ORIGINAL ARTICLE

Phase 3 Trial of Oral Infigratinib in Children with Achondroplasia

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ABSTRACT

BACKGROUND

Achondroplasia is a genetic skeletal condition caused by *FGFR3* pathogenic variants. Infigratinib, an oral FGFR1–3 tyrosine kinase inhibitor, down-regulates key pathways in the pathogenesis of achondroplasia.

METHODS

In this phase 3, multicenter, double-blind, placebo-controlled trial, we randomly assigned children with achondroplasia (3 to 17 years of age) in a 2:1 ratio to receive infigratinib (at a dose of 0.25 mg per kilogram of body weight) or placebo once daily for 52 weeks. The primary end point was the change from baseline in the annualized height velocity in the infigratinib group as compared with the placebo group at week 52. Key secondary end points were the change from baseline in the height z score and in the upper-to-lower body segment ratio at week 52. The primary analysis evaluated the treatment effect at week 52 in the full analysis population, with missing data handled with a prespecified imputation approach.

RESULTS

In all, 114 patients underwent randomization: 75 patients to receive infigratinib (with 1 withdrawal before treatment) and 39 patients to receive placebo. The difference between infigratinib and placebo in the least-squares mean change from baseline to week 52 was 1.74 cm per year (95% confidence interval [CI], 1.31 to 2.17; P<0.001) for the annualized height velocity, 0.32 (96% CI, 0.23 to 0.41; P<0.001) for the height z score, and −0.02 (96% CI, −0.06 to 0.01) for the upper-to-lower body segment ratio. Adverse events occurred in 71 of 74 patients (96%) in the infigratinib group and in 37 of 39 patients (95%) in the placebo group; serious adverse events occurred in 4 of 74 patients (5%) and 1 of 39 patients (3%), respectively. No serious adverse events or adverse events leading to treatment discontinuation were considered by the investigator to be related to infigratinib or placebo.

CONCLUSIONS

In children with achondroplasia, treatment with once-daily oral infigratinib for 52 weeks resulted in a significantly greater increase from baseline in the annualized height velocity than placebo. (Funded by BridgeBio Pharma; PROPEL 3 ClinicalTrials.gov number, NCT06164951; EudraCT number, 2023-506130-67.)

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A list of investigators in the PROPEL 3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Achondroplasia, a skeletal dysplasia that is characterized by disproportionate short stature, can lead to medical, functional, and psychosocial challenges.[1] This condition is caused by pathogenic gain-of-function variants in the gene encoding fibroblast growth factor receptor 3 (*FGFR3*), which causes overactivity in downstream pathways, such as mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 1 (STAT1). These changes result in impaired endochondral skeletal ossification through inhibition of chondrocyte proliferation and differentiation.[2,3]

Current therapies that are available for children with achondroplasia include the C-type natriuretic peptide analogues vosoritide[4] (approved by the Food and Drug Administration [FDA] and European Medicines Agency) and navepegritide[5] (approved by the FDA). These therapies are administered by subcutaneous injection and bind to the natriuretic peptide receptor B to inhibit the overactive MAPK pathway downstream of FGFR3. Because oral administration is the preferred route to deliver medication to pediatric patients,[6] an oral therapeutic option remains an unmet need for children with achondroplasia.

Infigratinib is an orally bioavailable FGFR1–3 selective tyrosine kinase inhibitor in development for achondroplasia. Infigratinib directly inhibits the phosphorylation of FGFR3 and attenuates key downstream signaling pathways, including MAPK and STAT1.[7] In an open-label, dose-finding, phase 2 study (PROPEL 2), oral infigratinib (at a dose of 0.25 mg per kilogram of body weight) resulted in sustained increases in the annualized height velocity and height z score, along with a decrease in the upper-to-lower body segment ratio at 18 months.[8] We conducted the present phase 3 trial (PROPEL 3) to further evaluate the efficacy and safety of infigratinib in children with achondroplasia.

Methods

Trial Design and Oversight

This phase 3, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of infigratinib in children with achondroplasia who had completed at least 26 weeks of participation in the observational PROPEL study (Clinical Trials.gov number, NCT04035811). Details regarding the trial design are provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was conducted at 27 sites in 10 countries. After completion of the 52-week treatment period, eligible patients had the option to receive infigratinib in an ongoing long-term open-label extension trial, PROPEL OLE (NCT05145010) until they reached adult height.

