%)	1 (9%)	2 (20%)	1 (9%)	6 (14%)	3 (20%)
Height, cm						
Mean (SD)	90.63 (8.97)	92.29 (12.10)	86.61 (12.97)	89.23 (12.82)	89.74 (11.61)	90.85 (14.92)
Median (IQR)	90.25 (84.97, 100.33)	93.70 (81.13, 103.80)	84.70 (72.53, 96.07)	90.23 (74.73, 98.37)	90.08 (80.73, 98.37)	89.70 (73.33, 104.43)
Height SDS[a]						
Mean (SD)	−5.45 (1.05)	−4.87 (0.67)	−4.85 (0.80)	−4.92 (0.83)	−5.02 (0.85)	−4.85 (0.96)
Median (IQR)	−5.80 (−6.44, −4.19)	−4.66 (−5.39, −4.28)	−5.14 (−5.29, −3.90)	−4.64 (−5.80, −4.27)	−5.12 (−5.69, −4.27)	−4.69 (−5.60, −3.96)
Height SDS, ACH-specific[b]						
Mean (SD)	−0.20 (0.70)	0.28 (0.68)	0.21 (0.67)	0.11 (0.77)	0.11 (0.70)	0.43 (0.91)
Median (IQR)	−0.36 (−0.76, 0.49)	0.28 (−0.28, 0.94)	0.09 (−0.33, 0.52)	0.02 (−0.65, 0.61)	0.02 (−0.38, 0.61)	0.65 (−0.21, 0.96)

Data are mean (SD), median (IQR), or n (%). ACH = achondroplasia; CDC=Centers for Disease Control and Prevention; CNP]C-type natriuretic peptide; IQR = interquartile range; SDS = standard deviation score. [a]According to CDC 2000 Stature-for-Age Charts, available at https://www.cdc.gov/growthcharts/data_tables.htm. Accessed January 31, 2023. [b]According to Hoover-Fong JE et al. *Orphanet J Rare Dis*. 2021; 16 (1):522.[20]

Table 1: **Baseline characteristics (full analysis set).**

reaction, injection site pain, injection site erythema, injection site discolouration, injection site haemorrhage, and injection site swelling, were reported in 19% of participants (8 of 42) receiving TransCon CNP and 13% of participants (2 of 15) receiving placebo (Appendix Table S2). Out of 2212 injections, there were 11 injection site reactions (all grade 1) reported in eight participants across the TransCon CNP treatment groups.

	TransCon CNP				Total placebo (n = 15)
	6 µg CNP/kg/week (n = 10)	20 µg CNP/kg/week (n = 11)	50 µg CNP/kg/week (n = 10)	100 µg CNP/kg/week (n = 11)	
Any TEAE	9 (90%)	11 (100%)	10 (100%)	10 (91%)	14 (93%)
Grade 1	9 (90%)	11 (100%)	10 (100%)	9 (82%)	14 (93%)
Grade 2	3 (30%)	3 (27%)	3 (30%)	1 (9%)	5 (33%)
Grade ≥3	0	0	0	0	0
Serious TEAEs	1 (10%)	0	1 (10%)	0	0
Treatment-related TEAEs	3 (30%)	2 (18%)	3 (30%)	2 (18%)	5 (33%)
Achondroplasia-related TEAEs[a]	3 (30%)	4 (36%)	5 (50%)	1 (9%)	9 (60%)
Infections and infestations	1 (10%)	2 (18%)	3 (30%)	0	5 (33%)
Otitis media	1 (10%)	2 (18%)	2 (20%)	0	3 (20%)
Musculoskeletal and connective tissue disorders	1 (10%)	1 (9%)	3 (30%)	1 (9%)	2 (13%)
Respiratory, thoracic, and mediastinal disorders	1 (10%)	2 (18%)	1 (10%)	0	3 (20%)
Snoring	1 (10%)	1 (9%)	1 (10%)	0	3 (20%)

Data are n (%). CNP]C-type natriuretic peptide; TEAE = treatment-emergent adverse events. [a]Adverse events reported by the investigator as related to comorbidity of achondroplasia.

