Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial

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Summary

Background There are no effective therapies for achondroplasia. An open-label study suggested that vosoritide administration might increase growth velocity in children with achondroplasia. This phase 3 trial was designed to further assess these preliminary findings.

Methods This randomised, double-blind, phase 3, placebo-controlled, multicentre trial compared once-daily subcutaneous administration of vosoritide with placebo in children with achondroplasia. The trial was done in hospitals at 24 sites in seven countries (Australia, Germany, Japan, Spain, Turkey, the USA, and the UK). Eligible patients had a clinical diagnosis of achondroplasia, were ambulatory, had participated for 6 months in a baseline growth study and were aged 5 to less than 18 years at enrolment. Randomisation was done by means of a voice or web-response system, stratified according to sex and Tanner stage. Participants, investigators, and trial sponsor were masked to group assignment. Participants received either vosoritide 15·0 µg/kg or placebo, as allocated, for the duration of the 52-week treatment period administered by daily subcutaneous injections in their homes by trained caregivers. The primary endpoint was change from baseline in mean annualised growth velocity at 52 weeks in treated patients as compared with controls. All randomly assigned patients were included in the efficacy analyses (n=121). All patients who received one dose of vosoritide or placebo (n=121) were included in the safety analyses. The trial is complete and is registered, with EudraCT, number, 2015-003836-11.

Findings All participants were recruited from Dec 12, 2016, to Nov 7, 2018, with 60 assigned to receive vosoritide and 61 to receive placebo. Of 124 patients screened for eligibility, 121 patients were randomly assigned, and 119 patients completed the 52-week trial. The adjusted mean difference in annualised growth velocity between patients in the vosoritide group and placebo group was 1·57 cm/year in favour of vosoritide (95% CI [1·22–1·93]; two-sided p<0·0001). A total of 119 patients had at least one adverse event; vosoritide group, 59 (98%), and placebo group, 60 (98%). None of the serious adverse events were considered to be treatment related and no deaths occurred.

Interpretation Vosoritide is an effective treatment to increase growth in children with achondroplasia. It is not known whether final adult height will be increased, or what the harms of long-term therapy might be.

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Introduction

Achondroplasia is a primary skeletal dysplasia caused by heterozygous, gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene[1] that leads to impaired endochondral ossification. This results in various medical complications, functional limitations and psychosocial challenges.[2] Achondroplasia is the most common form of disproportionate short stature in humans, affecting approximately 250 000 people worldwide.[3] Approved therapies that specifically address the underlying pathophysiology of this condition are currently lacking.

Previous studies in mouse models that recapitulate the skeletal phenotype observed in achondroplasia suggested that administration of vosoritide, a biological analogue of C-type natriuretic peptide, could restore and increase long-bone and craniofacial growth in these mice, through a mitogen-activated protein kinase-dependent pathway.[4,5] These results led to a phase 2, open-label, safety and dose finding study in 35 children aged 5 to 14 years with achondroplasia, all of whom had participated for at least 6 months in a lead-in growth study to calculate their baseline annualised growth velocity.[6] This trial had an open-label, sequential cohort design to evaluate the safety and tolerability of vosoritide administered by daily subcutaneous injection at escalating doses of 2·5, 7·5, 15·0, and 30·0 µg/kg of bodyweight. Administration of vosoritide at the doses

Research in context

Evidence before this study

We searched PubMed on April 6, 2020, for original research and review articles published in English since January, 2000, with the following search terms: "achondroplasia", "C-natriuretic peptide", "growth hormone", "FGFR3", "management", AND "treatment". The literature indicates that treatment of achondroplasia, to date, has been solely focused on management of symptoms. Research is focusing on the therapeutic manipulation of fibroblast growth factor receptor 3 (FGFR3) activity with C-type natriuretic peptide, as this might be associated with increased skeletal growth. Human growth hormone has been administered to children with achondroplasia but does not have a significant or durable effect on growth or on final height and has unknown effects on body proportionality. A precision therapy to address the pathogenesis of this condition has been lacking. C-type natriuretic peptide is a potent stimulator of endochondral ossification through downregulation of the intracellular signalling pathway of the FGFR3 receptor. Achondroplasia is caused by a gain-of-function mutation in the *FGFR3* gene, which results in constitutive overactivity of the receptor and impaired endochondral ossification. The first clinical trial to assess the safety of administration of the C-type natriuretic peptide analogue, vosoritide, was done in 35 children with achondroplasia, and reported in 2019. This phase 2, dose-finding study showed a generally mild side-effect profile and dose-related increases in annualised growth velocity. Limitations of this study were that participants acted as their own controls with regard to growth velocity comparisons, and that the design was open-label, with no placebo group enrolled.

Added value of this study

To our knowledge, this study is the first phase 3, randomised, double blind, placebo-controlled study done to assess the effect of vosoritide on growth in children with achondroplasia. Children administered vosoritide had a highly significant and potentially clinically important increase in annualised growth velocity over baseline after 1 year of treatment as compared with those who received placebo with similar adverse effect profiles. We believe that this study provides the first (level 1) randomised controlled trial evidence that vosoritide effectively enhances growth of children aged from 5 to less than 18 years with achondroplasia.