The trial was performed in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Approval was obtained from the institutional review board or independent ethics committee at each participating site. Written informed consent was obtained from the parents or legal guardians of the patients; assent from patients who were 3 to 17 years of age was also obtained according to the country-specific requirements.

The trial was designed by representatives of the funder, BridgeBio Pharma, and by three investigators not employed by the funder. All the investigators worked under confidentiality agreements with BridgeBio Pharma. Representatives of the funder analyzed the data. The first author had full access to the raw data, and all the authors had access to the analyses. The first draft of the manuscript was written by the first and last authors. All the authors participated in data interpretation, provided critical review of the manuscript, and agreed to submit the manuscript for publication. The first and last authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, available at NEJM.org.

Patients

Eligible children were 3 to 17 years of age at the time of screening and had a confirmed genetic diagnosis of achondroplasia. All the eligible children had a growth potential that was defined as an annualized height velocity of more than 1.5 cm per year over a period of at least 26 weeks in the PROPEL observational study, a pubertal Tanner stage of 4 or less, and a bone age of 13 years or less in girls and 15 years or less in boys. Key exclusion criteria were a corneal or retinal disorder or keratopathy, treatment with any other investigational product for achondroplasia or short stature, and previous limb-lengthening surgery. Full inclusion and exclusion criteria are available in the protocol.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Infigratinib (N=74)	Placebo (N=39)	All Patients (N=113)
Age†			
Mean — yr	7.9±2.7	7.7±2.5	7.9±2.7
Median (range) — yr	7.3 (3.7–14.4)	7.2 (3.9–14.9)	7.3 (3.7–14.9)
Distribution — no. (%)			
3 to 7 yr	43 (58)	23 (59)	66 (58)
8 to 17 yr	31 (42)	16 (41)	47 (42)
Sex — no. (%)			
Male	42 (57)	23 (59)	65 (58)
Female	32 (43)	16 (41)	48 (42)
Race — no. (%)‡			
White	46 (62)	22 (56)	68 (60)
Asian	15 (20)	6 (15)	21 (19)
Black	3 (4)	2 (5)	5 (4)
Multiple	4 (5)	4 (10)	8 (7)
Tanner stage at baseline — no. (%)§			
1	61 (82)	33 (85)	94 (83)
2 to 4	13 (18)	6 (15)	19 (17)
2	12 (16)	5 (13)	17 (15)
3	1 (1)	0	1 (1)
4	0	1 (3)	1 (1)

* Plus–minus values are means ±SD.
† A detailed summary of the age distribution is provided in Table S2.
‡ Race was reported by the patient or by a parent or guardian. Race was not reported for six patients in the infigratinib group and five patients in the placebo group.
§ The Tanner stage was defined according to breast development and pubic hair development for girls and according to testicular volume, genital development, and pubic hair development for boys. Tanner stages range from 1 to 5, with higher stages indicating more advanced pubertal development.

RANDOMIZATION AND TREATMENT

Eligible patients were randomly assigned in a 2:1 ratio to receive either infigratinib or placebo for 52 weeks. Randomization was stratified according to a prespecified combination of age, sex, and pubertal stage as follows: an age of 3 or 4 years (in <20% of the patients); an age of 5 years or older and a Tanner stage of 1 (in ≥60% of the patients); and a Tanner stage of 2 or higher (in <20% of the patients [approximately 50% girls and 50% boys], including <5% with a Tanner stage of 4).

The patients received daily treatment with oral infigratinib (sprinkle capsules) at a dose of 0.25 mg per kilogram of body weight or placebo. Treatment could be paused and resumed at the same dose or decreased to a lower dose if a criterion for dose reduction or discontinuation was met.

END POINTS

The primary end point was the change from baseline in the annualized height velocity in the infigratinib group as compared with the placebo group at week 52. Key secondary end points were the change from baseline in the height z score and the change from baseline in the upper-to-lower body segment ratio as compared with placebo at week 52. The full list of end points is provided in the protocol.

