ORIGINAL ARTICLE

Oral Infigratinib Therapy in Children with Achondroplasia

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ABSTRACT

BACKGROUND

Achondroplasia is a genetic skeletal condition that results in disproportionately short stature and medical complications throughout life. Infigratinib is an orally bioavailable FGFR1–3 selective tyrosine kinase inhibitor in development for achondroplasia.

METHODS

In this phase 2 dose-finding study, we evaluated the safety and efficacy of oral infigratinib in children with achondroplasia between the ages of 3 and 11 years. A total of 72 children were enrolled in five sequential cohorts to receive daily infigratinib at doses of 0.016 mg per kilogram of body weight (cohort 1), 0.032 mg per kilogram (cohort 2), 0.064 mg per kilogram (cohort 3), 0.128 mg per kilogram (cohort 4), and 0.25 mg per kilogram (cohort 5) for 6 months, followed by 12 months of extended treatment in which the dose in cohorts 1 and 2 could be escalated to the next ascending level at months 6 and 12. The primary safety outcome was the incidence of adverse events that led to a decrease in the dose or discontinuation of infigratinib. The primary efficacy outcome was the change from baseline in the annualized height velocity.

RESULTS

During treatment, all the children had at least one adverse event, most of which were mild or moderate in severity; none resulted in treatment discontinuation. In cohort 5, an increased annualized height velocity was observed, which persisted throughout the duration of the study, with a mean change from baseline at 18 months of 2.50 cm per year (95% confidence interval [CI], 1.22 to 3.79; P=0.001). The mean change from baseline in height z score was 0.54 (95% CI, 0.35 to 0.72) relative to an untreated achondroplasia reference population at 18 months; the mean change from baseline in the upper-to-lower body segment ratio was −0.12 (95% CI, −0.18 to −0.06).

CONCLUSIONS

The administration of oral infigratinib did not result in any apparent major safety signal and increased the annualized height velocity and z score and decreased the upper-to-lower body segment ratio at 18 months of treatment in cohort 5. (Funded by BridgeBio Pharma; PROPEL2 ClinicalTrials.gov number, NCT04265651.)

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Achondroplasia, which is the most common heritable cause of disproportionate short stature, is caused by gain-of-function pathogenic variants in the gene encoding fibroblast growth factor receptor 3 (*FGFR3*). This alteration impairs the process of endochondral skeletal ossification through inhibition of chondrocyte proliferation and differentiation and extracellular matrix synthesis.[1] This inhibition occurs through the signal transducer and activator of transcription 1 (STAT1) and mitogen-activated protein kinase (MAPK) pathways in chondrocytes.[2] Persons with achondroplasia can have a variety of medical complications, functional limitations, and psychosocial challenges.[3] To date, the only drug that has been approved for targeting the underlying pathophysiological mechanisms of achondroplasia is vosoritide, which is administered as a once-daily subcutaneous injection.[4] An oral therapeutic option remains an unmet need for patients with this condition.

Infigratinib is an orally bioavailable FGFR1–3 selective tyrosine kinase inhibitor in development for patients with achondroplasia. Infigratinib was previously assessed in adult patients with cancers that have FGFR alterations, including cholangiocarcinoma and urothelial carcinoma.[5,6] More than 1100 adult patients have been exposed to infigratinib monotherapy at doses up to 200 mg per day in oncology studies. To date, doses of infigratinib that were lower by a factor of 10 to 100 than those used in oncology studies have been used in children with achondroplasia.