Table 2: **Overview of TEAEs during the randomised double-blind period.**

	AGV (cm/year), LS mean, n [95% CI]	p value
TransCon CNP 6 µg CNP/kg/week	4.09, n = 10 [3.34–4.84]	0.6004
TransCon CNP 20 µg CNP/kg/week	4.52, n = 11 [3.82–5.22]	0.7022
TransCon CNP 50 µg CNP/kg/week	5.16, n = 10 [4.43–5.90]	0.0849
TransCon CNP 100 µg CNP/kg/week	5.42, n = 11 [4.74–6.11]	0.0218
Pooled placebo	4.35, n = 15 [3.75–4.94]	NA

AGV = annualised growth velocity; CNP = C-type natriuretic peptide; LS = least squares; NA = not applicable.

Table 3: **AGV with TransCon CNP vs placebo at week 52.**

Other treatment-related AEs were upper abdominal pain and urticaria, occurring in one participant (2%) each in the TransCon CNP group and overdose, dizziness, and sleep terror in one participant (7%) each in the placebo group. Achondroplasia-related AEs, as reported by the investigator, generally occurred less frequently among participants receiving TransCon CNP (31%; 13 of 42 participants) compared with placebo (60%; 9 of 15), including, otitis media, which occurred in 12% (5 of 42) and 20% (3 of 15) of participants, respectively. Similar trends were observed regardless of age, with achondroplasia-related AEs occurring in 31% (8 of 26) in the TransCon CNP group and 57% (4 of 7) in the placebo group among participants aged >5 years, and 31% (5 of 16) in the TransCon CNP group and 63% (5 of 8) in the placebo group among participants aged ≤5 years. No serious TEAEs related to treatment were reported, and no AEs of symptomatic hypotension were observed.

A transient and low titre anti-CNP antibody response was observed in one participant who received TransCon CNP dosed at 100 µg CNP/kg/week; no clinically relevant impact on safety or efficacy was identified in this participant.

TransCon CNP dosed at the 100 µg CNP/kg/week resulted in significantly higher AGV than placebo (least squares mean AGV of 5.42 cm/year [95% CI 4.74–6.11] vs 4.35 cm/year [95% CI 3.75–4.94], p = 0.0218). A dose-dependent increase in AGV was observed with TransCon CNP across the four cohorts, with the 6, 20, and 50 µg CNP/kg/week dose cohorts showing non-significant increases compared with placebo (Table 3, Fig. 2A). Furthermore, the change in achondroplasia-specific height SDS with TransCon CNP dosed at 100 µg CNP/kg/week was significantly greater than with placebo (least squares mean of 0.22 [95% CI 0.02–0.41] and –0.08 [95% CI –0.25 to 0.10], p = 0.0283; Fig. 2B, Appendix Table S3). Similar to AGV, a dose-dependent increase in achondroplasia-specific height SDS was observed with TransCon CNP across the four cohorts, with the 6, 20, and 50 µg CNP/kg/week dose cohorts showing non-significant differences compared with placebo.

Across all groups, there were no trends to suggest a clinically meaningful change in body proportionality of upper to lower body segment ratio at week 52. For the 100 µg CNP/kg/week cohort of TransCon CNP, the least squares mean change from baseline in upper-to-lower body ratio was –0.098 (Appendix Table S4).

No trends suggesting worsening of symptom severity or decreases in health-related quality of life measures were observed based on PGI-S, CGI-S, SF-10, and QoLISSY assessments. For the SF-10 assessment, participants receiving TransCon CNP dosed at 100 µg CNP/kg/week had a non-significant numerical improvement in the Physical and Psychosocial