Implications of all the available evidence

This randomised controlled study provides strong evidence that daily subcutaneous administration of vosoritide (at a dose of 15·0 µg/kg of bodyweight) has a significant effect on growth velocity in children with achondroplasia aged 5 to less than 18 years. The balance of benefits and harms reported here are consistent with the previously published phase 2, open-label dose-finding studies. The children enrolled in these studies will be followed until they achieve final adult height to assess durability of response and whether a pubertal growth velocity increase is restored (as it is normally absent in children with achondroplasia). Studies are also under way to assess the use of vosoritide in children aged 0 to <5 years to evaluate whether earlier treatment will lead to better outcomes in terms of final height, body segment proportionality, and other comorbidities observed such as symptomatic foramen magnum stenosis, sleep disordered breathing, and spinal canal stenosis. We believe that this study provides the first, robust evidence for an effective, precision therapy for achondroplasia, underpinning a fundamental change in the clinical management policies, natural growth history, and treatment recommendations for children affected by this condition. It will serve as a benchmark against which other, emerging precision therapies for achondroplasia (including tyrosine kinase inhibitors, long acting forms of C-type natriuretic peptide, and fibroblast growth factor receptor ligand traps) can be measured.

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tested in these children was associated with a side-effect profile that was generally mild, and it resulted in sustained dose-related increases in annualised growth velocity for up to 42 months in patients compared with their baselines. The annualised growth velocity observed in patients who received doses of 15·0 µg/kg per day and 30·0 µg/kg per day were similar, and approximated those of age-matched, average-statured children.

The balance of benefits and harms from this study supported selection of the 15·0 µg/kg-per-day dose for further investigation of vosoritide in children with achondroplasia in larger, randomised controlled studies.

This study aimed to assess the change from baseline in mean annualised growth velocity (at 52 weeks) in patients administered vosoritide as compared with controls who received placebo injections.

Methods

Study design

This phase 3, randomised, double-blind, placebo-controlled, multicentre trial (study 111-301) compared once-daily subcutaneous administration of vosoritide, at a dose of 15·0 µg/kg of bodyweight, with placebo in children with achondroplasia. The trial was done in hospitals at 24 study sites in seven countries (Australia, Germany, Japan, Spain, Turkey, the USA, and the UK). The studies were done in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by the relevant ethics boards at each site.

Participants

Eligible children were aged 5 to less than 18 years, had completed at least 6 months of a lead-in, observational growth study (study 111-901; ClinicalTrials.gov number,

NCT01603095), and were ambulatory. The clinical diagnosis of achondroplasia was confirmed by genetic testing in all patients. Patients with radiographic evidence of closed growth plates, planned bone surgery, severe untreated sleep apnoea, and other medical conditions or treatments known to affect growth were excluded. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate, before enrolment. The protocol is included in the appendix.

See Online for appendix

Randomisation and masking

In this double-blind trial, patients were randomly assigned 1:1 to receive either vosoritide or matched, identical placebo. Randomisation was done with the use of an interactive, automated voice-response or web-response system run by ALMAC with stratification according to sex and Tanner stage (either Tanner stage 1, or Tanner stage more advanced than stage 1). No more than 20% of the total number of enrolled patients were prespecified to be more advanced than Tanner stage 1. SAS version 9.3 was used to create the randomisation list with block size 4 applied within each strata. A separate randomisation was done for the seven Japanese participants to assure that the Japanese participants were balanced across treatment arms. Participants, investigators, caregivers administering injections, and assessors analysing outcome data were all masked to group assignment. The randomisation list was received by the BioMarin Biometrics group after the final database lock.

Procedures

Patients received either vosoritide 15·0 µg/kg or placebo, as allocated, for the duration of the 52-week treatment period administered by daily subcutaneous injections in their homes by trained caregivers. The dosing schedule was a single, daily subcutaneous injection given 7 days a week, with site rotation. Vosoritide or placebo were initially administered by site staff in the clinic. After patients were seen to be tolerating vosoritide or placebo and specified criteria had been met, trained caregivers were authorised to administer vosoritide or placebo at home. Participants were required to attend the study site for scheduled visits at screening, days 1, 2, 3, and 10, week 6, and months 3, 6, 9, and 12. Full medical clinical assessments were done at each visit in addition to vital sign assessment and anthropometric measurements. For full study assessments, see protocol in the appendix (p 34). The funder or its designee provided the study sites with a supply of investigational product sufficient for the completion of the study.

An electronic data capture system, Medidata Rave, was used to collect study data at each site. Data was entered into the electronic data capture system by site staff, source data was verified by the site responsible clinical research associate and all data was reviewed and cleaned by means of a combination of electronic edit checks, manual checks, and data listing review. Serious adverse events were all reconciled against the content of the Argus safety database and all medical conditions and medications were coded with Medidata Coder by means of MedDRA v22.0 and WHO Drug B3 Global, March 2019 dictionaries. External vendor data underwent formal reconciliation procedures on receipt and all data stored within the electronic data capture system was approved via eSignature by each site's principal investigator. The study database was locked on Dec 5, 2019.

Outcomes

The primary efficacy outcome was change from baseline in annualised growth velocity at 52 weeks in patients administered daily subcutaneous injections of vosoritide compared with controls who received placebo injections. Key secondary outcomes comprised: change from baseline in height Z score and change from baseline in upper to lower segment body ratio. Other secondary outcomes comprised evaluation of the safety and tolerability of vosoritide; evaluation of the pharmacokinetics and immunogenicity of vosoritide; and evaluation of change from baseline in bone metabolism markers including serum collagen type X marker, a biomarker of endochondral ossification.[7] Initial exploratory endpoints comprising, change from baseline in extremity body proportion ratios, evaluation of effect of vosoritide on bone quality, evaluation of potential changes in health-related quality of life, and evaluation of potential changes in functional independence, were changed to secondary endpoints during the trial by protocol amendment (on Feb 1, 2019), owing to their potential clinical importance and health authority feedback.