Infigratinib acts directly at the source of the pathophysiological cause of achondroplasia by inhibiting the phosphorylation of FGFR and, as a result, attenuates both main downstream signaling pathways that are involved in the condition, which potentially offers a direct therapeutic strategy to reduce the hyperactivity of FGFR3 in this condition. Preclinical data in an Fgfr3 Y367C/+ mouse model of achondroplasia showed that infigratinib reduced FGFR3 phosphorylation and restored activity of FGFR3 downstream signaling pathways to levels observed in wild-type mice. The drug also improved appendicular and axial skeletal growth as well as the shape and size of the foramen magnum, as compared with untreated controls.[7] On the basis of these observations, we initiated this phase 2 trial (PROPEL2) to identify a dose of infigratinib for additional study and to assess the preliminary safety and efficacy of once-daily oral infigratinib therapy in children with achondroplasia between the ages of 3 and 11 years.

Methods

Trial Design

In July 2020, this multicenter, multinational, open-label study was initiated at 19 sites (6 in the United Kingdom, 5 in the United States, 3 each in Spain and France, and 1 each in Australia and Canada) to assess the preliminary safety and efficacy of oral infigratinib in children with achondroplasia and to identify the dose of infigratinib to be explored in future studies. The study design was described previously[8] and is detailed in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Briefly, the study consists of a dose-escalation phase with an extended-treatment period, a dose-expansion phase to confirm the selected dose, and a pharmacokinetic substudy to characterize the pharmacokinetics of infigratinib and its major active metabolites.[8] During the dose-escalation and pharmacokinetic phases, patients were enrolled sequentially in five dose cohorts to receive daily oral infigratinib at 0.016 mg per kilogram of body weight (cohort 1), 0.032 mg per kilogram (cohort 2), 0.064 mg per kilogram (cohort 3), 0.128 mg per kilogram (cohort 4), or 0.25 mg per kilogram (cohort 5) for 6 months. These patients continued treatment for an additional 12 months (extended-treatment period), during which time the dose in cohorts 1 and 2 could be escalated to the next ascending level at month 6 and month 12 (maximum, two increases allowed). The dose for further exploration was selected on the basis of safety and efficacy data from the five cohorts after all the patients had completed 6 months of treatment at their assigned dose. Their outcomes were evaluated on the basis of maximum efficacy while balancing safety considerations, including the potential for excessive growth. After completion of the 12-month extended-treatment period, the patients were eligible to enroll in a long-term extension study (ClinicalTrials.gov number, NCT05145010).[8]

Infigratinib was orally administered as minitablets in individualized daily-dose packets, which minimized any potential risk of overdose. This report includes cumulative 18-month results re-

garding linear growth and body proportions for patients who completed the 6-month dose-escalation phase with 12 months of extended treatment. The dose-expansion phase is ongoing.

OVERSIGHT

The study is being performed in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Approval was obtained from the institutional review board at each participating site. Confidentiality agreements were in place between the sponsor (BridgeBio Pharma) and the study sites. Written informed consent from a parent or legal guardian was obtained.

The study was designed by representatives of the sponsor and four authors who were not employed by the sponsor. The sponsor funded the study, and its representatives analyzed the data. The first draft of the manuscript was written by the first and last authors; all the authors provided critical review and input on all draft versions of the manuscript and made the decision to submit the manuscript for publication. All the authors had access to the complete analyses. The first author had access to all the raw data and vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

PATIENTS

Eligible patients were children between the ages of 3 and 11 years with a confirmed genetic diagnosis of achondroplasia. All the patients had completed at least 6 months of growth assessments in the observational PROPEL study (NCT04035811). Exclusion criteria included a height that was less than 2 SD below the mean or greater than 2 SD above the mean on achondroplasia growth charts, along with an annualized height velocity of 1.5 cm per year or less, treatment with any other investigational product for achondroplasia or short stature, or previous limb-lengthening surgery. Complete eligibility criteria are provided in the study protocol.

