Vosoritide therapy in children with achondroplasia aged 3–59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Vosoritide is a recombinant C-type natriuretic peptide analogue that increases annualised growth velocity in children with achondroplasia aged 5–18 years. We aimed to assess the safety and efficacy of vosoritide in infants and children younger than 5 years.

Methods This double-blind, randomised, placebo-controlled, phase 2 trial was done in 16 hospitals across Australia, Japan, the UK, and the USA. Children younger than 60 months with a clinical diagnosis of achondroplasia confirmed by genetic testing and who had completed a baseline growth study or observation period were enrolled into one of three sequential cohorts based on age at screening: 24–59 months (cohort 1); 6–23 months (cohort 2); and 0–5 months (cohort 3). Each cohort included sentinels who received vosoritide to determine appropriate daily drug dose, with the remainder randomly assigned (1:1) within each age stratum (except in Japan, where participants were randomly assigned within each cohort) to receive daily subcutaneous injections of vosoritide (30·0 µg/kg for infants aged 0–23 months; 15·0 µg/kg for children aged 24–59 months) or placebo for 52 weeks. Participants, caregivers, investigators, and the sponsor were masked to treatment assignment. The first primary outcome was safety and tolerability, assessed in all participants who received at least one study dose. The second primary outcome was change in height Z score at 52 weeks from baseline, analysed in all randomly assigned participants. This trial is registered with EudraCT, 2016-003826-18, and ClinicalTrials.gov, NCT03583697.

Findings Between May 13, 2018, and March 1, 2021, 75 participants were recruited (37 [49%] females). 11 were assigned as sentinels, whereas 32 were randomly assigned to receive vosoritide and 32 placebo. Two participants discontinued treatment and the study: one in the vosoritide group (death) and one in the placebo group (withdrawal). Adverse events occurred in all 75 (100%) participants (annual rate 204·5 adverse events per patient in the vosoritide group and 73·6 per patient in the placebo group), most of which were transient injection-site reactions and injection-site erythema. Serious adverse events occurred in three (7%) participants in the vosoritide group (decreased oxygen saturation, respiratory syncytial virus bronchiolitis and sudden infant death syndrome, and pneumonia) and six (19%) participants in the placebo group (*petit mal* epilepsy, autism, gastroenteritis, vomiting and parainfluenza virus infection, respiratory distress, and skull fracture and otitis media). The least-squares mean difference for change from baseline in height Z score between the vosoritide and placebo groups was 0·25 (95% CI −0·02 to 0·53).

Interpretation Children with achondroplasia aged 3–59 months receiving vosoritide for 52 weeks had a mild adverse event profile and gain in the change in height Z score from baseline.

Funding BioMarin Pharmaceutical.

Introduction

Achondroplasia is the most common heritable disorder of the skeleton, causing disproportionate short stature. Globally, more than 360 000 individuals are estimated to have achondroplasia, with the potential for medical complications, functional limitations, and psychosocial challenges.[1] Management of achondroplasia is evolving from purely symptomatic treatment of medical complications to identification of drugs that ameliorate the abnormal skeletal growth that underpins nearly all the morbidity and mortality in achondroplasia. Achondroplasia is caused by a gain-of-function mutation in the gene encoding fibroblast growth factor receptor 3 (FGFR3), which results in impaired endochondral ossification. Human growth hormone has been administered to children with achondroplasia but does not have a significant or durable effect on growth.[2] Vosoritide, a recombinant C-type natriuretic peptide analogue and the first drug addressing the underlying molecular defect in achondroplasia, was approved for children with achondroplasia in 2021 by the European Medicines Agency and the US Food and Drug Administration based primarily

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Research in context

Evidence before this study

We searched PubMed on Sept 5, 2023, for original research and reviews published in English since Jan 1, 2000, using the following search terms: "achondroplasia", "C-natriuretic peptide", "growth hormone", "FGFR3", "management", and "treatment". The development of potential new therapies for children with achondroplasia has been an area of interest in the past decade. Vosoritide was the first C-type natriuretic peptide analogue to be approved for children with achondroplasia: aged 5 years or older in the USA; aged 2 years or older in Australia, Brazil, and Europe; and from birth in Japan, until closure of epiphyses. TransCon CNP, a C-type natriuretic product with a longer half-life than vosoritide and engineered for weekly administration by subcutaneous injection, is in clinical development for children with achondroplasia. Other therapies that address the underlying pathogenesis of achondroplasia in mouse models, and are in clinical development, include infigratinib (selective oral tyrosine kinase fibroblast growth factor [FGF] receptor 3 inhibitor), RMB-007 (FGF2 aptamer), and meclozine (histamine 1 receptor blocker that inhibits the FGFR3–extracellular signal-regulated kinase pathway). Phase 2 clinical trials of a soluble FGFR3 molecule used as a ligand trap (recifercept) were ceased due to futility. At the time of this search, no peer-reviewed safety or efficacy data for TransCon CNP, infigratinib, RMB-007, or meclozine support their use in children with achondroplasia.

Added value of this study

To our knowledge, this is the first randomised, double-blind, placebo-controlled trial to assess the balance of harms and benefits of daily subcutaneous administration of vosoritide treatment in children with achondroplasia aged 3–59 months. The age at which vosoritide therapy can be commenced for children with achondroplasia varies internationally. The data from this study have recently informed on decisions by health authorities to expand this use from birth in the USA and from age 4 months in Europe.

Implications of all the available evidence

We report harms and benefits of vosoritide treatment that are consistent with findings from the open-label, dose-finding phase 2 study and the randomised, placebo-controlled phase 3 trial in children aged 5 years and older. The children enrolled in these studies will be followed up until they reach final adult height to assess durability of response. To our knowledge, this study provides the first evidence for a precision therapy for infants and toddlers with achondroplasia. It will serve as a benchmark against which other emerging precision therapies for achondroplasia can be compared.

on studies in children aged 5 years and older that supported its safety profile and efficacy, as assessed by increased annualised growth velocity.[3,4] The safety and efficacy of vosoritide treatment in younger children with achondroplasia are unknown.