Harms were evaluated by the incidence of adverse events, serious adverse events, laboratory test results, vital signs, physical examination, electrocardiogram and echocardiogram results, clinical hip assessment, and antivosoritide immunogenicity responses. Imaging assessments provided measurements of the spine and long bones of the arms and legs, along with data regarding growth plate, bone mineral density and bone age (see appendix p 6).

Statistical analysis

With 55 patients planned in each of the two randomised groups, the power to detect a difference of 1·75 cm/year between the vosoritide group and the placebo group in change from baseline in annualised growth velocity at 12 months was approximately 90%. This assumed the pooled SD of the change from baseline in annualised growth velocity was 2·80 cm/year, using a two-sided, two-sample *t* test at the 0·05 significance level. The power calculation was based on data from the phase 2, open-label, study of vosoritide in children with achondroplasia.[6] All analyses were done with SAS version 9.4, using the Proc MIXED procedure.

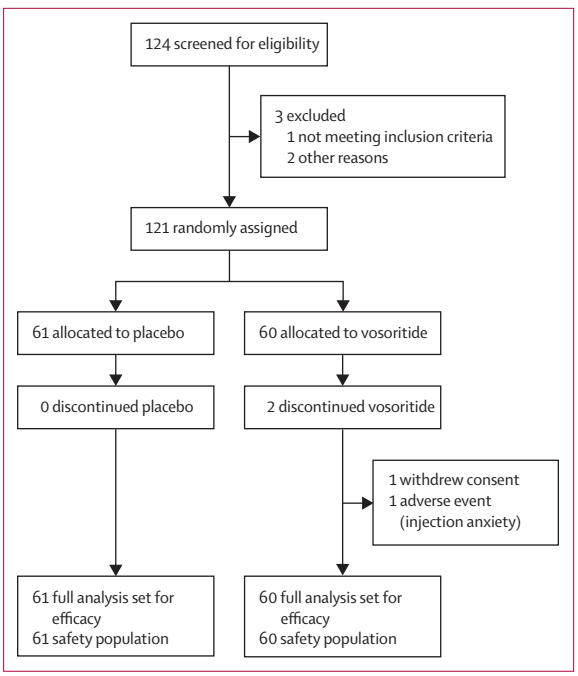

Figure 1: **Trial profile**
Once the 52-week placebo-controlled study was completed, 119 patients had enrolled in the ongoing extension study, in which all participants are receiving vosoritide (study 111-302; ClinicalTrials.gov number, NCT03424018).

	Placebo (n=61)	15 µg/kg vosoritide (n=60)
Age at day 1 (years)	9·06 (2·47)	8·35 (2·43)
Sex*		
Female	28 (46%)	29 (48%)
Male	33 (54%)	31 (52%)
Race*		
White	41 (67%)	45 (75%)
Ethnicity*		
Not Hispanic or Latino	55 (90%)	59 (98%)
Annualised growth velocity, cm/year		
Mean	4·06 (1·20)	4·26 (1·53)
Median	4·13	4·14
25th, 75th percentile	3·40, 4·86	3·10, 5·47
Minimum, maximum	1·5, 6·7	−0·1, 6·9
Height Z score		
Mean	−5·14 (1·07)	−5·13 (1·11)
Median	−5·15	−5·27
25th, 75th percentile	−5·78, −4·44	−5·93, −4·39
Minimum, maximum	−7·9, −2·7	−7·7, −1·1
Upper to lower body segment ratio		
Mean	2·01 (0·21)	1·98 (0·20)
Median	1·99	2·01
25th, 75th percentile	1·90, 2·12	1·89, 2·13
Minimum, maximum	1·5, 2·6	1·3, 2·3
Standing height		
Mean	102·94 (10·98)	100·20 (11·90)
Median	104·63	98·58
25th, 75th percentile	94·10, 111·47	90·82, 105·68
Minimum, maximum	79·9, 129·3	80·1, 136·8

Data are n (%) or mean (SD). *Percentages were calculated using the total number of patients in the full analysis set (n for each treatment group) as the denominator. No missing data for any of the variables.

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

All randomised and consented patients, constituting the full analysis set, were included according to intention-to-treat principles for the efficacy analyses (n=121). All patients who received at least one dose of vosoritide or placebo (n=121) were included in the safety analyses. Baseline annualised growth velocity was calculated from standing height measured over the last 6 months of the run-in study. Post-baseline annualised growth velocity was calculated from standing height at 52 weeks, and then summarised by treatment group. Change from baseline in annualised growth velocity was derived for each patient as the difference between the post-baseline and baseline annualised growth velocity. This individual patient data for the 121 randomised patients was then assessed in the ANCOVA model. Standing height was converted to an age-appropriate and sex-appropriate Z score by comparison with Centers for Disease Control and Prevention reference standards.[8] The upper to lower body segment ratio was calculated as the ratio between sitting height and standing height minus sitting height. The overall type I family-wise error rate for testing the primary and key secondary efficacy endpoints using an ANCOVA model was controlled at the two-sided 0·05 significance level using a three-step serial gatekeeping multiple comparisons procedure. Following this multiple comparisons procedure, advancement to the next step only occurred if the null hypotheses within a step and the previous step(s) were all rejected at the significance level of 0·05 in favour of vosoritide. If any null hypothesis within a step was not rejected or was rejected but not in favour of vosoritide, the hypothesis tests corresponding to all subsequent steps would not be considered confirmatory. All hypothesis tests were two-sided. The models which tested the treatment difference always included the following baseline covariates: strata (male Tanner stage I, female Tanner stage I, male Tanner Stage >I, female Tanner Stage >I); age, annualised growth velocity and height Z score.