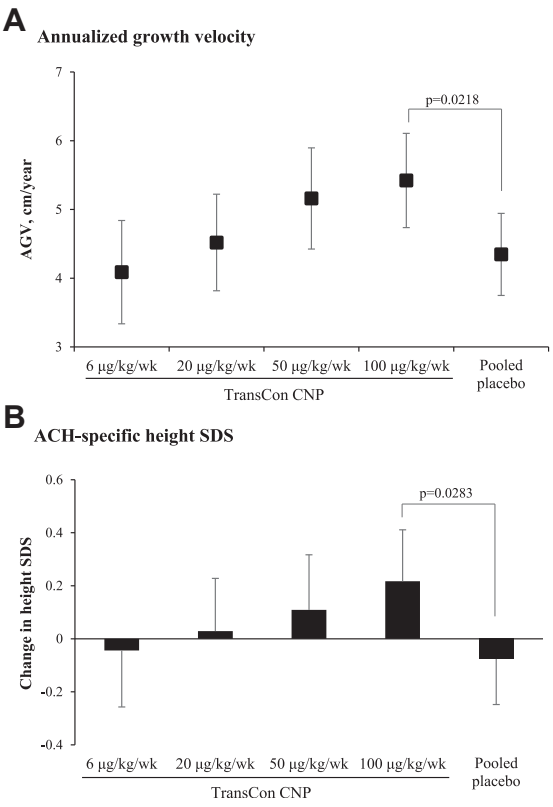

Fig. 2: **Annualised growth velocity (A) and ACH-specific height SDS (B) with TransCon CNP vs placebo.** ANCOVA model was used for statistical analysis. ACH = achondroplasia; AGV = annualised growth velocity; ANCOVA = analysis of covariance; CNP = C-type natriuretic peptide; SDS = standard deviation score.

summary measures, with an additional non-significant numerical improvement in those who were older than 5 years of age, while participants receiving placebo had worsening scores for both summary measures (Appendix Figure S2). For QoLISSY, TransCon CNP dosed at the 100 μg CNP/kg/week dose showed trends of improvements in all domains from baseline while response patterns among participants receiving placebo were inconsistent and variable. Furthermore, there were no statistically significant differences for any of the QoLISSY survey domain items between participants receiving TransCon CNP 100 μg CNP/kg/week and placebo.

Discussion

This phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial showed that weekly subcutaneous injection of TransCon CNP exhibited a dose-dependent improvement in AGV, with the 6, 20, and 50 μg CNP/kg/week dose cohorts showing non-significant increases compared with placebo. At a dose of 100 μg per kg per week, TransCon CNP was associated with a favourable safety and tolerability profile, including an overall low frequency of injection site reactions, fewer achondroplasia-related adverse events, and resulted in significant increases in AGV as compared to placebo in children with achondroplasia aged 2–10 years after 52 weeks of treatment.

Designing clinical trials to assess potential therapeutic interventions in children with achondroplasia is challenging. While hallmarks of the condition include short stature and disproportional skeletal growth, associated complications can cause substantial morbidities and impact quality of life. The FDA has acknowledged AGV at week 52 as a reasonable, clinically and statistically meaningful primary efficacy endpoint in children with achondroplasia.[21,22] Regulatory guidance also recommends measuring additional clinically meaningful outcomes, such as frequency of achondroplasia-specific adverse events, including otitis media, and quality-of-life assessments.[22]

ACcomplisH assessed the primary endpoint of AGV at week 52 in children as young as 2 years of age treated with TransCon CNP as compared with placebo. Natural history studies show that the growth in children aged 2–5 years is relatively high compared to those older than 5 years of age and prior to puberty.[20,23,24] Results from previous studies have shown higher variability (i.e., standard deviation) in change in AGV at week 52 from a 6-month run-in at baseline compared with AGV at week 52.[13,25] This variability might be even more pronounced in a younger trial population when relative AGV is higher. AGV, previously accepted as a primary endpoint within the field of growth disorders, was selected as an age-appropriate endpoint for this trial investigating children as young as 2 years of age. To align with the abovementioned regulatory guidance, exploratory endpoints beyond linear growth were also included.