OUTCOMES

The primary objective of the dose-escalation phase of the study was to identify an optimum dose of oral infigratinib, on the basis of safety and efficacy evaluations, to be used for further study in children with achondroplasia. The primary safety outcome was the incidence of adverse events that led to a decrease in the dose or discontinuation of infigratinib. Safety was evaluated according to the incidence, type, severity, and causality of adverse events. Assessments included physical examination, laboratory testing, vital signs, electrocardiograms, and imaging. The primary efficacy outcome was the change from baseline in the annualized height velocity. Key secondary outcomes were the changes from baseline in the height z score, body proportions, and level of collagen X biomarker (a molecular component of type X collagen released to circulation during the ossification process that is used as a marker of bone growth).[9,10] A full list of secondary and exploratory outcomes is provided in the protocol.

STATISTICAL ANALYSIS

The safety analysis was conducted in the safety population, which consisted of all the patients who had received at least one dose of the study drug. Efficacy analyses were conducted in the efficacy population, which included all the patients in the safety population who had available data regarding both the baseline measurement and at least one postbaseline standing-height measurement. Standing-height measurements were obtained every 3 months after the baseline assessment.

The baseline annualized height velocity was determined from a minimum of 6 months of observation in the PROPEL study. Postbaseline annualized height velocity was recalculated every 6 months on the basis of the baseline standing-height measurement. Standing-height measurements were converted to z scores after adjustment for sex and age on the basis of comparisons with reference standards from a population of persons with untreated achondroplasia.[11] The upper-to-lower body segment ratio (a measurement of the ratio of the head and trunk [upper-body segment] to the legs) was calculated from standing and sitting height measurements.

Descriptive statistics were used to present the absolute values and changes from baseline in the annualized height velocity, z score, and upper-to-lower body segment ratio. Changes from baseline values were evaluated with the use of the one-sample Student's t-test. No adjustments for multiple comparisons were applied. The only P value that is provided is for the primary efficacy out-

Table 1. Demographic Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1: 0.016 mg/kg (N=8)	Cohort 2: 0.032 mg/kg (N=19)	Cohort 3: 0.064 mg/kg (N=16)	Cohort 4: 0.128 mg/kg (N=16)	Cohort 5: 0.25 mg/kg (N=13)	All Dose Cohorts (N=72)
Age						
Mean — yr	7.69±2.83	8.29±1.84	7.70±2.40	6.61±2.08	7.05±1.99	7.50±2.20
Median (range) — yr	8.7 (3.4–11.2)	8.9 (4.3–10.7)	8.1 (3.1–11.5)	7.0 (3.7–10.3)	6.5 (4.8–11.3)	7.9 (3.1–11.5)
Distribution — no. (%)						
3 to <5 yr	2 (25)	1 (5)	2 (12)	5 (31)	2 (15)	12 (17)
5 to <8 yr	1 (12)	6 (32)	5 (31)	6 (38)	7 (54)	25 (35)
<8 yr	3 (38)	7 (37)	7 (44)	11 (69)	9 (69)	37 (51)
≥8 yr	5 (62)	12 (63)	9 (56)	5 (31)	4 (31)	35 (49)
Sex — no. (%)						
Male	2 (25)	5 (26)	9 (56)	9 (56)	5 (38)	30 (42)
Female	6 (75)	14 (74)	7 (44)	7 (44)	8 (62)	42 (58)
Race or ethnic group — no. (%)†						
White	5 (62)	10 (53)	13 (81)	9 (56)	7 (54)	44 (61)
Black	2 (25)	1 (5)	0	0	1 (8)	4 (6)
Asian	0	2 (11)	0	2 (12)	2 (15)	6 (8)
Multiple	0	1 (5)	0	0	1 (8)	2 (3)
Other	1 (12)	1 (5)	0	1 (6)	0	3 (4)

* Plus–minus values are means ±SD.
† Race or ethnic group was not reported for 13 patients. Information regarding race or ethnic group was reported by the patient or by the patient's family or guardian where allowed by country regulations.