Distinct patterns of linear growth are driven by differences in growth velocity between children with achondroplasia and those of average stature. Differences in growth velocity are particularly apparent during infancy. Growth velocity in children with achondroplasia younger than 2 years is characterised by wide variability and a rapid decline, especially during the first 6 months. The height deficit (measured by decrease in height Z score in reference to children with average stature) accumulates rapidly up to age 2 years, with a more gradual decline at age 2–5 years.[5] In children with achondroplasia aged 2–10 years, median annual growth velocity is 4–5 cm, compared with 5–7 cm in children with average stature.[5] The pubertal growth spurt during adolescence is absent in children with achondroplasia, with growth continuing at a gradually declining, pre-adolescent rate until attainment of final height.[5]

At birth, children with achondroplasia have abnormalities in the base of the skull and boundaries of the foramen magnum due to defective endochondral ossification, resulting in stenosis of the foramen magnum and compression of the vital neural and vascular structures passing through this region. Foramen magnum stenosis has been implicated as the major underlying cause of an increased risk of sudden death in children younger than 5 years with achondroplasia.[6,7]

The aim of this study was to assess the balance of harms and benefits of vosoritide in children with genetically confirmed achondroplasia aged 3–59 months.

Methods

Study design and participants

This was a double-blind, randomised, placebo-controlled, phase 2 trial. Across 16 hospitals (nine in the USA, three in Japan, two in Australia, and two in the UK), children age 3–59 months with a genetically confirmed clinical diagnosis of achondroplasia and baseline annualised growth velocity were screened, during which detailed medical history was obtained and physical examination was completed to collect data on vital signs, growth parameters, clinical laboratory results, health-related quality of life, and concomitant treatments. Exclusion criteria included other short stature conditions, coexisting endocrine disorders, abnormal cardiac function or rhythm, evidence of cervicomedullary spinal cord compression, bodyweight less than 5·0 kg, past or planned limb-lengthening surgery, and fractures of the long bones during the 6 months before enrolment. Full eligibility criteria are provided in the appendix (pp 12–14).

Eligible participants were enrolled into one of three sequential cohorts based on age at screening: 24–59 months (cohort 1), 6–23 months (cohort 2), and

See Online for appendix

0–5 months (cohort 3; appendix p 55). At least three participants in each cohort were directly assigned as sentinels and received vosoritide. Previous analyses of pharmacokinetic data from phase 1 in healthy adults aged 18 years or older (NCT01590446) and phase 2 in children with achondroplasia aged 5–12 years (NCT03583697) had indicated that bodyweight had a non-linear effect on vosoritide clearance, resulting in the same weight-based dose yielding lower exposure (maximum drug concentration and area under the curve) in children with achondroplasia than in healthy adults. The sentinels yielded pharmacokinetic data of vosoritide that was evaluated by an independent data monitoring committee to determine the daily dose of vosoritide to use for the remaining randomly assigned participants (appendix pp 7, 23, 24). Following study completion, participants in all groups were eligible to receive vosoritide in an ongoing open-label extension study (NCT03989947) to assess the long-term safety and efficacy of treatment.

This trial was performed in accordance with the Declaration of Helsinki. The study protocol (appendix pp 176–311) was approved by the relevant ethics boards at each site. Participants' legally authorised representatives provided written informed consent and sex data. Investigators and participants could suspend or discontinue administration of vosoritide at any time.

Randomisation and masking

Once sentinel data were evaluated, the remaining participants were randomly assigned (1:1) to receive vosoritide or matched, identical placebo. Randomisation was done by age strata (≥24 to <36 months and ≥36 to <60 months in cohort 1; 6 to <15 months and ≥15 to <24 months in cohort 2; no age stratification in cohort 3) using an interactive, automated voice-response or web-response system by SUVODA (Conshohocken, PA, USA). The randomisation list was created with FlexRandomizer (Cytel, Waltham, MA, USA), using block size of four applied within each age stratum. To fulfil requirements in Japan for registration, participants were randomly assigned separately (among Japanese participants and not within the global trial cohort) to ensure that around half of the Japanese participants would be allocated to treatment. The Japanese randomisation was performed within each cohort but not within the age stratification because of the small number of participants.

An independent third-party vendor developed the randomisation schedule so that BioMarin (London, UK, and Novato, CA, USA) staff and trial site personnel were masked to treatment assignments. Participants, investigators, caregivers administering injections, and assessors analysing outcome data were also masked to treatment assignment. A masking plan was also used to ensure that study personnel could not be unmasked by certain post-baseline data such as pharmacokinetic and specific laboratory parameters.The randomisation list was received by the BioMarin Data Science group after the final database lock.

Procedures

For 52 weeks, participants received vosoritide or placebo, as per randomly assigned treatment allocation, by daily subcutaneous injection. Vosoritide or placebo was initially administered (with site rotation) in the clinic by site staff. Once participants were tolerating vosoritide or placebo and specified criteria had been met (appendix p 69), treatment was administered at home by authorised caregivers who were trained in storage, reconstitution, and administration of vosoritide, as well as on reporting of adverse events and vigilance for signs of hypotension.

Participants were required to attend the study site for scheduled visits on days 1, 2, 3, and 8, at weeks 3, 6, and 20, and at months 3, 6, 9, and 12 after treatment initiation. Full medical clinical assessments, vital sign assessment, and anthropometric measurements were completed at each visit. Blood pressure and pulse rate were monitored frequently during the initial study visits, for 2 h after each dose during the first 3 days of treatment, and for 1 h on subsequent visits. Serum immunogenicity samples for assessment were collected pre-dose on day 1, and at weeks 3, 13, 26, and 52. Study assessments are described in full in the appendix (pp 16–17).

An electronic data capture system (EDCS; Medidata Rave New York City, NY, USA) was used to collect study data at each site. Data were entered into the EDCS by site staff, source data were verified by the clinical research associate responsible at each site, and all data were reviewed and cleaned using a combination of electronic edit checks, manual checks, and data listing review. Serious adverse events were reconciled against the Argus safety database. Medical conditions and medications were coded with Medidata Coder using the Medical Dictionary for Regulatory Activities (version 24.1) and WHO Drug Global B3 (for studies starting after March 1, 2021) dictionaries and graded for severity using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). External vendor data underwent formal reconciliation procedures upon receipt, and all stored data in the EDCS were approved via eSignature by each site's principal investigator. Both the funder and an independent, external data monitoring committee regularly reviewed all safety and pharmacokinetic data.

Outcomes

This trial had two co-primary outcomes, the first of which was the safety and tolerability of a once-daily subcutaneous dose of vosoritide in children with achondroplasia aged 3–59 months. Safety was evaluated by the incidence of adverse events, serious adverse events, laboratory test results, vital signs, results of physical examination, electrocardiogram and echocardiogram results, clinical hip assessment, and anti-vosoritide immunogenicity responses. Imaging assessments

provided measurements of the spine and long bones of the legs, along with data on the growth plate, bone mineral density, and bone age (appendix p 8). The second co-primary outcome was change in height Z score between baseline and week 52.