The results presented here suggest that TransCon CNP may be a novel treatment option for children with achondroplasia. Currently, the only approved treatment for children with achondroplasia is vosoritide, a once-daily subcutaneous injection of CNP, which is approved by the FDA in children with achondroplasia 5 years of age and older with open epiphyses.[14] In the phase 3 trial, vosoritide was associated with a higher reported incidence of injection site reactions compared to placebo.[13] In ACcomplisH, a relatively low incidence of injection site reactions was reported with TransCon CNP administered once weekly. This might reduce the burden of treatment on young children with achondroplasia and their caregivers and improve long-term compliance rates and outcomes in this population. In addition, there were no reported cases of symptomatic hypotension with TransCon CNP, potentially due to the sustained-release profile and low maximum concentration that has been observed. In the phase 3 trial of vosoritide, symptomatic hypotension was observed in 2% of patients treated with vosoritide.[13] It should be noted that TransCon CNP and vosoritide have not been studied in the same trial and cross-trial comparisons should be interpreted with caution given differences in study design. For example, this was a phase 2 dose-finding study (n = 11 treated TransCon CNP at 100 μg CNP/kg/week; n = 57 overall) with patients as young as 2 years of age vs the phase 3 pivotal study of vosoritide (n = 60 treated with vosoritide; n = 121 overall) of patients aged 5 years of age and older.[13] Furthermore, as discussed above, the primary endpoint of these trials was AGV observed at week 52 in this study vs change from baseline for the phase 3 trial of vosoritide,[13] as was appropriate for their respective trial designs as it relates to participant age.

This trial showed that 52 weeks of once-weekly TransCon CNP at a dose of 100 μg CNP/kg/week resulted in a statistically significant increase in AGV vs placebo, with an AGV of 5.42 cm/year in children aged 2–10 years. These results demonstrate the viability of TransCon CNP in improving linear growth similar to the phase 3 trial of vosoritide that demonstrated an AGV of 5.61 cm/year, which was a secondary endpoint for this trial at week 52.[13] Furthermore, the results of ACcomplisH offer a favourable safety and tolerability profile that will be further explored in future studies, which will include assessments of achondroplasia-related comorbidities and complications. Collectively, these data support the advancement of TransCon CNP (at a dose of 100 μg CNP/kg/week) in a pivotal, double-blind, randomised controlled trial in children with achondroplasia aged 2–11 years (ClinicalTrials.gov Identifier: NCT05598320).

The main limitation of this trial, like other studies of new precision therapies in children with

achondroplasia, is that a direct evaluation of the effect of TransCon CNP treatment on final adult height is not possible. In this trial, the primary outcome focuses on increases in AGV with extrapolated increases in final adult height. Additionally, due to the dose-finding nature of the trial and the small sample size, the cohorts may have had greater variation in baseline characteristics, such as median age, which may have led to apparent differences in outcomes. Furthermore, due to the small sample size, the magnitude of the treatment effect could be over- or under-estimated, and the trial could not be powered for quantifying the trends observed in achondroplasia-related complications and impacts beyond linear growth. These findings and any results that further divide patient subgroups should be interpreted with caution and validated in a larger study to confirm the observed treatment benefits. While this trial was not designed and powered to detect differences in quality of life, SF-10 and QoLISSY did show some trends in improvements in several summary measures. A patient-centric approach to evaluating achondroplasia that assesses the broader clinical sequelae of the condition will be further investigated in the ongoing long-term, open-label extension trial of TransCon CNP that will follow participants until near-final adult height, as well as in the pivotal, randomised, controlled trial.

Due to the relatively short duration of this trial, it is yet to be seen if the improvements in bone growth observed in children with achondroplasia treated with TransCon CNP will lead to improved quality of life, and decreased morbidity and mortality compared with untreated children. As most of the comorbidities in individuals with achondroplasia are directly linked to the impaired bone growth of their axial and appendicular skeleton,[2,4] it is not unreasonable to expect that improvements in this underlying basic pathology will likely improve these complications.