As specified in the statistical analysis plan, a multiple imputation procedure, namely, PROC MI would be used for the primary endpoint analysis to account for missing data. However, in the event that there was insufficient data to apply this procedure, then a pre-specified alternative approach would be used by applying the baseline annualised growth velocity to the last available height assessment. As there were only two patients with missing data, this imputation approach was therefore used for the primary endpoint analysis.

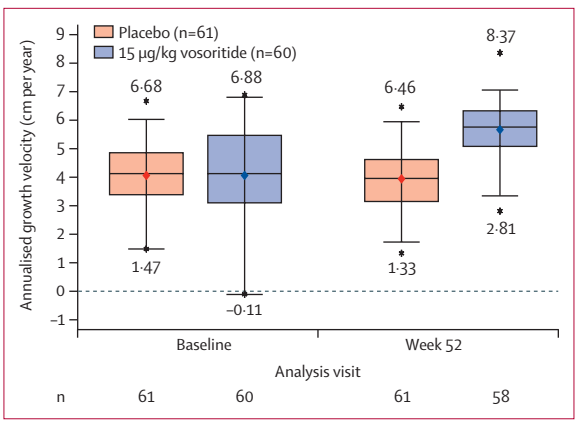

Figure 2: **Box and whisker plot of annualised growth velocity at baseline and 52 weeks by treatment arm**

Red boxes represent annualised growth velocity for patients in the placebo study treatment arm and blue boxes represent annualised growth velocity for patients in the vosoritide study treatment group. Baseline annualised growth velocity was established using data from the last 6 months of the observational run-in study before the screening visit. Annualised growth velocity at the week 52 visit was based on standing height calculated as [(height at week 52 visit – height at baseline visit) / (date at week 52 visit – baseline visit date)] × 365·25. Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (diamond symbol) and the 2·5th and 97·5th percentiles (whiskers). *Outliers.

	Placebo (n=61)	Vosoritide (n=60)	Difference in least-squares means*	Two-sided p value
Primary endpoint change from baseline in annualised growth velocity				
Least-squares mean change from baseline	0·13 (−0·18 to 0·45)	1·71 (1·40 to 2·01)	1·57 (1·22 to 1·93)	p<0·0001
Key secondary endpoint change from baseline in height Z score				
Least-squares mean change from baseline	−0·01 (−0·10 to 0·09)	0·27 (0·18 to 0·36)	0·28 (0·17 to 0·39)	p<0·0001
Key secondary change from baseline in upper to lower body segment ratio				
Least-squares mean change from baseline	−0·02 (−0·05 to 0·01)	−0·03 (−0·06 to 0·00)	−0·01 (−0·05 to 0·02)	p=0·51

Data are least-squares means (95% CI). *Difference is 15 µg/kg vosoritide minus placebo. Missing standing height at week 52 (ie, day 365) will be imputed by applying the baseline annualised growth velocity (cm/year) to the last available height. Least-squares means and difference in least-squares means were obtained from an ANCOVA model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline annualised growth velocity, baseline height Z score (and in the case of upper to lower body segment ratio, baseline body ratio was also included). Annualised growth velocity at a post-baseline visit is defined as [(height at post-baseline visit – height at baseline) / (date of post-baseline visit – date of baseline assessment)] × 365·25.

Table 2: **Analysis of covariance of primary and key secondary endpoints (full analysis set)**

The two patients in the vosoritide treatment arm, without a standing height assessment at week 52, had their missing standing height at week 52 imputed by applying baseline annualised growth velocity to the last available height assessment. Subsequently, these imputed standing height values were used to calculate their annualised growth velocity and height Z score at week 52.

Sensitivity analyses, where an alternative multiple imputation procedure (a washout model) was used to account for the missing assessment data of those patients (n=2) who discontinued the trial before 52 weeks of participation, are described in the Appendix (p 9).

Six prespecified subgroup analyses were also done on each of the primary, and two key secondary efficacy endpoints. Forest plots provide an overall summary for the primary and key secondary endpoints, and of each subgroup, showing the difference between the treatment group least-squares mean change from baseline and the 95% CI for the difference, at week 52 (see appendix pp 224–303).

The safety population was defined as all patients in the full analysis set who received at least one dose of vosoritide or placebo. Safety was assessed by examining the incidence, severity (determined using the Common Terminology Criteria for Adverse Events, version 4), and relationship to study drug of all treatment-emergent adverse events was reported during the study period. In addition, changes from baseline in clinical laboratory results and vital signs were assessed. Summary tables by treatment group included all safety events up to 30 days following treatment discontinuation (see appendix pp 27–32).

An independent Data Monitoring Committee overviewed the study, and reviewed all safety data every 6 months. The trial was first registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT number, 2015-003836-11) on Oct 20, 2016, and the first patient was enrolled into the trial on Dec 12, 2016.

Role of the funding source

The funder designed the studies with input from the investigators, provided the study medication and matching placebo, and analysed the data collected from the trial sites. Confidentiality agreements were in place between the funder and the investigators. The corresponding author had full access to the data in the study and made the decisions concerning the content of the submitted manuscript. All authors reviewed the manuscript before submission for publication and approved its submission.