Secondary efficacy outcomes were change, from baseline to week 52, in standing height or body length, annualised growth velocity, and upper-to-lower body segment ratio. We also compared effects of vosoritide on sleep apnoea using polysomnography (appendix p 7), skull and brain morphology using MRI (appendix p 8), pharmacokinetics and immunogenicity of vosoritide, change from baseline in bone metabolism markers including serum collagen type X marker (a biomarker of endochondral ossification[8]), change from baseline in extremity body proportion ratios, and bone quality and age. We used the Infant Toddler Quality of Life Questionnaire (ITQoL), Functional Independence Measure for Children II (WeeFIM II, version 6.4), and the Bayley Scales of Infant and Toddler Development (Third Edition; BSID-III) to assess changes in health-related quality of life and functional independence.

Statistical analysis

No formal sample size calculations were made to power the study because there was no confirmatory testing. The statistical analysis plan was written before the database was locked and hence before unblinding of the study.

The safety population included all participants who received at least one dose of vosoritide or placebo during the study. Two analysis populations were prespecified in the statistical analysis plan to assess efficacy: all treated participants and all randomly assigned participants. Efficacy outcomes are summarised only by treatment allocation in randomly assigned participants and by cohort. Results for the all-treated population are not reported. Safety outcomes are summarised for the overall population by treatment allocation.

For the primary efficacy outcome and the secondary efficacy outcomes, we used ANCOVA models to determine the least-squares mean difference for change from baseline between vosoritide minus placebo. The models included the following covariates: baseline age, sex, randomisation strata, annualised growth velocity, and baseline values for the study outcomes. All analyses are descriptive, with no control for type I error. ANCOVA models were produced for the primary efficacy analysis population and by cohort. Missing data at week 52 were imputed for the models by applying either linear interpolation or multiple imputation using placebo data from participants in the same cohort. We did sensitivity analyses to assess the effect of missing data, including

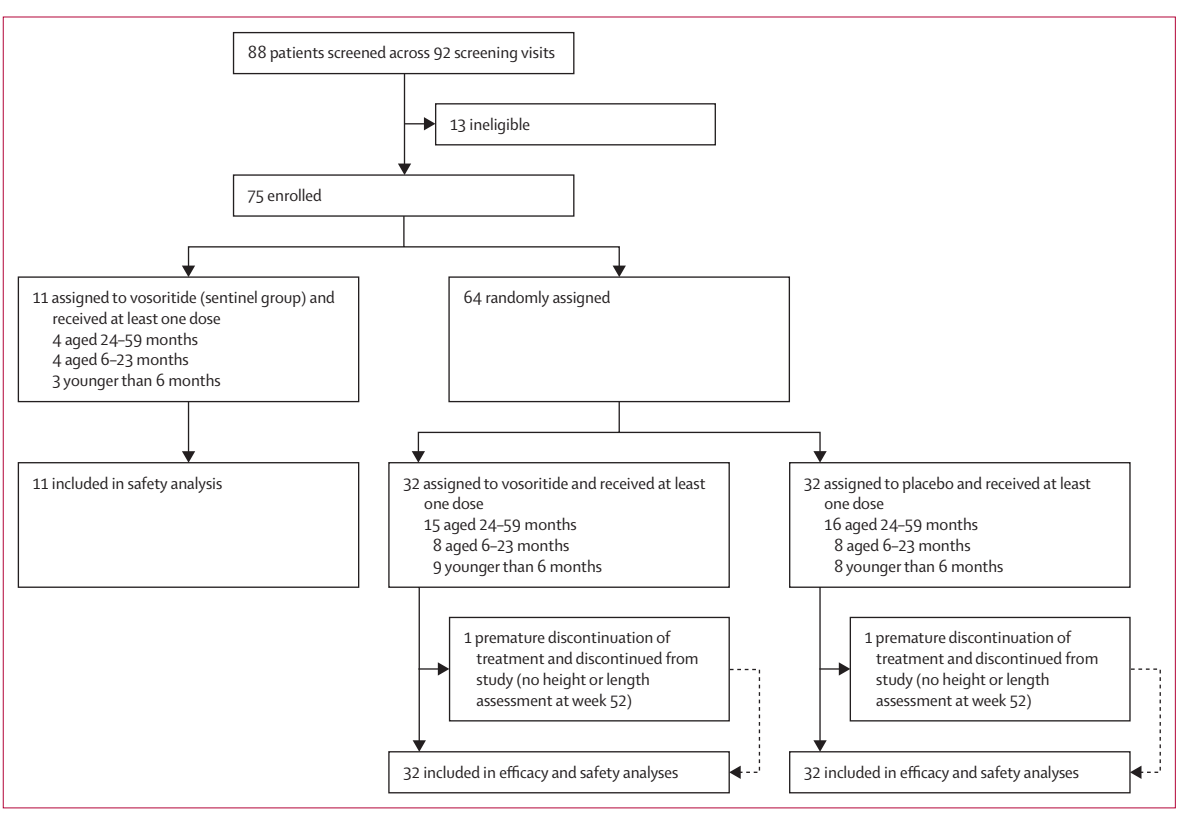

Figure 1: **Trial profile**
Enrolled participants had completed at least 3 months (for those aged <6 months) or at least 6 months (for those aged 6–59 months) of an observational run-in growth study (the present study or NCT01603095) to establish baseline annualised growth velocity.

only participants with a height assessment within the analysis window at week 52.

For height Z score, height measurements were converted to an age-standardised and sex-standardised score referenced to height for children of average stature in US Centers for Disease Control and Prevention height charts.[8] We did a post-hoc statistical analysis to assess the percentage height gain (least-squares mean change from baseline) for study participants versus average stature of children the same age and sex, based on the 50th percentile height data from height charts.[8] Data were imputed for the two participants with missing data at week 52 only for these model-based analyses. SAS (version 9.4) was used for all analyses. The trial was registered with EudraCT, 2016-003826-18, and ClinicalTrials.gov, NCT03583697.

Role of the funding source

Confidentiality agreements were in place between the funder and the investigators. The funder designed the study with input from the trial investigators, provided study sites with vosoritide and matching placebo, and centrally analysed data collected at trial sites. A medical writer was paid by the funder to assist with manuscript preparation. The funder had no role in data collection.

Results

Participants were recruited to the trial between May 13, 2018, and March 1, 2021. Of 88 infants and children screened for eligibility (figure 1), 13 were ineligible (appendix pp 18–19). Of the 75 eligible participants (37 [49%] female; aged 4·4–59·8 months on day 1 of treatment), 11 were assigned as sentinels to receive vosoritide, 32 were randomly assigned to receive vosoritide, and 32 were randomly assigned to receive placebo. As a result of an administrative error, one child who met all eligibility criteria was enrolled before the study was registered at EudraCT.