Safety assessments included the incidence and severity of adverse events, vital signs, physical examinations, clinical safety laboratory tests (serum chemistry and hematology tests and urinalysis), radiographic imaging (including bone age), bone mineral density by dual-energy x-ray absorptiometry, electrocardiograms, ophthalmic examinations, and dental examinations. Serum phos-

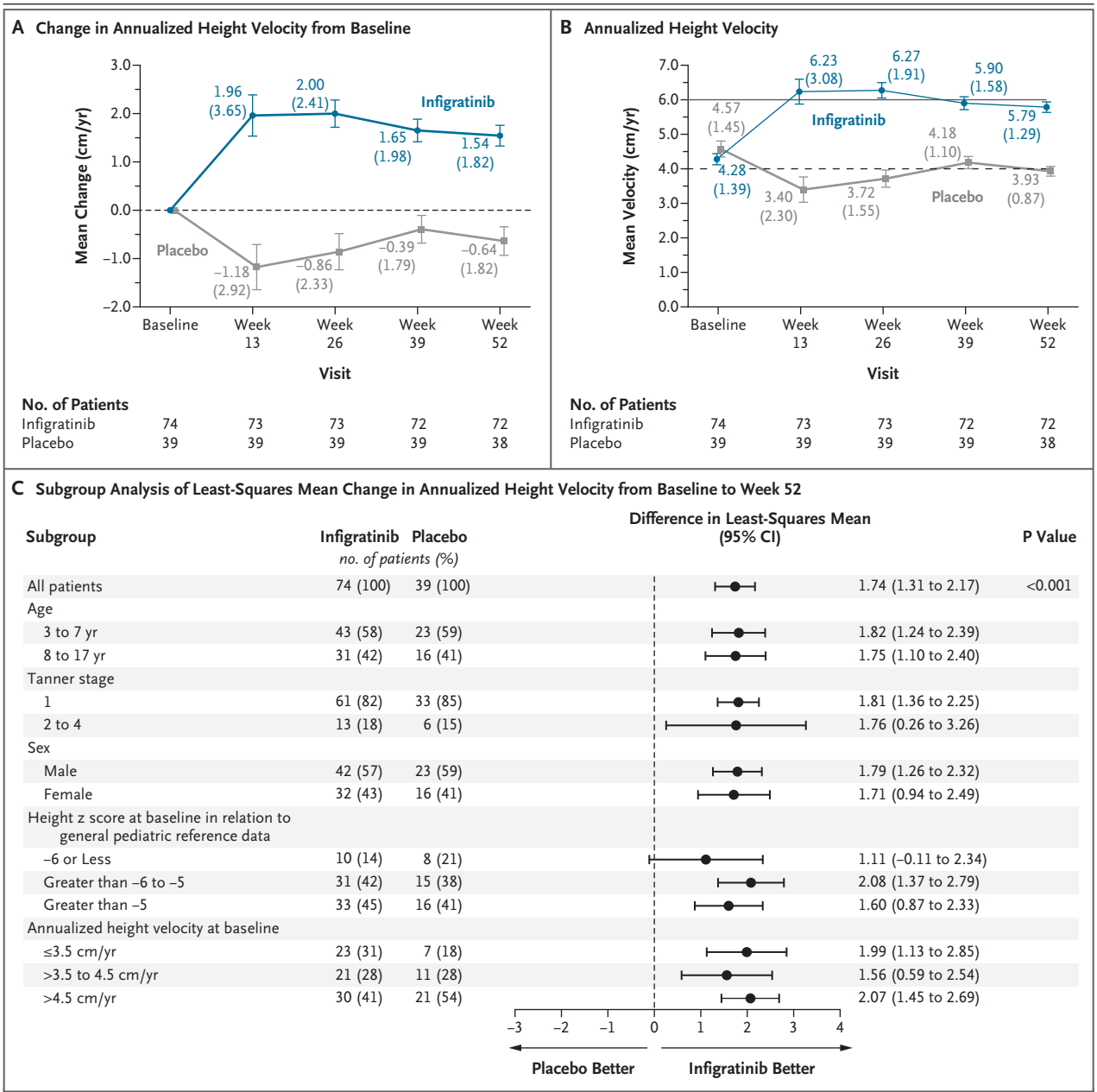


Figure 1. Annualized Height Velocity.