Results

Participants were recruited to this trial between Dec 12, 2016, and Nov 7, 2018. 124 patients were screened for eligibility (figure 1) with 121 assessed as eligible (57 female patients, 64 male patients). These patients were enrolled and randomly assigned, with 60 assigned to receive vosoritide and 61 to receive placebo. The baseline characteristics were similar between the two treatment groups (table 1). As of Oct 31, 2019, the 52-week placebo-controlled study was completed, and 119 patients had enrolled in the extension study, in which all participants are receiving vosoritide (study 111-302; ClinicalTrials.gov number, NCT03424018). During the 52-week study, two patients in the vosoritide group discontinued, one after 2 days owing to pain from injections and one after 6 days owing to fear of needles (figure 1).

All randomised patients were included in the efficacy analyses, using an ANCOVA model including four covariates that adjusted for baseline differences between

	Number of subjects (%)		LS mean change from baseline
	15 µg/kg vosoritide	Placebo	Difference (cm)
Sex			
Male	31 (51·7)	33 (54·1)	1·36
Female	29 (48·3)	28 (45·9)	1·91
Age group (years)			
≥5 to <8	31 (51·7)	24 (39·3)	1·35
≥8 to <11	17 (28·3)	24 (39·3)	2·32
≥11 to <15	12 (20·0)	13 (21·3)	0·77
Tanner stage			
I	48 (80·0)	48 (78·7)	1·38
>I	12 (20·0)	13 (21·3)	1·47
Strata			
Male Tanner Stage I	28 (46·7)	28 (45·9)	1·27
Female Tanner Stage I	20 (33·3)	20 (32·8)	1·57
Male Tanner Stage >I	3 (5·0)	5 (8·2)	0·76
Female Tanner Stage >I	9 (15·0)	8 (13·1)	1·65
Height Z score category			
≤–6	15 (25·0)	10 (16·4)	1·69
>–6 to ≤ –5	18 (30·0)	24 (39·3)	1·14
>–5 to ≤ –4	22 (36·7)	19 (31·1)	2·09
>–4	5 (8·3)	8 (13·1)	2·90
Annualised growth velocity category			
≤3·5 cm/year	19 (31·7)	19 (31·1)	0·90
>3·5 to ≤4·5 cm/year	14 (23·3)	18 (29·5)	1·84
≥4·5 cm/year	27 (45·0)	24 (39·3)	1·42
Overall	**60 (100·0)**	**61 (100·0)**	**1·57**

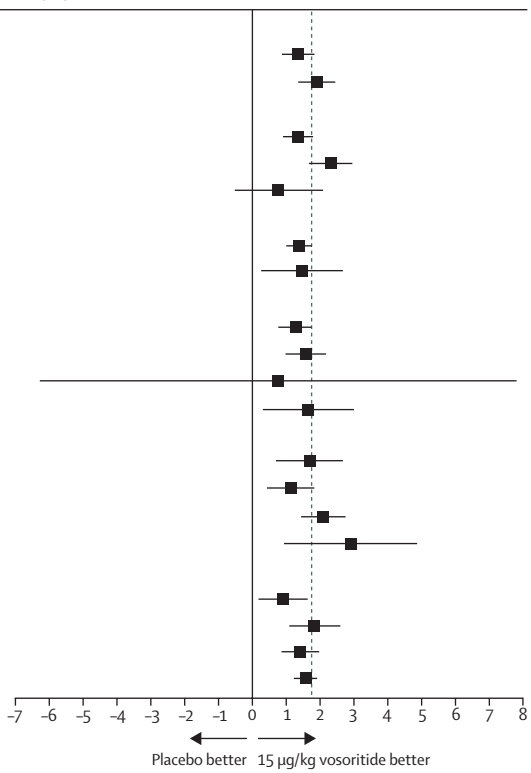

Figure 3: **Forest plot of least-squares mean difference in mean change from baseline in annualised growth velocity at week 52 by subgroup**
ANCOVA models were applied to determine the least squares mean change from baseline treatment difference at 52 weeks and 95% CIs. All models provide the treatment difference adjusted for the following baseline covariates: strata: (male Tanner stage I, female Tanner stage I, male Tanner stage >I, female Tanner Stage >I); age; annualised growth velocity; and height Z score. Subgroup analyses were done by applying the ANCOVA model used for the primary analysis to each subgroup category. The vertical dashed line represents the change from baseline difference of 1·75 cm/year for which the study was powered.

treatment groups. After 52 weeks of treatment, there was an increase in annualised growth velocity in patients treated with vosoritide versus placebo of 1·57 cm/year, (95% CI 1·22–1·93, with a two-sided p-value of <0·0001) (see figure 2, table 2, and appendix p 17). At the 15·0 µg/kg dose, the least-squares mean change from baseline that adjusted for baseline differences between the treated and placebo groups represented a 1·71 cm/year (95% CI 1·40 to 2·01) change from baseline annualised growth velocity versus 0·13 cm/year (95% CI –0·18 to 0·45) for placebo. Serum collagen type X marker concentrations, a real-time marker of endochondral ossification, were elevated through 52 weeks in vosoritide treated patients versus placebo (appendix p 10). Bone age progressed normally in both study arms (appendix pp 11, 12), and dual energy x-ray absorptiometry showed no significant changes in bone mineral content or bone mineral density over the 52-week trial period in either the treatment or the placebo group (data not shown).