Vosoritide was rapidly absorbed in participants with achondroplasia age 3–59 months, with median peak time values ranging from 5·0 min (IQR 5·0–9·5) and 15·5 min (15·0–16·0) after subcutaneous injection. Vosoritide was rapidly removed from the plasma, with a half-life ranging from 19·2 min to 41·1 min on average. Sentinel participants in cohort 1 received a daily dose of 15·0 µg/kg and maintained an exposure that was within the exposure characterised in the phase 2 study in children with achondroplasia aged 5–12 years, indicating that the 15·0 µg/kg per day dose was appropriate for the rest of the cohort. All participants in cohort 1 therefore received a daily dose of 15·0 µg/kg. Sentinel participants in cohort 2 initially received 15·0 µg/kg per day vosoritide, but the mean exposure was less than that characterised in phase 2 studies at the 15·0 µg/kg per day dose. The daily dose was therefore adjusted to 30·0 µg/kg for both sentinels and for randomly assigned participants in this cohort while they were younger than 2 years.

	Total population		Cohort 1 (age 24–59 months)		Cohort 2 (age 6–23 months)		Cohort 3 (age <6 months)	
	Vosoritide (n=32)	Placebo (n=32)	Vosoritide (n=15)	Placebo (n=16)	Vosoritide (n=8)	Placebo (n=8)	Vosoritide (n=9)	Placebo (n=8)
Age on day 1*, months	24·39 (16·83)	27·82 (19·25)	39·62 (10·11)	44·33 (11·54)	17·00 (5·79)	16·87 (6·21)	5·56 (0·44)	5·76 (0·59)
Sex								
Male	17 (53%)	13 (41%)	7 (47%)	7 (44%)	5 (63%)	5 (63%)	5 (56%)	1 (13%)
Female	15 (47%)	19 (59%)	8 (53%)	9 (56%)	3 (38%)	3 (38%)	4 (44%)	7 (88%)
Race								
White	21 (66%)	25 (78%)	8 (53%)	13 (81%)	6 (75%)	6 (75%)	7 (78%)	6 (75%)
Asian	10 (31%)	6 (19%)	6 (40%)	3 (19%)	2 (25%)	1 (13%)	2 (22%)	2 (25%)
Japanese	4 (13%)	4 (13%)	2 (13%)	3 (19%)	1 (13%)	1 (13%)	1 (11%)	0
Other	6 (19%)	2 (6%)	4 (27%)	0	1 (13%)	0	0	0
Multiple	1 (3%)	0	1 (7%)	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (3%)	0	0	0	1 (13%)	0	0
Hispanic or Latino ethnicity	3 (9%)	3 (9%)	1 (7%)	1 (6%)	0	0	2 (22%)	2 (25%)
Height Z score†	−3·79 (0·97)	−4·28 (1·48)	−4·27 (0·81)	−5·13 (1·15)	−3·39 (0·84)	−4·21 (1·24)	−3·34 (1·02)	−2·65 (0·79)
Annualised growth velocity, cm per year	11·06 (7·57)	9·60 (7·74)	4·74 (1·68)	4·20 (1·78)	11·51 (4·66)	10·55 (4·78)	21·19 (2·80)	19·45 (7·55)
Upper-to-lower body segment ratio	2·60 (0·41)	2·52 (0·36)	2·35 (0·17)	2·25 (0·19)	2·65 (0·30)	2·68 (0·33)	2·99 (0·47)	2·87 (0·21)

Data are mean (SD) or n (%). Percentages are given as integers might not sum to 100 as a result of rounding. *Day 1 of treatment. †Z scores were derived using age-specific and sex-specific reference data (means and SD) for average stature children according to the US Centers for Disease Control and Prevention.[8] For height used for BMI calculation, in participants younger than 24 months, body length took precedence over standing height. In participants younger than 24 months at baseline and 24 months or older at week 52, body length took precedence. BMI Z scores were derived only for participants aged 24 months or older.

Table 1: **Baseline characteristics and growth parameters of the randomly assigned population**

	Randomly assigned to placebo (n=32; total treatment exposure 32·03 person-years)		Randomly assigned to vosoritide (n=32; total treatment exposure 31·63 person-years)		Sentinel participants receiving vosoritide (n=11; total treatment exposure 11·10 person-years)		All vosoritide (n=43; total treatment exposure 42·73 person-years)	
	Frequency*	Event rate†	Frequency*	Event rate†	Frequency*	Event rate†	Frequency*	Event rate†
Participants with any serious adverse event	6 (19%)	8 (0·2)	3 (9%)	4 (0·1)	0	0	3 (7%)	4 (0·1)
Participants with any adverse event	32 (100%)	2357 (73·6)	32 (100%)	6564 (207·5)	11 (100%)	2173 (195·8)	43 (100%)	8737 (204·5)
Injection site reaction	13 (41%)	154 (4·8)	26 (81%)	2304 (72·8)	8 (73%)	753 (67·9)	34 (79%)	3057 (71·5)
Injection site erythema	13 (41%)	1738 (54·3)	25 (78%)	3849 (121·7)	8 (73%)	1251 (112·7)	33 (77%)	5100 (119·4)
Pyrexia	19 (59%)	37 (1·2)	14 (44%)	35 (1·1)	2 (18%)	2 (0·2)	16 (37%)	37 (0·9)
Vomiting	17 (53%)	47 (1·5)	5 (16%)	8 (0·3)	6 (55%)	14 (1·3)	11 (26%)	22 (0·5)
Upper respiratory tract infection	11 (34%)	30 (0·9)	12 (38%)	28 (0·9)	4 (36%)	7 (0·6)	16 (37%)	35 (0·8)
Teething	10 (31%)	19 (0·6)	8 (25%)	21 (0·7)	4 (36%)	11 (1·0)	12 (28%)	32 (0·7)
Nasopharyngitis	9 (28%)	15 (0·5)	7 (22%)	12 (0·4)	5 (45%)	9 (0·8)	12 (28%)	21 (0·5)
Diarrhoea	7 (22%)	15 (0·5)	7 (22%)	13 (0·4)	1 (9%)	1 (0·1)	8 (19%)	14 (0·3)
Ear infection	6 (19%)	13 (0·4)	5 (16%)	6 (0·2)	3 (27%)	7 (0·6)	8 (19%)	13 (0·3)
Rhinorrhoea	6 (19%)	11 (0·3)	6 (19%)	10 (0·3)	2 (18%)	3 (0·3)	8 (19%)	13 (0·3)
Conjunctivitis	6 (19%)	8 (0·2)	6 (19%)	7 (0·2)	0	0	6 (14%)	7 (0·2)
Nasal congestion	6 (19%)	8 (0·2)	5 (16%)	9 (0·3)	1 (9%)	1 (0·1)	6 (14%)	10 (0·2)
Otitis media	6 (19%)	14 (0·4)	4 (13%)	7 (0·2)	2 (18%)	2 (0·2)	6 (14%)	9 (0·2)
Viral infection	4 (13%)	8 (0·2)	5 (16%)	19 (0·6)	3 (27%)	9 (0·8)	8 (19%)	28 (0·7)
Cough	7 (22%)	9 (0·3)	3 (9%)	4 (0·1)	1 (9%)	1 (0·1)	4 (9%)	5 (0·1)
Injection site bruising	6 (19%)	39 (1·2)	4 (13%)	16 (0·5)	1 (9%)	10 (0·9)	5 (12%)	26 (0·6)
Rash	4 (13%)	4 (0·1)	4 (13%)	7 (0·2)	3 (27%)	3 (0·3)	7 (16%)	10 (0·2)
Fall	3 (9%)	5 (0·2)	3 (9%)	3 (0·1)	4 (36%)	6 (0·5)	7 (16%)	9 (0·2)
Injection site swelling	2 (6%)	3 (0·1)	7 (22%)	30 (0·9)	1 (9%)	6 (0·5)	8 (19%)	36 (0·8)
Arthropod bite	2 (6%)	2 (0·1)	6 (19%)	6 (0·2)	0	0	6 (14%)	6 (0·1)
Ear pain	4 (12·5%)	6 (0·2)	2 (6%)	3 (0·1)	2 (18%)	2 (0·2)	4 (9%)	5 (0·1)
Gastroenteritis	5 (16%)	5 (0·2)	2 (6%)	6 (0·2)	1 (9%)	3 (0·3)	3 (7%)	9 (0·2)