Table 2. Common Adverse Events.*

Adverse Event	Cohort 1: 0.016 mg/kg (N=8)	Cohort 2: 0.032 mg/kg (N=19)	Cohort 3: 0.064 mg/kg (N=16)	Cohort 4: 0.128 mg/kg (N=16)	Cohort 5: 0.25 mg/kg (N=13)	All Dose Cohorts (N=72)
	number of patients (percent)					
Event						
Nasopharyngitis	4 (50)	9 (47)	7 (44)	4 (25)	5 (38)	29 (40)
Covid-19	1 (12)	9 (47)	8 (50)	5 (31)	1 (8)	24 (33)
Headache	1 (12)	6 (32)	7 (44)	4 (25)	6 (46)	24 (33)
Vomiting	3 (38)	4 (21)	5 (31)	6 (38)	4 (31)	22 (31)
Limb pain	2 (25)	4 (21)	8 (50)	2 (12)	4 (31)	20 (28)
Ear infection	3 (38)	3 (16)	2 (12)	7 (44)	4 (31)	19 (26)
Pyrexia	1 (12)	4 (21)	6 (38)	4 (25)	3 (23)	18 (25)
Abdominal pain	0	3 (16)	2 (12)	4 (25)	2 (15)	11 (15)
Cough	0	1 (5)	3 (19)	4 (25)	3 (23)	11 (15)
Diarrhea	0	1 (5)	4 (25)	3 (19)	3 (23)	11 (15)
Rhinitis	0	2 (11)	4 (25)	3 (19)	2 (15)	11 (15)
Viral infection	1 (12)	2 (11)	1 (6)	3 (19)	4 (31)	11 (15)
Upper respiratory tract infection	3 (38)	1 (5)	1 (6)	3 (19)	2 (15)	10 (14)
Upper abdominal pain	1 (12)	0	4 (25)	2 (12)	1 (8)	8 (11)
Ear pain	0	3 (16)	2 (12)	1 (6)	2 (15)	8 (11)
Nausea	0	0	4 (25)	2 (12)	2 (15)	8 (11)
Oropharyngeal pain	0	2 (11)	4 (25)	1 (6)	1 (8)	8 (11)
Otitis media	0	2 (11)	2 (12)	2 (12)	2 (15)	8 (11)

* Shown are adverse events that were reported in at least 10% of the overall study population, according to the preferred term in the *Medical Dictionary for Regulatory Activities*, version 23.1. Preferred terms are ordered according to the descending incidence in the All Cohorts column. Adverse events include all events that had an onset after the first administration of the study drug and up to the administration of the last dose plus 30 days if patients had ended the study treatment. Covid-19 denotes coronavirus disease 2019.

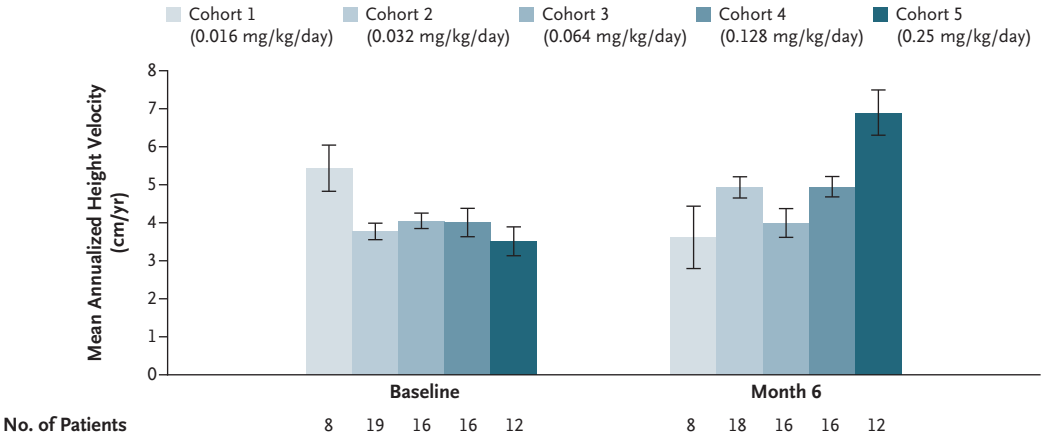

Figure 1. Mean Annualized Height Velocity in Cohorts 1 through 5.