The results of the subgroup analyses for change from baseline in annualised growth velocity are summarised in figure 3. All estimates of the mean difference between treatment groups are in the favour of vosoritide and all 95% CIs are overlapping.

Height Z score was analysed using the same methods as the primary analysis. The least-squares mean difference between vosoritide and placebo at week 52 was +0·28 in favour of vosoritide (95% CI 0·17–0·39, two-sided p value <0·0001; see table 2, appendix p 13). Prespecified, three-step serial gatekeeping was applied and since the primary endpoint test was positive, the type I error rate was controlled for testing on this key secondary endpoint. The results of the subgroup analyses show that all estimates of the mean difference between treatment groups are greater than or equal to zero and the 95% CIs are overlapping (see appendix p 14).

The change from baseline in upper to lower body segment ratio was also analysed using the same methods as the primary analysis. The least squares mean difference in change from baseline between vosoritide and placebo at week 52 was –0·01 (95% CI –0·05–0·02; two-sided p=0·51; see table 2, appendix pp 15, 16). Change from baseline in extremity body proportion ratios, including lower limb, upper limb, and arm span, also showed no

	Placebo (n=61)		15 µg/kg vosoritide (n=60)	
	Incidence*	Event rate†	Incidence*	Event rate†
Total treatment exposure, person-years	··	60·93	··	57·99
Patients with event of special interest				
Fractures	0	0	1 (2%)	1 (0·02)
Slipped capital femoral epiphysis	0	0	0	0
Avascular necrosis or osteonecrosis	0	0	0	0
Patients with any serious adverse event	4 (7%)	5 (0·1)	3 (5%)	4 (0·1)
Influenza	0	0	1 (2%)	1 (0·02)
Appendicitis	1 (2%)	1 (0·02)	0	0
Radius fracture	0	0	1 (2%)	1 (0·02)
Adenoidal hypertrophy	1 (2%)	1 (0·02)	1 (2%)	1 (0·02)
Sleep apnoea syndrome	0	0	1 (2%)	1 (0·02)
Dyspnoea	1 (2%)	1 (0·02)	0	0
Intracranial pressure increased	1 (2%)	1 (0·02)	0	0
Spinal cord compression	1 (2%)	1 (0·02)	0	0
Patients with any adverse event	60 (98%)	2121 (34·8)	59 (98%)	7345 (126·7)
Injection site reaction	29 (48%)	229 (3·8)	44 (73%)	2280 (39·3)
Injection site erythema	40 (66%)	1215 (19·9)	41 (68%)	3987 (68·7)
Injection site swelling	6 (10%)	53 (0·9)	23 (38%)	322 (5·6)
Nasopharyngitis	18 (30%)	29 (0·5)	16 (27%)	26 (0·4)
Vomiting	12 (20%)	16 (0·3)	16 (27%)	25 (0·4)
Headache	16 (26%)	30 (0·5)	14 (23%)	23 (0·4)
Pyrexia	13 (21%)	22 (0·4)	10 (17%)	11 (0·2)
Arthralgia	4 (7%)	7 (0·1)	9 (15%)	11 (0·2)
Injection site urticaria	2 (3%)	5 (0·1)	8 (13%)	71 (1·2)
Upper respiratory tract infection	10 (16%)	12 (0·2)	8 (13%)	8 (0·1)
Blood pressure decreased	3 (5%)	3 (0·05)	7 (12%)	10 (0·2)
Cough	8 (13%)	10 (0·2)	7 (12%)	8 (0·1)
Diarrhoea	2 (3%)	2 (0·03)	6 (10%)	8 (0·1)
Ear infection	6 (10%)	6 (0·1)	6 (10%)	8 (0·1)
Ear pain	3 (5%)	3 (0·05)	6 (10%)	11 (0·2)
Influenza	3 (5%)	3 (0·05)	6 (10%)	8 (0·1)
Oropharyngeal pain	4 (7%)	4 (0·1)	6 (10%)	13 (0·2)
Otitis media	6 (10%)	9 (0·1)	6 (10%)	7 (0·1)

Data are n (%) or m (rate). 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 Medical Dictionary for Regulatory Activities version 22.0. *Percentages were calculated using the total number of patients in the safety population (n for each treatment group) as the denominator. Patients with more than one adverse event of the same preferred term were counted only once for that preferred term. †Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group. Multiple occurrences of an adverse event with the same preferred term for a patient were counted for each occurrence for that preferred term.

Table 3: **Incidence and exposure-adjusted event rates for common (≥10%) treatment-emergent adverse events in the vosoritide treatment group, all serious adverse events, and events of special interest (full safety population)**

difference (data not shown). For the secondary endpoint of standing height see the appendix (p 20).

No clinically meaningful differences were observed in change from baseline between the placebo and vosoritide groups in health-related quality of life, assessed by the Pediatric Quality of Life Inventory (PedsQL), and the Quality of Life of Short Statured Youth (QoLISSY) tools, or functional independence, as assessed by the Functional Independence Measure for children (WeeFIM), after completion of the 52-week study period (see appendix pp 6, 21–25).

Sensitivity analyses using a multiple imputation washout model to impute missing assessments for two patients who discontinued treatment before 52 weeks were consistent with the main results (see appendix p 26). SAS procedure Proc MI with the missing-not-at-random option was used for the washout model, which only used placebo data to impute the missing week 52 assessment.