Adverse events with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 24.1) and were graded for severity using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). *Percentages were calculated using the total number of participants in the safety population of each column as the denominator. Participants with more than one adverse event of the same preferred term were counted once for that preferred term. †Exposure-adjusted event rates were calculated by dividing the total number of events by the total treatment exposure up to the last dose. Multiple occurrences of an adverse event with the same preferred term were counted for each occurrence for that preferred term.

Table 2: **Incidence of and exposure-adjusted event rates of treatment-emergent adverse events by preferred term (>10% incidence overall) in the safety population**

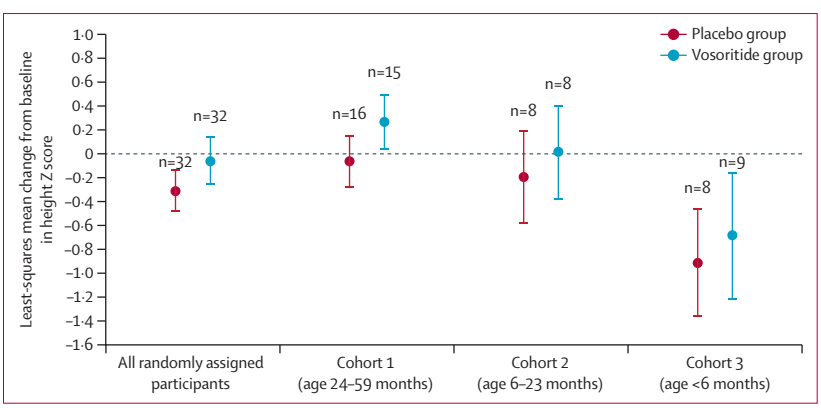

Figure 2: **Least-squares mean change (95% CI) from baseline for height Z score at week 52 in the randomly assigned population**

Least-squares mean change in Z scores for height from baseline to week 52 are shown for cohorts 1, 2, and 3. For participants younger than 24 months at baseline, body length took precedence over standing height. The plot displays the least-squares mean (circular symbol) and the 2·5th and 97·5th percentiles (whiskers).

Subsequently, both sentinels and randomly assigned participants in cohort 3 also received 30·0 µg/kg per day vosoritide, which resulted in exposures within the same range as observed in phase 2 studies. Participants in cohorts 2 and 3 received 30·0 µg/kg while they were younger than 2 years. The daily dose for participants in cohort 2 was adjusted to 15·0 µg/kg during the visit immediately preceding the participant's second birthday. After sentinel dosing was established, all randomly assigned participants also underwent pharmacokinetic evaluation with the data analysed after completion of the study (appendix pp 23, 24).

All 75 participants who received at least one dose of study drug were included in the safety population. 64 randomly assigned participants were included in the primary efficacy analysis. Baseline characteristics and growth parameters were generally representative of the paediatric population with achondroplasia, but some growth characteristics varied between treatment groups (table 1). 46 (61%) participants were White, and 16 (21%)

were Asian. Two participants discontinued treatment and left the study: one in the vosoritide group in cohort 3 (due to death initially reported as sudden infant death, but later clarified to be in the presence of significant underlying morbidity); and one in the placebo group (withdrawal) in cohort 2. By Jan 26, 2022, the 52-week, placebo-controlled study was completed, and the study database was locked on Feb 14, 2022.

Mean treatment duration was similar between the vosoritide and placebo groups (mean 363·0 days [SD 25·3] *vs* 365·5 days [10·2]), and few doses were missed (mean 4·8 [SD 8·1] *vs* 7·5 [10·9]; appendix p 21). Total treatment exposure duration was 42·7 person-years for vosoritide and 32·0 person-years for placebo (appendix p 31).

All participants in the safety population reported at least one adverse event during the study, most of which were transient injection-site reactions and injection-site erythema. 8737 adverse events were recorded in 43 participants in the vosoritide group (annual rate of 204·5 adverse events per patient), and 2357 adverse events were recorded in 32 participants in the placebo group (annual rate of 73·6; table 2).

Serious adverse events occurred in three (7%) participants in the vosoritide group (decreased oxygen saturation, respiratory syncytial virus bronchiolitis and sudden infant death syndrome, and pneumonia) and six (19%) participants in the placebo group (*petit mal* epilepsy, autism, gastroenteritis, vomiting and parainfluenza virus infection, respiratory distress, and skull fracture and otitis media). (appendix pp 31–39). One participant in the vosoritide group died: a boy aged 1 year with pre-existing pharyngeal dysphagia, nasal congestion, gastro-oesophageal reflux, and obstructive sleep apnoea syndrome requiring supplemental oxygen. The child had multiple respiratory tract infections during the study, including respiratory syncytial virus bronchiolitis, requiring hospitalisation and treatment with continuous positive airway pressure. These medical issues, combined with compression of the cervicomedullary region of the spinal cord due to foramen magnum stenosis, were considered the cause of his death.