Shown is the mean change from baseline in the annualized height velocity in the infigratinib group and the placebo group (Panel A) and the overall mean annualized height velocity in each trial group (Panel B) at 52 weeks. Points represent the mean values at each visit, and I bars indicate the standard deviation. In Panel B, the reference annualized height velocity for children with achondroplasia and children with average stature are represented by the dashed horizontal line at 4.0 cm per year and the solid horizontal line at 6.0 cm per year, respectively.[13,14] Also shown is the difference in the least-squares mean change from baseline to week 52 in the annualized height velocity, according to subgroup (Panel C). The height z score indicates the height of the patient as compared with a reference population; a negative number indicates that the height is below the mean of the reference population, and a positive number indicates that the height is above the mean of the population. The P value is reported only for the alpha-controlled end point of the difference in the least-squares mean change from baseline to week 52 in the annualized height velocity for infigratinib as compared with placebo in the overall trial population. For all subgroups, the widths of the 95% confidence intervals have not been adjusted for multiplicity, so the results should not be used for formal hypothesis testing. Additional results according to baseline strata are provided in Table S4.

phate levels and ophthalmic examinations were closely monitored because the inhibition of FGFR1 and FGFR2 has been associated with hyperphosphatemia and ocular adverse events in other clinical settings in which infigratinib was administered at doses that were approximately 10 times as high as the weight-based dose studied here.[9-12]

STATISTICAL ANALYSIS

We determined that 93 patients would provide the trial with approximately 90% power to detect a between-group difference of 1.3 cm per year in the change from baseline to week 52 in the annualized height velocity, assuming a pooled standard deviation of 1.8 cm per year and a two-sided significance level of 0.05. So we planned to enroll approximately 110 patients for randomization in a 2:1 ratio to receive infigratinib or placebo, allowing for up to 15% dropout.

Efficacy analyses were performed in the full analysis population, which included all the patients who had undergone randomization and who had received at least one dose of infigratinib or placebo, as prespecified in the statistical analysis plan and consistent with the intention-to-treat principle. The safety population included all the patients who had received at least one dose of infigratinib or placebo.

Multiplicity was controlled to maintain the overall familywise error rate with a sequential testing procedure with fallback and Holm methods. The primary end point was tested at a two-sided significance level of 0.05. Formal testing of the key secondary and selected other secondary end points was performed only if the primary end point was significant. The key secondary end points were tested sequentially at a reduced significance level of 0.04 in the following order: height z score relative to the achondroplasia population and the upper-to-lower body segment ratio. An alpha level of 0.01 was reserved for the testing of other selected secondary end points with the Holm procedure. Under the fallback procedure, after rejection of all relevant preceding hypotheses, the 0.04 alpha that was reserved for the key secondary end points was transferred and combined with the existing 0.01 alpha, which resulted in a total available alpha of 0.05 for the testing of the other secondary end points.

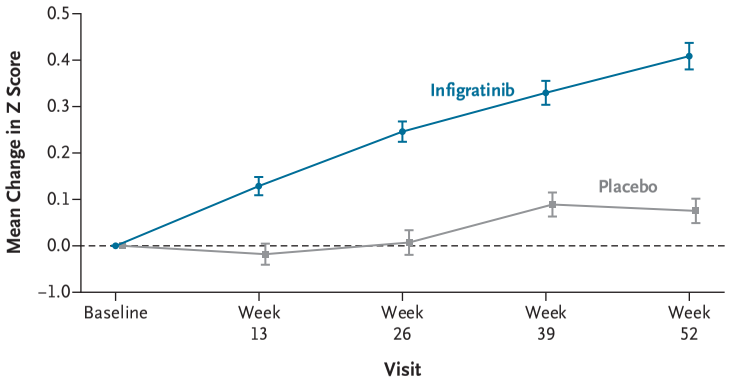
We derived the baseline annualized height velocity by calculating the difference between the patients' standing height at baseline and the standing height obtained at least 6 months before baseline during the preceding observational study and dividing the difference by the interval between the two measurements. The postbaseline annualized height velocity was derived at each visit (starting at week 13) from the baseline standing height measurement. Standing height measurements were converted to z scores after adjustment for sex and age on the basis of reference standards for an untreated achondroplasia population.[13] The upper-to-lower body segment ratio was calculated as the ratio of sitting height to (standing height minus sitting height).

We used an analysis of covariance model to estimate treatment effects for the primary and key secondary end points. This model included trial group, randomization stratum, sex, age, baseline general pediatric height z score, and baseline annualized height velocity as covariates. For the primary end point, we calculated the treatment difference as the least-squares mean change from baseline and the corresponding 95% confidence interval; a 96% confidence interval was calculated for the key secondary end points that were tested at the 0.04 level. Sensitivity analyses were performed to assess the robustness of the primary efficacy analysis under alternative assumptions for missing data, including more conservative imputation approaches for the patients who discontinued the trial regimen early. Subgroup analyses were conducted as exploratory analyses. To reduce the risk of overinterpretation arising from small sample sizes within certain subgroups, categories that had a limited number of patients were combined with adjacent categories where appropriate.