Shown is the change from baseline to 6 months in the mean annualized height velocity, the primary efficacy outcome in the study. Baseline values were derived from standing-height measurements (in centimeters) from day 1 of the study and from a minimum of 6 months of observation in the PROPEL study. The annualized height velocity at 6 months was derived from the baseline standing-height measurement with the use of the following formula: (height at postbaseline visit − height at the baseline visit) × 365.25 / (date of postbaseline visit − date of baseline visit + 1). I bars represent standard errors.

come of the change from baseline in the annualized height velocity. Correspondingly, the widths of confidence intervals have not been adjusted for multiplicity and the intervals should not be used in place of hypothesis testing.

The effect of missing data on the annualized height velocity, height z score, and upper-to-lower body segment ratio was assessed through sensitivity analyses conducted in cohorts 1, 2, and 5; there were no missing data in cohorts 3 and 4. The multiple imputations were applied solely to the efficacy population. Nonparametric analyses were conducted to assess the robustness of the results. Details regarding these analyses are provided in the Supplementary Appendix. Statistical analyses were conducted with the use of SAS software, version 9.4.

RESULTS

BASELINE CHARACTERISTICS

A total of 72 patients were enrolled sequentially in the five dose cohorts. The mean (±SD) age at screening was 7.5±2.2 years (range, 3.1 to 11.5), and 58% were female. The demographic characteristics of the patients are shown in Table 1. The study population is representative of the broader population with achondroplasia (Table S1).

As of May 8, 2024, a total of 67 patients had completed 18 months of infigratinib treatment. Two patients (1 each from cohort 2 and 5) withdrew from the study during the 6-month escalation phase (at month 3 and week 6, respectively), and 3 patients (1 each from cohorts 1, 2, and 5) withdrew during the 12-month extended-treatment period (months 11, 11, and 9, respectively). None of these discontinuations were due to safety or efficacy issues or concerns. Four patients withdrew because of personal reasons that would not allow them to adhere to the study requirements, and 1 patient (in cohort 2) discontinued the study drug to undergo a surgery (ventriculoperitoneal shunt placement) that would have confounded the assessment of safety. The disposition of the patients is summarized in Figure S2.

EXPOSURE AND ADVERSE EVENTS

The 72 patients who were enrolled in the study received daily doses of oral infigratinib for a mean (±SD) of 485±83 days (range, 22 to 520). All the patients had at least one adverse event during treatment (Table S2). Adverse events that were reported in at least 10% of the patients are listed in Table 2. The majority of children had adverse events that were mild (in 39 of 72 of patients [54%]) or moderate (in 28 of 72 patients [39%])

in severity (worst severity reported). The incidence and severity of adverse events were similar across all dose cohorts. No patient had a serious adverse event or a grade 4 or 5 event. In addition, no patients discontinued the study drug because of an adverse event.

Grade 3 adverse events occurred in five children (7%) and consisted of hydrocephalus, adenoidal hypertrophy, and tonsillar hypertrophy (in cohort 2), sleep apnea syndrome and cholesteatoma (in cohort 3), and bacillus infection (in cohort 4). Seven patients (10%) had adverse events that were assessed by the investigator as being related to the study drug, all of which were mild in severity; these events were dyspepsia and flatulence (in cohort 2), a decrease in the vitamin D level (in cohorts 3 and 4), decreased appetite (in cohort 4), and hyperphosphatemia (in cohort 3) (Table S3). Regarding the latter, one patient in cohort 3 (who received a daily dose of 0.064 mg per kilogram) presented on treatment day 3 with grade 1 hyperphosphatemia (phosphorous level, 6.2 mg per deciliter; upper limit of normal range, 6.0 mg per deciliter), which was confirmed with a repeat value. In accordance with the protocol, treatment was interrupted and resumed at a lower daily dose of 0.032 mg per kilogram after normalization of values within 1 week after drug interruption, with no further increase in phosphorus levels. The incidence of grade 3 adverse events, including those related to the study drug, is summarized in Table S4.