Adverse events of special interest included fractures, which occurred in one (2%) participant receiving vosoritide and one (3%) receiving placebo (appendix pp 31–39). Obstructive sleep apnoea syndrome was reported in three participants receiving vosoritide but was not associated with deterioration in sleep study indices. No grade 3 or higher hypersensitivity reactions or cases of anaphylaxis were reported.

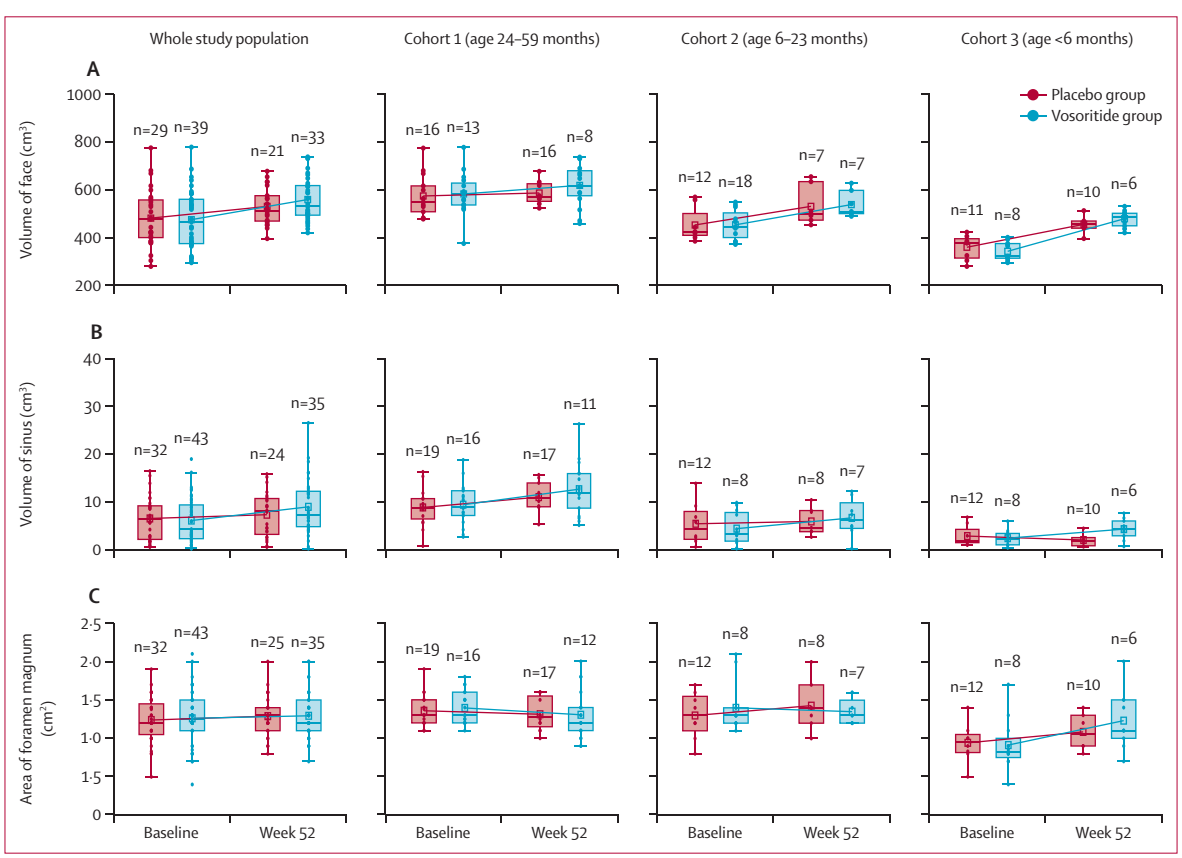

Figure 3: **Changes in volume of face (A), volume of sinus (B), and area of foramen magnum (C) in the safety population**
Data were acquired from MRI. Box plot displays the 25th and 75th percentiles (box edges), the median (midline), mean (open square symbol), and the 2·5th and 97·5th percentiles.

No clinically significant cardiovascular changes were observed; post-dose decreases in systolic blood pressure less than 70 mm Hg (plus two times age) were reported in four (9%) participants receiving vosoritide and in eight (25%) receiving placebo. Post-dose decreases in diastolic blood pressure less than 40 mm Hg were reported in 20 (47%) participants receiving vosoritide and in 12 (38%) receiving placebo (appendix p 41). All changes in blood pressure were mild, transient, and asymptomatic, except in one participant receiving vosoritide who had a single symptomatic hypotensive event that resolved without intervention.

Eight (19%) of 43 participants in the vosoritide group were positive for antidrug antibodies (ADAs). All ADA-positive participants tested negative for neutralising antibodies at all timepoints. ADA development had no effect on the safety, efficacy, or pharmacokinetics of vosoritide.

At week 52, ANCOVA analyses showed a 0·25 (95% CI –0·02 to 0·53) gain in least-squares mean height Z score

	Cohort 1 (age 24–59 months)		Cohort 2 (age 6–23 months)		Cohort 3 (age <6 months)	
	Vosoritide (n=15)	Placebo (n=16)	Vosoritide (n=8)	Placebo (n=8)	Vosoritide (n=9)	Placebo (n=8)
ITQoL*: overall health score						
Baseline						
n	15	14	8	7	9	6
Mean (SD)	82·67 (17·71)	82·14 (15·90)	87·50 (13·36)	93·57 (8·02)	84·44 (15·50)	95·00 (7·75)
Week 52						
n	12	14	7	6	8	8
Mean (SD)	88·33 (14·97)	87·50 (10·52)	87·86 (14·39)	90·83 (16·25)	88·13 (18,11)	85·63 (12·37)
Change from baseline to week 52†						
n	12	12	7	5	8	6
Mean (SD)	5·42 (16·85)	3·75 (17·60)	–3·57 (12·82)	–5·00 (15·41)	0·63 (14·74)	–5·00 (7·75)
ITQoL*: physical abilities						
Baseline						
n	15	15	8	8	6	7
Mean (SD)	68·44 (31·25)	77·90 (21·07)	75·16(16·95)	72·80 (26·89)	87·88(10·79)	77·76 (18·51)
week 52						
n	14	15	8	7	8	8
Mean (SD)	79·29 (16·70)	74·74 (23·35)	78·98 (16·70)	84·97 (8·46)	76·90 (19·33)	82·13 (17·29)
Change from baseline to week 52†						
n	14	14	8	7	5	7
Mean (SD)	7·38 (23·94)	–6·01 (9·83)	3·82 (18·05)	3·36 (8·62)	–14·64 (25·19)	2·35 (29·29)
ITQoL*: growth and development scores						
Baseline						
n	15	15	8	8	9	8
Mean (SD)	77·00 (17·22)	76·17 (13·95)	71·56 (29·82)	82·50 (12·46)	83·61 (9·36)	85·49 (9·33)
Week 52						
n	14	15	8	7	8	8
Mean (SD)	83·13 (16·03)	82·83 (8·86)	78·13 (26·52)	84·29 (14·34)	79·06 (20·04)	89·06 (5·66)
Change from baseline to week 52†						
n	14	14	8	7	8	8
Mean (SD)	3·66 (9·05)	4·82 (11·62)	6·56 (30·79)	–0·71 (8·75)	–5·00 (12·10)	3·57 (6·35)
WeeFIM II*: total score						
Baseline						
n	15	14	7	8	NA‡	NA‡
Mean (SD)	63·7 (29·5)	74·8 (20·4)	32·3 (13·1)	28·3 (13·5)	..	..
Week 52						
n	15	16	7	6	8	8
Mean (SD)	76·0 (26·0)	85·2 (18·1)	47·0 (12·3)	43·5 (11·3)	34·5 (10·8)	32·9 (12·4)
Change from baseline to week 52†						
n	15	14	7	6	NA‡	NA‡
Mean (SD)	12·3 (18·1)	11·2 (11·1)	14·7 (18·9)	16·2 (14·6)	..	..