We used a placebo-washout method to impute missing postbaseline height measurements and upper-to-lower body segment ratios after trial discontinuation. In this method, we assumed that patients in the infigratinib group who had missing data after trial discontinuation followed a placebo-like trajectory. We then used Rubin's rules for statistical inference to combine the results.

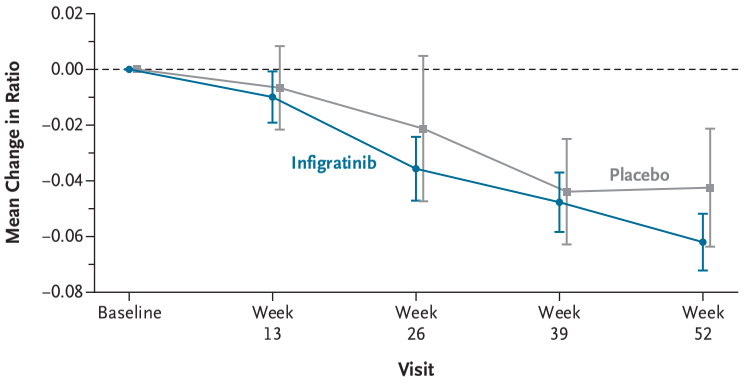
All statistical analyses were performed with the use of SAS software, version 9.4 or higher (SAS Institute). Additional information regarding the statistical analysis plan is provided in the protocol.

A Change in Height z Score Relative to Achondroplasia Reference Data from Baseline



No. of Patients					
Infigratinib	74	73	73	72	72
Placebo	39	39	39	39	38

B Change in Upper-to-Lower Body Segment Ratio from Baseline



No. of Patients					
Infigratinib	74	73	73	72	72
Placebo	38	38	38	38	37

C Subgroup Analyses of Least-Squares Mean Changes in Height z Score Relative to Achondroplasia Reference Data and in the Upper-to-Lower Body Segment Ratio from Baseline to Week 52

Subgroup	Infigratinib	Placebo	Difference in Least-Squares Mean Change in Height z Score (95% CI)	P Value	Difference in Least-Squares Mean Change in Upper-to-Lower Body Segment Ratio (95% CI)
	no. of patients (%)				
All patients	74 (100)	39 (100)	0.32 (0.24 to 0.41)	<0.001	−0.02 (−0.06 to 0.01)
Age					
3 to 7 yr	43 (58)	23 (59)	0.39 (0.27 to 0.51)		−0.05 (−0.10 to 0.00)
8 to 17 yr	31 (42)	16 (41)	0.26 (0.16 to 0.37)		0.01 (−0.04 to 0.05)
Tanner stage					
1	61 (82)	33 (85)	0.35 (0.26 to 0.45)		−0.03 (−0.07 to 0.01)
2 to 4	13 (18)	6 (15)	0.22 (−0.01 to 0.45)		0.03 (−0.07 to 0.12)
Sex					
Male	42 (57)	23 (59)	0.33 (0.23 to 0.44)		−0.02 (−0.07 to 0.03)
Female	32 (43)	16 (41)	0.31 (0.17 to 0.46)		−0.03 (−0.09 to 0.03)
Height z score at baseline in relation to general pediatric reference data					
−6 or Less	10 (14)	8 (21)	0.25 (0.02 to 0.49)		−0.15 (−0.28 to −0.01)
Greater than −6 to −5	31 (42)	15 (38)	0.41 (0.26 to 0.56)		−0.04 (−0.10 to 0.02)
Greater than −5	33 (45)	16 (41)	0.27 (0.13 to 0.40)		−0.01 (−0.07 to 0.04)
Annualized height velocity at baseline					
≤3.5 cm/yr	23 (31)	7 (18)	0.39 (0.22 to 0.55)		0.01 (−0.10 to 0.13)
>3.5 to 4.5 cm/yr	21 (28)	11 (28)	0.32 (0.12 to 0.52)		0.00 (−0.07 to 0.06)
>4.5 cm/yr	30 (41)	21 (54)	0.37 (0.24 to 0.49)		−0.04 (−0.09 to 0.01)

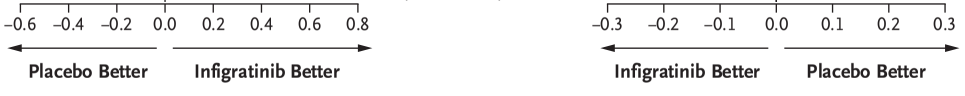


Figure 2 (facing page). Height z Score Relative to Achondroplasia Reference Data and Upper-to-Lower Body Segment Ratio.