No corneal or retinal disorders were reported or identified by ophthalmic examination. No accelerated progression of bone age, changes in bone mineral density, or other bone-related adverse events were reported (Tables S5 and S6).

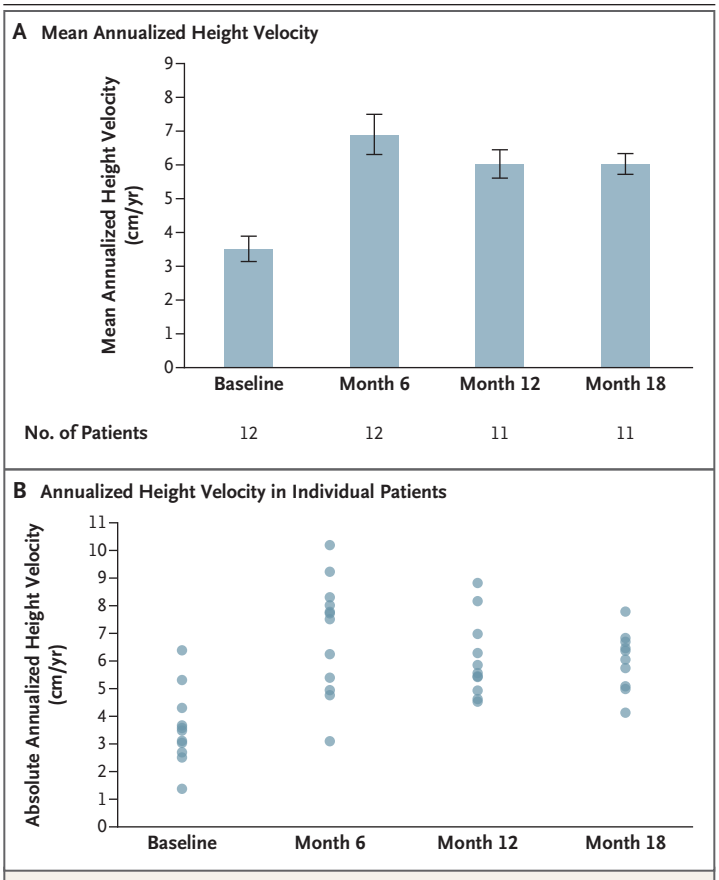

Figure 2. Annualized Height Velocity during the Treatment Period in Cohort 5.

Panel A shows the mean annualized height velocity up to 18 months in cohort 5. Only patients who had available data at baseline and at the relevant postbaseline time point were included in these analyses. I bars represent standard errors. Panel B shows a vertical scatter plot of the annualized height velocity in centimeters per year up to 18 months in individual patients.

EFFICACY

Dose-Escalation Phase: Cohorts 1 to 5

The primary efficacy outcome in this study was the change from baseline in the height velocity (annualized to centimeters per year). A dose-dependent increase in the annualized height velocity was observed after 6 months of treatment with infigratinib (Fig. 1). The change from baseline to month 6 in the annualized height velocity was −1.82 cm per year (95% confidence interval [CI], −4.96 to 1.32) in cohort 1, 1.13 cm per year (95% CI, 0.47 to 1.79) in cohort 2, −0.06 cm per year (95% CI, −0.93 to 0.81) in cohort 3, 0.94 cm per year (95% CI, 0.15 to 1.74) in cohort 4, and 3.38 cm per year (95% CI, 1.67 to 5.10) in cohort 5. The dose among children in cohorts 1 and 2 was subsequently escalated to a higher level after month 6 and after month 12 in accordance with the protocol. Changes in the annualized height velocity were supported by an increase in the level of collagen X marker[9,10] (Fig. S3).