(Table 3 continues on next page)

	Cohort 1 (age 24–59 months)		Cohort 2 (age 6–23 months)		Cohort 3 (age <6 months)	
	Vosoritide (n=15)	Placebo (n=16)	Vosoritide (n=8)	Placebo (n=8)	Vosoritide (n=9)	Placebo (n=8)
(Continued from previous page)						
BSID-III*: motor composite score						
Baseline						
n	9	9	8	8	9	8
Mean (SD)	82·6 (20·6)	84·1 (17·9)	80·1 (18·1)	79·0 (11·3)	71·1 (14·4)	76·4 (15·6)
Week 52						
n	3	2	6	4	6	5
Mean (SD)	80·0 (17·6)	100·0 (17·0)	81·0 (6·2)	81·3 (18·2)	88·0 (11·2)	85·6 (7·2)
Change from baseline to week 52†						
n	3	2	6	4	6	5
Mean (SD)	3·3 (13·7)	−2·0 (5·7)	−7·5 (11·8)	12·0 (17·5)	15·8 (18·4)	5·4 (22·2)

BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition. ITQoL=Infant Toddler Quality of Life Questionnaire. NA=not applicable. WeeFIM II=Functional Independence Measure for Children II (version 6.4). *For BSID-III and ITQoL, a higher score indicates a higher performance. For WeeFIM II, a higher score reflects a higher level of independence. †Change from baseline was based on the participants with available measurements at both timepoints. Baseline is defined as day 1 or screening if a day 1 assessment is not available. ‡WeeFIM II is only validated in children aged 6 months to 18 years; therefore, participants in cohort 3 who were older than 6 months do not have WeeFIM II scores at baseline. For BSID-III, composite scores were scaled to a metric with a mean of 100, a SD of 15, and a range of 40 to 160.

Table 3: **Change from baseline at week 52 for ITQoL, WeeFIM II, and BSID-III scores by cohort in the randomly assigned population**

change from baseline in the vosoritide group relative to the placebo groups (figure 2; appendix p 42). The least-squares mean difference in height Z score was consistent across the three cohorts, although 95% CIs widened from cohort 1 to cohort 3. The vosoritide group also showed a gain in least squares mean annualised growth velocity of 0·78 cm per year (95% CI 0·02 to 1·54) relative to the placebo group (appendix pp 43, 56).

The vosoritide group showed a least-squares mean gain in standing height or body length of 0·77 cm per year (95% CI −0·02 to 1·56) relative to the placebo group (appendix pp 44, 57). The least-squares mean difference in height was consistent across cohorts, with 95% CIs that increased from cohort 1 to cohort 3. The height gain in the vosoritide group versus the placebo group, as a percentage of height gain in children (same age and sex) of average stature[9] was 91% versus 77% in cohort 1, 84% versus 75% in cohort 2, and 72% versus 68% in cohort 3 (appendix p 45).

For change from baseline to week 52 in upper-to-lower body proportion ratio, for which a negative change is synonymous with improvement, the ANCOVA analyses showed a least-squares mean difference between the vosoritide group and the placebo group of −0·07 (95% CI −0·17 to 0·04; appendix pp 46, 58).

Changes in other body proportion growth measures from baseline to week 52 are detailed in the appendix (p 47). We found no evidence of disproportionate skeletal growth, acceleration of bone age, or abnormal bone morphology as assessed by dual energy x-ray absorptiometry.

Changes from baseline to week 52 in skull and brain morphology, including foramen magnum, and ventricular and brain parenchymal dimensions are summarised in the appendix (p 51). The most rapid growth was observed in the youngest children in cohort 3 and was most pronounced among those who received vosoritide (figure 3). The comparison of MRI variables from baseline to week 52 of the vosoritide group against the placebo group within cohort 3 showed that facial volume increased by 44% versus 34%, sinus volume increased by 129% versus 48%, and the foramen magnum area increased by 44% versus 25% (appendix p 51). In the older children in cohorts 1 and 2, growth relative to baseline values was less rapid, and the magnitude of these changes was smaller with no apparent differences between the vosoritide group and the placebo group.

Following vosoritide administration, the mean plasma cGMP in the treatment group increased from pre-dose levels and reached a maximum 1 h post dose, but mean plasma cGMP in the placebo group remained unchanged. The mean change in serum collagen X marker with vosoritide was greater than in the placebo group (appendix p 24).

No worsening in sleep study indices was observed with vosoritide at week 52 compared with placebo. Most sleep study indices indicated small numerical improvements on vosoritide, whereas results in the placebo group were mixed (appendix p 30).

We found no clinically meaningful differences in change from baseline to 52 weeks in health-related quality of life between the placebo and vosoritide groups (table 3; appendix pp 25–29).

Discussion

In this randomised, phase 2, double-blind, placebo-controlled study, vosoritide administered subcutaneously at a daily dose of 15·0 µg/kg or 30·0 µg/kg in children with achondroplasia aged 3–59 months was associated

with no serious treatment-related adverse events and resulted in changes in height Z scores, and in facial volume, sinus volume, and foramen magnum area. All data should be interpreted with caution since all analyses, which were predefined in the statistical analysis plan, are descriptive with no control for type I error.