Panel A shows the mean change from baseline in the height z score relative to achondroplasia reference data according to visit in the infigratinib group and the placebo group. Points represent mean values at each visit. Panel B shows the mean change from baseline in the upper-to-lower body segment ratio according to visit in each trial group. In Panels A and B, the I bars indicate the standard deviation. Panel C shows the subgroup analyses of the least-squares mean change in the height z score relative to achondroplasia reference data and in the upper-to-lower body segment ratio from baseline to week 52. Additional results of subgroup analyses according to baseline strata are provided in Tables S5 and S6.

RESULTS

PATIENTS

From November 2023 through December 2024, a total of 127 children from the observational PROPEL study were screened for eligibility. Of the 114 children who underwent randomization, 75 were assigned to receive infigratinib and 39 were assigned to receive placebo. One patient in the infigratinib group withdrew from the trial before treatment.

The characteristics of the patients were well balanced between the groups at baseline (Table 1). The trial population was representative of the broader population with achondroplasia (Table S1). Previous medications and medical history were in line with those in previous studies involving patients with achondroplasia, and there were no clinically meaningful differences between the trial groups. Participation in the trial was discontinued by 3 patients in the infigratinib group and by 1 patient in the placebo group (Fig. S2). The median follow-up was 366 days (range, 63 to 391) in the infigratinib group and 366 days (range, 356 to 374) in the placebo group; the mean (±SD) duration of follow-up was 361±37 and 366±6 days, respectively.

PRIMARY END POINT

The least-squares mean change from baseline in the annualized height velocity at week 52 was 1.58 cm per year (95% confidence interval [CI], 1.21 to 1.94) in the infigratinib group and −0.16 cm per year (95% CI, −0.61 to 0.28) in the placebo group, for a between-group difference of 1.74 cm per year (95% CI, 1.31 to 2.17; P<0.001). The mean changes from baseline in the annualized height velocity and the mean annualized height velocity are shown in Figure 1A and 1B.

The mean (±SE) change in the annualized height velocity from baseline at week 52 was 1.48±0.22 cm per year in the infigratinib group and −0.62±0.29 cm per year in the placebo group, for a between-group difference of 2.10±0.36 cm per year at week 52 (Table S3). The sensitivity analyses showed results that were consistent with those of the primary analysis, which supports the robustness of the treatment effect under alternative assumptions for missing data. The treatment effect appeared to be favorable with infigratinib across all subgroup categories (Fig. 1C).

KEY SECONDARY END POINTS

Height z Score

The mean changes from baseline in the height z score (referenced to achondroplasia growth charts[14]) are shown in Figure 2A. The difference between infigratinib and placebo in the least-squares mean change from baseline to week 52 in the achondroplasia-specific height z score was 0.32 (96% CI, 0.23 to 0.41; P<0.001). The treatment effect appeared to consistently favor infigratinib across all subgroup categories (Fig. 2C).

Upper-to-Lower Body Segment Ratio

The mean changes in the upper-to-lower body segment ratios over the course of the trial are shown in Figure 2B. The difference between infigratinib and placebo in the least-squares mean change from baseline at week 52 was −0.02 (96% CI, −0.06 to 0.01). In the subgroup of children who were between the ages of 3 and less than 8 years, the between-group difference was −0.05 (95% CI, −0.10 to −0.00) (Fig. 2C).

OTHER END POINTS

The least-squares mean annualized height velocity at week 52 was 5.96 cm per year (95% CI, 5.59 to 6.32) with infigratinib and 4.22 cm per year (95% CI, 3.77 to 4.66) with placebo, for a between-group difference of 1.74 cm per year (95% CI, 1.31 to 2.17). In the children who were 5 years of age or older, the least-squares mean change from baseline in the annualized height velocity at week 52 was 1.57 cm per year (95% CI, 1.08 to 2.06) with infigratinib and −0.19 cm per year (95% CI, −0.75 to 0.36) with placebo, for a