Extended-Treatment Period: Cohort 5

At the highest dose level of 0.25 mg per kilogram per day in cohort 5, the increased annualized height velocity persisted throughout the 12-month extended-treatment period (18 months of total treatment). At month 12, the mean change from baseline in the annualized height velocity was 2.51 cm per year (95% CI, 1.02 to 3.99), which

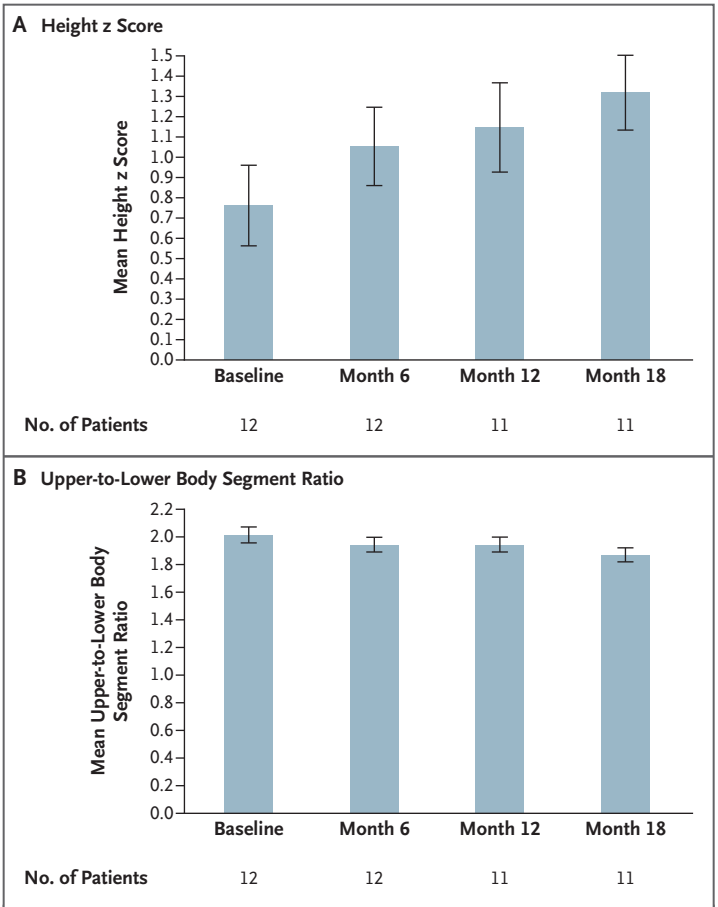

Figure 3. Mean Height z Score and Upper-to-Lower Body Segment Ratio in Cohort 5.

Panel A shows the mean height z score up to 18 months in cohort 5. The standing-height measurements were converted to z scores after adjustment for sex and age on the basis of comparisons with reference standards for an untreated achondroplasia population. Panel B shows the mean upper-to-lower body segment ratio up to 18 months. The upper-to-lower body segment ratio was calculated from standing- and sitting-height measurements in centimeters with the use of the following formula: sitting height / (standing height − sitting height). In Panels A and B, only patients with available data at baseline and at the relevant postbaseline time point were included in the analyses. I bars represent standard errors.

was sustained at month 18 (change from baseline, 2.50 cm per year; 95% CI, 1.22 to 3.79; P=0.001) (Fig. 2). Increases in height velocity were observed in 10 of 11 patients (91%) at month 18; in 8 of 11 patients (73%), the increase was at least 25% over baseline. This cumulative increase in linear growth corresponds to an increase in the height z score (referenced to achondroplasia-specific growth charts) of 0.54 (95% CI, 0.35 to 0.72) at month 18 (Fig. 3A). The mean upper-to-lower body segment ratio also decreased, from 2.02 at baseline to 1.88 at month 18 (mean change, −0.12; 95% CI, −0.18 to −0.06) (Fig. 3B).