Common treatment-emergent adverse events are shown in table 3 and all adverse events are shown in the appendix (pp 28–32). Most adverse events were mild with no new safety findings. Injection site reactions were most commonly reported and were all non-serious and transient. Additionally, there were no grade 3 or higher hypersensitivity reactions, or anaphylaxis reported. Blood pressure and pulse rate were monitored frequently during the initial study visits, for 2 h post-dose during the first 3 days of treatment, and for 1 h on subsequent visits. No clinically significant cardiovascular changes were observed and post-dose decreases in systolic blood pressure <70 mm Hg (plus two times age) were reported in 14 (23%) of 60 patients on vosoritide treatment and 15 (25%) of 61 on placebo, whereas post-dose decreases in diastolic blood pressure less than 40 mm Hg were reported in 10 (17%) of 60 patients receiving vosoritide and six (10%) of 61 receiving placebo (appendix p 27).[9] All changes in blood pressure were asymptomatic, except for one patient treated with vosoritide, who had a single symptomatic hypotensive event associated with sitting up suddenly before a blood draw (associated with a post-dose systolic blood pressure decrease of <20 mm Hg, and a diastolic decrease of <10 mm Hg), which was transient and resolved without medical intervention.

A total of nine serious adverse events were reported in seven patients, which included four patients on placebo with grade 3 appendicitis, grade 3 adenoidal hypertrophy, grade 2 dyspnoea, grade 3 intracranial pressure increased, and grade 3 spinal cord compression, and three patients on vosoritide with grade 3 influenza, grade 3 radial fracture, grade 2 adenoidal hypertrophy and grade 3 sleep apnoea syndrome. None of the serious adverse events were considered by the investigator to be related to study drug and no deaths occurred. There were no adverse events related to disproportionate skeletal growth.

Serum immunogenicity samples for assessment were collected predose at baseline and every 12 weeks through to the end of the study. Serum total antidrug antibody titres were detected in 42% of patients (25 out of 60) at one or more assessment visits. Serum total antidrug antibody titres were positive either at a single visit (n=8) or two or more visits (n=17) during the study. No neutralising antibodies were detected in any patients. There was no association between the presence of total antidrug antibodies and change in annualised growth

velocity or frequency or severity of hypersensitivity or injection site reactions.

Discussion

In this phase 3 trial, vosoritide, administered to children with achondroplasia at a dose of 15·0 μg/kg per day resulted in a highly significant increase in annualised growth velocity and height Z scores after 52 weeks of treatment as compared with placebo. There were no adverse effects on, or significant improvements in upper to lower body segment proportionality in children receiving vosoritide during this 52 week study. This suggests that either a longer treatment period or earlier treatment initiation might be required to detect these changes. These data are consistent with those observed in the phase 2 trials of vosoritide,[6] and provide further clinical evidence that vosoritide represents the first therapy to address the underlying molecular pathology in individuals with achondroplasia. The absence of any observed adverse effects on bone maturation or upper to lower body segment proportionality strengthens the prediction that longer periods of treatment might result in durable and proportionate effects on skeletal growth, leading to increased final adult height. Human growth hormone, which is approved for use in achondroplasia in Japan, has failed to show durable or significant effects on growth and final adult height,[10] and does not address the underlying pathogenesis.

This study is limited in that direct evaluation of the effect of vosoritide treatment on final adult height and how this relates to functionality, quality of life, and activities of daily living in people with achondroplasia cannot be evaluated at this time. In addition, whether treatment with vosoritide will ameliorate the medical complications associated with achondroplasia and decrease the need for surgical interventions is unknown.

Concerns around these limitations are shared by some in the short-statured community, and their support groups, who consider that a treatment that only increases height in achondroplasia is not a priority, and that the short-term and long-term health of individuals must also be enhanced. These perspectives are balanced by the views of some participants in this trial and their families, who agree that while better health is an important outcome, increased height in itself will facilitate better access to the environment, less discrimination, and higher self-esteem.

To address these limitations, concerns, and unanswered questions, an ongoing, open-label, phase 3, extension study (ClinicalTrials.gov number, NCT03424018) will continue to evaluate the balance of benefits and harms of vosoritide until the patients reported in this study reach final adult height. This study will collect data regarding vosoritide therapy on wider health measures including quality of life, activities of daily living, and frequency and type of medical and surgical interventions compared with registry data of untreated children with achondroplasia. This long-term study will also provide data on whether treatment of children with achondroplasia with vosoritide will result in a pubertal growth spurt, which appears to be absent in this condition[11] and provide the opportunity to detect any harms associated with long-term therapy.

In addition, a phase 2, randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov number, NCT03583697) of vosoritide in infants and younger children (aged 3 months to <60 months) with achondroplasia has been designed to provide further insights into the long-term treatment effects on body proportionality and growth, as well as how earlier treatment might affect the most substantial medical complications (eg, foramen magnum stenosis with brainstem compression).

No new harms associated with vosoritide treatment were identified in this trial. There was no difference in the incidence of side-effects between the treated and control groups, no drug-related serious adverse events, and the safety profile of vosoritide remained generally mild (table 3). Given the concern regarding the vascular side-effects of vosoritide, based on the structural similarity of C-type natriuretic peptide with atrial natriuretic peptide, pulse rate and blood pressure were monitored frequently in this trial (see appendix p 75). Vosoritide administration was associated with mild, transient, and clinically inconsequential blood pressure changes, that were self-limiting. These results are consistent with those observed in the phase 2 studies of vosoritide and strengthen its vascular safety profile.