Table 2. Common Adverse Events.*

Adverse Event	Infigratinib (N=74)	Placebo (N=39)	Risk Difference (95% CI)
	number of patients (percent)		*percentage points*
Pyrexia	16 (22)	10 (26)	–4 (–21 to 11)
Vomiting	14 (19)	9 (23)	–4 (–21 to 11)
Cough	13 (18)	9 (23)	–5 (–22 to 9)
Upper respiratory tract infection	13 (18)	7 (18)	0 (–17 to 13)
Headache	13 (18)	6 (15)	3 (–14 to 15)
Otitis media	11 (15)	6 (15)	0 (–16 to 12)
Nasopharyngitis	10 (14)	5 (13)	1 (–14 to 13)
Ear pain	8 (11)	2 (5)	6 (–7 to 16)
Dental caries	7 (9)	3 (8)	1 (–12 to 12)
Otitis externa	6 (8)	2 (5)	3 (–10 to 12)
Gastroenteritis			
Any	6 (8)	1 (3)	5 (–6 to 14)
Viral	5 (7)	1 (3)	4 (–7 to 13)
Arthralgia	5 (7)	3 (8)	–1 (–14 to 9)
Nasal congestion	5 (7)	3 (8)	–1 (–14 to 9)
Skin laceration	5 (7)	3 (8)	–1 (–14 to 9)
Tympanic membrane disorder	5 (7)	1 (3)	4 (–7 to 13)
Viral upper respiratory tract infection	5 (7)	0	7 (–3 to 15)
Abdominal pain			
Any	4 (5)	2 (5)	0 (–12 to 9)
Upper abdomen	4 (5)	3 (8)	–3 (–15 to 7)
Influenza	4 (5)	2 (5)	0 (–12 to 9)
Vitamin D deficiency	4 (5)	2 (5)	0 (–12 to 9)
Limb pain	4 (5)	1 (3)	2 (–8 to 11)
Rhinorrhea	4 (5)	1 (3)	2 (–8 to 11)

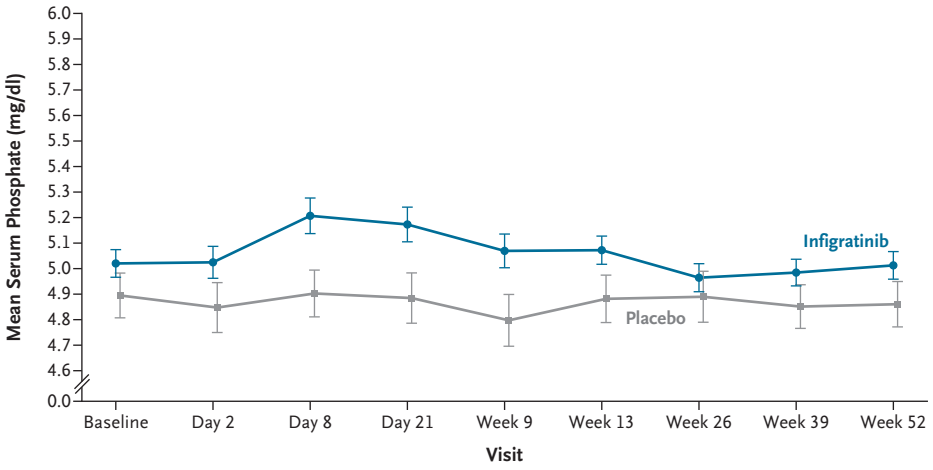
* Shown are adverse events that were reported in at least 5% of the patients in either trial group, according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 26.1. Preferred terms are ordered according to the descending incidence in the infigratinib group. Adverse events include all events that had an onset after the first administration of infigratinib or placebo and up to the administration of the last dose plus 30 days if the patients had discontinued the trial regimen.

between-group difference of 1.76 cm per year (95% CI, 1.30 to 2.23; P<0.001). The mean (±SD) change from baseline to week 52 in the collagen X marker level was 2.95±4.23 μg per liter with infigratinib and −0.95±4.17 μg per liter with placebo (Table S7).

SAFETY

One or more adverse events occurred in 71 of 74 patients (96%) in the infigratinib group and in 37 of 39 patients (95%) in the placebo group. Of these events, those that occurred in 6 patients (8%) in the infigratinib group and in 6 patients (15%) in the placebo group were determined by the investigator to be related to infigratinib or placebo (Table S8). Common adverse events that were reported in at least 5% of the patients in either group are listed in Table 2. Most adverse events were mild to moderate in severity (grade 1 or 2).