Results from sensitivity analyses of the annualized growth velocity, height z score, and upper-to-lower body segment ratio were consistent with those of the primary analyses (Tables S7 through S12).

DISCUSSION

In this phase 2 dose-finding study involving children with achondroplasia, we evaluated the safety, side-effect profile, and preliminary efficacy of infigratinib, administered orally at once-daily doses ranging from 0.016 to 0.25 mg per kilogram for up to 18 months. Treatment with infigratinib had a side-effect profile that was mostly mild with respect to adverse events at all daily doses tested, with no serious adverse events; no adverse events led to treatment discontinuation (the primary safety outcome). Phosphorus levels and ocular events were closely monitored because the use of infigratinib in oncology studies at higher dose levels (by a factor of 10 to 100) has been associated with hyperphosphatemia and ocular adverse events. Only one case of mild hyperphosphatemia was reported (in cohort 3 with a daily dose of 0.064 mg per kilogram), an event that resolved after drug interruption and did not recur at a lower dose level (0.032 mg per kilogram). No corneal or retinal disorders were reported or identified by ophthalmic examination at any of the doses evaluated. In addition, no safety concerns at the bone or dental level were observed.

Treatment with daily oral infigratinib at the highest dose of 0.25 mg per kilogram (in cohort 5) resulted in an increase in annualized height velocity (primary efficacy outcome), which persisted at up to 18 months of treatment. This increase translated to a cumulative increase in height z score. The decrease in the upper-to-lower body segment ratio that was observed after 18 months of once-daily treatment with the highest dose of infigratinib is noteworthy because children with achondroplasia have short stature with disproportionate limb shortening in comparison to their truncal height. Such shortening results in a mean upper-to-lower segment ratio of 2.0 from the age of 4 years in both boys and girls, as compared with 1.0 in children with average stature.[12] This disproportionality, combined with a head circum-

ference that is typically above the 98th percentile for age on the basis of average growth charts, is an underlying factor in the delayed gross motor milestones shown by children with achondroplasia during the first 5 years of life[13] and contributes to challenges with respect to the completion of self-care, driving, independent ambulation, and daily functioning.[3] Additional treatment duration will be required to determine whether the improvement in the upper-to-lower body segment ratio observed in these children at 18 months will continue and be associated with improvements in functionality. The patients in this study continue to receive treatment with infigratinib in an open-label extension study (NCT05145010) in which the safety and efficacy of long-term administration of infigratinib is being evaluated.

A limitation of the current study is the small sample size at the selected dose. On the basis of the safety and preliminary efficacy results from the dose-escalation portion of this study, infigratinib at a daily dose of 0.25 mg per kilogram is being evaluated in a pivotal, phase 3, double-blind, placebo-controlled trial that aims to enroll 110 children with achondroplasia between the ages of 3 years and less than 18 years who have the potential to grow (NCT06164951).

As a FGFR3 tyrosine kinase inhibitor, infigratinib acts at the primary source of the pathophysiological cause of achondroplasia and blocks all downstream inhibitory signaling on bone growth, including through the STAT1 and MAPK pathways. In contrast, vosoritide, a C-type natriuretic peptide analogue that is administered daily by subcutaneous injection, exerts its effect by down-regulating FGFR3 signaling through the MAPK pathway alone.[4] Infigratinib is currently the only investigational drug in clinical trials for children with achondroplasia that is administered orally. On the basis of World Health Organization guidelines for the development of pediatric medicines,[14] the oral route is the preferred and most appropriate route of drug administration in the pediatric population. Challenges to children and families have been reported in association with daily injections of vosoritide in young children with achondroplasia[15] and highlight the need for an oral treatment option for this condition.

Results from this phase 2 study show that oral, once-daily administration of infigratinib had a side-effect profile that was generally mild and resulted in a sustained increase in the annualized height velocity and a decrease in the upper-to-lower body segment ratio in children with achondroplasia between the ages of 3 and 11 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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