It is noteworthy that another C-type natriuretic product (TransCon CNP), with a longer half-life than vosoritide, and engineered to be administered as a weekly subcutaneous injection, is undergoing clinical development for the treatment of children with achondroplasia.[12] Other therapies that address the underlying pathogenesis of achondroplasia, including a soluble FGFR3 molecule used as a ligand trap[13] (recifercept), and a selective oral tyrosine kinase/FGFR3 inhibitor[14] (infigratinib), have shown efficacy in mouse models of achondroplasia and are now in early clinical development. It will be of interest to compare the safety and efficacy profiles of these potential therapeutic options with vosoritide as they progress through clinical trials, and whether any of their actions might be synergistic for possible future combination therapy.

In summary, daily subcutaneous administration of vosoritide to children with achondroplasia resulted in significantly increased growth velocity and height Z scores. There were no adverse effects on upper to lower body segment proportionality or bone maturation, and vosoritide was otherwise generally well tolerated. The vascular effects were mild, generally clinically inconsequential, and self-limiting.

To our knowledge, this study provides the first, robust evidence for an effective, precision therapy for achondroplasia that could fundamentally change the clinical management policies, growth trajectory, and treatment recommendations for children affected by this condition. It is envisaged that the results reported in this study

establish vosoritide as the first, precision treatment option in the care of children with achondroplasia.

Contributors

RS wrote the first draft of the manuscript, assisted by JD. JD, DMP, KJ, and EF wrote the first draft of the protocol and amendments with input from RS, MI, and JH-F. AH-L did the statistical analysis. RS, LT, MI, WW, CAB, JH-F, RUF, PH, FR, MBB, LEP, IG, KM, JC, DH, KO, YA, PA, SK, NY, KKW, HMS, AL-G, FL-G, HM, and DB recruited and enrolled patients to the trial, and managed them during the trial period according to the protocol. RS and JD vouch for the data as reported, adherence of the trial to the protocol, and complete reporting of all adverse events.

Declaration of interests

All authors were investigators in this clinical trial with the exception of DMP, KJ, EF, AH-L, and JD, who are employees of the funder (BioMarin). RUF, IG, KO, YA, DH, SK, NY, HMS, AL-G, FL-G, and HM declare no conflicts of interest. RS, LT, FR, and KM have received consulting fees and grants from BioMarin. MI and WW have received consulting fees from BioMarin. JC and DB have received grants from BioMarin. LEP and PA have received honoraria from BioMarin. CAB and PH have received consulting fees, honoraria and grants from BioMarin. JH-F has received consulting fees from BioMarin, Therachon and Ascendis, 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. KKW has received consulting fees from BioMarin and Sanofi–Genzyme, and grants from BioMarin, Ultragenyx, and Ascendis.

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 on request. Investigators will be able to request access to these data and supporting documents via a website beginning at 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 the BioMarin website to determine whether access will be given, contingent on execution of a data access agreement with BioMarin Pharmaceutical.

For **data access requests** see www.BioMarin.com

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References

1 Shiang R, Thompson LM, Zhu YZ, et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 1994; **78:** 335–42.

2 Ireland PJ, Pacey V, Zankl A, Edwards P, Johnston LM, Savarirayan R. Optimal management of complications associated with achondroplasia. *Appl Clin Genet* 2014; **7:** 117–25.

3 Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet* 2007; **370:** 162–72.

4 Lorget F, Kaci N, Peng J, et al. Evaluation of the therapeutic potential of a CNP analog in a Fgfr3 mouse model recapitulating achondroplasia. *Am J Hum Genet* 2012; **91:** 1108–14.

5 Yasoda A, Komatsu Y, Chusho H, et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med* 2004; **10:** 80–86.

6 Savarirayan R, Irving M, Bacino CA, et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med* 2019; **381:** 25–35.

7 Coghlan RF, Oberdorf JA, Sienko S, et al. A degradation fragment of type X collagen is a real-time marker for bone growth velocity. *Sci Transl Med* 2017; **9:** eaan4669.

8 National Center for Health Statistics. Growth charts: United States. Atlanta: Centers for Disease Control and Prevention. https://www.cdc.gov/growthcharts/index.htm (accessed Sept 29, 2018).

9 US Department for Health and Human Services. Definition of hypotension by systolic blood pressure and age. https://chemm.nlm.nih.gov/pals.htm (accessed Sept 8, 2019).

10 Harada D, Namba N, Hanioka Y, et al. Final adult height in long-term growth hormone-treated achondroplasia patients. *Eur J Pediatr* 2017; **176:** 873–79.

11 Hoover-Fong J, McGready J, Schulze K, Alade AY, Scott CI. A height-for-age growth reference for children with achondroplasia: Expanded applications and comparison with original reference data. *Am J Med Genet A* 2017; **173:** 1226–30.

12 Breinholt VM, Rasmussen CE, Mygind PH, et al. TransCon CNP, a sustained-release C-type natriuretic peptide prodrug, a potentially safe and efficacious new therapeutic modality for the treatment of comorbidities associated with fibroblast growth factor receptor 3-related skeletal dysplasias. *J Pharmacol Exp Ther* 2019; **370:** 459–71.

13 Garcia S, Dirat B, Tognacci T, et al. Postnatal soluble FGFR3 therapy rescues achondroplasia symptoms and restores bone growth in mice. *Sci Transl Med* 2013; **5:** 203ra124.

14 Komla-Ebri D, Dambroise E, Kramer I, et al. Tyrosine kinase inhibitor NVP-BGJ398 functionally improves FGFR3-related dwarfism in mouse model. *J Clin Invest* 2016; **126:** 1871–84.