Therapeutic options for treating children with achondroplasia have been historically limited until recently with the approval of vosoritide and with the clinical development of other treatments, including TransCon CNP described in this report, an oral tyrosine kinase inhibitor (infigratinib), and an FGFR3 antibody (SAR442501).[26,27] Clinical development of an FGFR3 ligand trap therapy (recifercept) was discontinued as an interim analysis of a phase 2 trial suggested the primary endpoint would not be met.[28,29] Time will tell which of these agents might prove to be the most effective for these children and at what age, including which will have the optimal overall benefit:risk ratio, and whether a combination of therapies may lead to more robust improvements than monotherapy.

Our trial data indicate that once-weekly TransCon CNP administration has the potential to be a viable longer-acting treatment option in children with achondroplasia. The main challenge in the field at this time relates to confirming that these new therapies will increase final adult height in children with achondroplasia, are safe in the long-term, and that height gains are accompanied by improved functionality and quality of life, and reduced burden of achondroplasia-related complications.

Contributors

RS prepared the initial draft of the manuscript, and all authors critically reviewed and revised the manuscript. RS, DGH, ML, YAZ, CAB, MBB, JML, WH, TQ, MJA, PLH, KKW, NSM, DS, SBS, and CM recruited and enrolled participants and contributed to the collection and interpretation of data. MM performed clinical statistical analyses, and AS conducted analyses of participant-/observer-reported outcomes. RS, MM, AS, MC, AG, BW, BV, and ADS had full access to the data and vouch for the data as reported.

Data sharing statement

Deidentified individual participant data, the trial protocol, data dictionaries, and other applicable supporting clinical trial documents will, absent legal reasons to the contrary, be made available for non-commercial, academic purposes upon request.

Declaration of interests

RS reports participation on advisory boards with Ascendis and BioMarin and consulting role for BridgeBio. AGH reports research funding from, speaker's bureau support for, and grants from Zimvie; patents and stock options with, consulting for, and travel support from Orthopediatrics; and honoraria from BioMarin. ML reports consulting role with and travel support from Ascendis. CAB reports research funding from Ascendis, BioMarin, Ionis, NIH, and Roche; board member for the American Board of Medical Genetics and Genomics; author for 8 chapters in Genetics in UpToDate. MBB reports research funding from Ascendis, BioMarin, QED, and Therachon/Pfizer; consulting fees from Tyra; honoraria from Novo Nordisk; participation on a data and safety monitoring board (DSMB) for BioMarin, QED, and Therachon/Pfizer; and leadership for SDMC. JML reports research funding and honoraria from BioMarin and travel support from Ascendis. WH reports research funding and consulting fees from Ascendis and consulting fees from BioMarin. TQ reports research funding from Ascendis, Janssen, Merck, NIH, and Provention Bio; consulting fees from Janssen and Provention Bio; honoraria from Merck and MH Life Sciences; expert testimony payment from Janssen; and travel support from Provention Bio. MJA reports research funding from Ascendis, Lumos, MannKind, Medtronic, Novo Nordisk, Rhythm, and Soleno; participation on a DSMB for Ascendis, Broad Group, Rhythm, and Pfizer; and leadership with Raymond A Wood Foundation. KKW reports honoraria from BioMarin; patents with UpToDate; and research funding from Ascendis, BioMarin, Pfizer, and Ultragenyx. NSM reports research funding from and consulting role for Ascendis. DS reports honoraria from Hexal/Sandoz, Kyowa Kirin, Novo Nordisk, and Pfizer; travel support from Ascendis and Novo Nordisk; participation on a DSMB for Ascendis, BioMarin, Hexal/Sandoz, Kyowa Kirin, and Novo Nordisk; and leadership with German Society for Pediatric Endocrinology and Diabetes. SBS reports honoraria from and advisory role for Ascendis and BioMarin; honoraria from Kiowa Kirin; and travel support from BioMarin. MM, AS, MC, AG, BW, BV, and ADS report employment and stock options with Ascendis. CM reports research funding and travel support from Ascendis; consulting role with BioMarin; travel support from Pfizer; leadership with International Society of Children's Bone Health. YAZ and PLH have no conflicts to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102258.

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