Serious adverse events, which were the only grade 3 adverse events that were reported, occurred in 4 patients (5%) in the infigratinib group and in 1 patient (3%) in the placebo group; none of



No. of Patients									
Infigratinib	74	73	72	74	72	72	73	71	71
Placebo	39	38	39	39	37	38	39	39	38

Figure 3. Mean Serum Phosphate Level.

Points represent mean values at each visit, and I bars indicate the standard deviation. Hyperphosphatemia was defined as a persistent serum phosphate level of more than 6.0 mg per deciliter in children aged 3 to 12 years, more than 5.4 mg per deciliter in children aged 13 to 15 years, and more than 5.0 mg per deciliter in children aged 16 years or older. Phosphate levels were considered to be elevated if the test result had no other reasonable explanation and was confirmed within 14 days by repeat testing.

these events were considered by the investigator to be related to infigratinib or placebo. No adverse events leading to treatment discontinuation were deemed to be related to infigratinib or placebo; no deaths occurred in either trial group.

Mean serum phosphate levels were similar in the two trial groups at all measured time points (Fig. 3). Adverse events involving hyperphosphatemia were reported in 2 patients (3%) in the infigratinib group. Both events (grade 1) were considered to be treatment-related and resolved after a protocol-specified dose interruption. Treatment was then resumed at a dose of 0.25 mg per kilogram per day without recurrence. One additional patient in the infigratinib group met the protocol criteria for an elevated serum phosphate level, which prompted a dose interruption, but the finding was not reported as an adverse event because it was consistent with that child's baseline levels. The elevation resolved and did not recur after treatment was resumed at a dose of 0.25 mg per kilogram per day.

No corneal or retinal disorders were reported or identified by ophthalmic examination. The incidence of dental and oral adverse events was balanced between the groups; no event was considered to be related to a trial regimen. No accelerated progression of bone age (Table S9) or changes in bone mineral density (Table S10) were observed. No clinically meaningful between-group differences in results on serum chemistry and hematology testing were observed (Tables S11 and S12).

DISCUSSION

In this phase 3, randomized, placebo-controlled trial, treatment with daily oral infigratinib at a dose of 0.25 mg per kilogram for 52 weeks led to significantly greater increases in the annualized height velocity and height z score than placebo in children with achondroplasia. Furthermore, the difference in the least-squares mean change from baseline at week 52 in the upper-to-lower body segment ratio between infigratinib and placebo was −0.02. This difference appeared to be more pronounced in the subgroup of children who were between the ages of 3 and less than 8 years, the age range in which changes in body proportions are more likely to be evident.[15]

No safety events that were related to the inhibition of FGFR1 or FGFR2 were observed during

the trial. We speculate that the infigratinib dose of 0.25 mg per kilogram per day that was used in this trial had no clinically significant effect on these FGFR receptors. Three cases of increased serum phosphate levels were noted at protocol-timed measurements. These changes in the serum phosphate level were interpreted as transient, asymptomatic, and not clinically meaningful, given the conservative protocol-defined criteria for dose modification and the fact that the three cases were mild, resolved with no specific treatment, and did not recur at the same dose. Furthermore, these elevations were no more than 0.6 mg per deciliter greater than baseline levels, an increase that falls within the expected range of variability in serum phosphate levels in the pediatric population.[16]

Our findings indicate that infigratinib may have potential as a targeted oral therapy for children with achondroplasia. Unlike C-type natriuretic peptide analogues that down-regulate FGFR3 signaling solely through the MAPK pathway, infigratinib binds directly to FGFR3, thereby inhibiting its phosphorylation and all consequent downstream signaling with respect to bone growth. Because multiple signaling pathways are implicated in the pathogenesis of achondroplasia,[3,17] this mechanism of action represents a possible therapeutic advantage. As an orally administered medication, infigratinib averts the issues of administering injectable therapies,[18,19] which makes it an attractive therapeutic option for children with achondroplasia.

A limitation of this trial was its relatively short duration, which precluded determination of the effect of infigratinib treatment on outcomes such as functionality, health-related quality of life, medical complications, and adult height. Long-term efficacy and safety are being evaluated to assess these outcomes in the ongoing PROPEL OLE study. A phase 2–2b trial, PROPEL Infant and Toddler (NCT07169279), is also currently underway to evaluate the safety and efficacy of infigratinib treatment in children with achondroplasia who are younger than 3 years of age.

Treatment with once-daily oral infigratinib for 52 weeks led to larger increases in the annualized height velocity and height z score than placebo in children with achondroplasia between the ages of 3 and 17 years.

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