In participants administered vosoritide, most adverse events were mild injection site reactions (redness and swelling) that resolved spontaneously within 1 h. We found no difference in the incidence of serious adverse events between the vosoritide and placebo groups (7% *vs* 19%). Given the concern regarding the potential vascular adverse effects of vosoritide in this age group, blood pressure and pulse rate were monitored frequently during the initial visits. There were no clinically significant changes in blood pressure or pulse in participants administered vosoritide versus placebo, none were reported as adverse events, and all recorded changes in blood pressure resolved without intervention.

The least-squares mean differences from the ANCOVA models for change from baseline in height Z scores after 52 weeks of vosoritide treatment compared with placebo for the 3–59 month age group were consistent with those observed in children with achondroplasia aged 5 years or older treated with vosoritide for 1 year.[3] A negative least-squares mean difference between the vosoritide and the placebo groups for the endpoint change from baseline in upper-to-lower body segment ratio leads us to conclude that vosoritide did not cause worsening of proportionality.[3] In the youngest cohort (cohort 3, aged <6 months), we found greater changes in facial volume, facial sinus volume, and foramen magnum area at 52 weeks among the vosoritide group than the placebo group.

The main limitation of this 52-week study is that the effect of vosoritide treatment on the expected final adult height and functionality, quality of life, and medical complications in these young children could not be assessed. To assess these important health outcomes, and any possible long-term harms of treatment, all participants who completed this study have been enrolled in an extension study (NCT03989947) and will be followed up until adulthood. Another limitation, common to many rare disease clinical trials, is the relatively small total number of study participants. The treatment effect on growth velocity in the youngest participants from cohort 3 reflects this, with measurements showing wide variability and large CIs.

The treatment effect of vosoritide on annualised growth velocity in this study was 0·78 cm per year after 52 weeks, whereas children with achondroplasia older than 5 years showed a 1·57 cm per year growth velocity in response to vosoritide.[3] This discrepancy can be explained by the highly variable and rapidly declining growth velocity in very young children with achondroplasia, in whom a small difference in age can have a large effect on growth measurements. It is also possible that vosoritide therapy is simply not as effective in promoting vertebral and long bone growth, especially in children younger than 6 months.

Although the difference between the vosoritide and placebo groups in change from baseline in height Z score is similar to that observed in participants aged 5 years or older, due to the larger variability in the height distribution between older and younger children, this does not translate into the same improvement in height. This is apparent in the Centers for Disease Control and Prevention height Z score charts, in which the spread in height distribution increases with age such that 1 SD score is 3·49 cm for a child aged 2 years , compared with 5·83 cm for a child aged 8 years.[10] The consistency of vosoritide treatment effect across age groups is therefore best illustrated by its effect on height Z score.

Vosoritide is now approved for young children with achondroplasia in many countries, and from birth in Japan and the USA. Young children treated with this drug must be followed closely and systematically to collect further real-world evidence (qualitative and quantitative) regarding its effects on growth, functionality, quality of life, and medical complications compared with natural history data. Long-term height and health outcome data will greatly inform and facilitate decision making for the physicians and families who are considering vosoritide therapy for their patients and children.

The MRI changes observed in participants younger than 6 months (cohort 3) are noteworthy. Abnormal craniofacial and base-of-skull endochondral ossification, combined with premature fusion of the cranial synchondroses, lead to midface hypoplasia and stenosis of the foramen magnum and are major contributors to the excess incidence of sudden death (observed in one participant in this study) reported in children with achondroplasia younger than 5 years[11,12] by causing sleep disordered breathing and brainstem compression.[11] Vosoritide ameliorates the craniofacial skeletal and foramen magnum abnormalities in mouse models of achondroplasia,[13,14] and accelerates endochondral ossification in children with achondroplasia,[3,4] so these MRI changes might reflect a direct effect of vosoritide on craniofacial and foramen magnum growth. Whether these observed MRI changes translate into a decrease in the incidence of sudden infant death, sleep disordered breathing, and necessity for neurosurgical decompression of the foramen magnum in these infants will be assessed in the long-term follow-up study (NCT03989947).

Another ongoing study comparing current standard of care versus vosoritide treatment in infants younger than 1 year with achondroplasia at risk of requiring surgical decompression of the foramen magnum will also directly address this issue (NCT04554940).[15] MRI changes were observed only in participants in cohort 3, consistent with the fact that the growth of the foramen magnum, especially in the transverse plane, is negligible after age 6 months.[16] Less rapid growth was observed relative to baseline values in the older children in cohorts 1 and 2, and the magnitude

of these changes was smaller with no apparent differences between vosoritide and placebo. The improvement in craniofacial growth observed in participants treated with vosoritide in cohort 3 might translate to a reduction in the need for corrective orthodontic treatments and craniofacial surgery, which are often required in older individuals with achondroplasia, and will be assessed as part of the long-term follow-up study (NCT03989947).

We hope these data will support paediatricians and other health-care specialists who are assessing the risks and benefits of initiating vosoritide treatment in children with achondroplasia younger than 5 years. They also provide a baseline against which the harms and benefits of other potential precision therapies for achondroplasia[17] in young children can be measured.

Contributors

RS wrote the first draft of the manuscript, assisted by JD and a medical writer (who provided formatting and style input). JD, AH-L, EF, YQ, and GJ wrote the first draft of the protocol and amendments with input from RS, WRW, MI, CA, YQ, and LH. A H-L and LH performed the statistical analysis. RS, WRW, PH, JP, LEP, LT, KO, PA, MI, CAB, DB, MBB, JC, HM, YK, and HMS recruited and enrolled participants to the trial, and managed them during the trial period according to the protocol. RS, EF, YQ, LH, AH-L, CA, and JD have accessed the data as reported, vouch for the data as reported, including adherence of the trial to the protocol, and complete reporting of all adverse events. All authors were responsible for the decision to submit for publication.

Declaration of interests

All authors were investigators in this clinical trial with the exception of CA, GJ, YQ, LH, EF, AH-L, and JD, who are employees of the funder (BioMarin). RS and LT have received consulting fees and grants from BioMarin. MI and WRW have received consulting fees from BioMarin. JC and DB have received grants from BioMarin. LEP and PA have received honoraria from BioMarin. CAB has received consulting fees, honoraria, and grants from BioMarin. MBB has received consulting fees from and grants from BioMarin, Ascendis, Therachon, QED, and Alexion; and grants from BioMarin, Ascendis, Therachon, QED, Medlife, SOBI, and Shire. PH, JP, KO, HM, YK, and HMS declare no competing interests.

Data sharing

The de-identified individual participant data that underlie the results reported in this Article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents might be available upon request to the corresponding author. Investigators will be able to request access to these data and supporting documents via www.BioMarin.com beginning 6 months and ending 2 years after publication. Data associated with any ongoing development programme will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical.

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