

# Growth in Prepubertal Children With Cystic Fibrosis Treated With Ivacaftor

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abstract

**BACKGROUND AND OBJECTIVES:** Cystic fibrosis (CF) is known for its impact on the lung and pancreas of individuals; however, impaired growth is also a common complication. We hypothesized that targeting the biological defect in the CF transmembrane conductance regulator (CFTR) protein may affect growth outcomes.

**METHODS:** In this post hoc analysis, we assessed linear growth and weight in 83 children (aged 6–11 years) enrolled in 2 clinical trials, the longitudinal-observation GOAL study and the placebo-controlled ENVISION study, to evaluate the effects of ivacaftor, a CFTR potentiator. We calculated height and weight z scores and height and weight growth velocities (GVs).

**RESULTS:** In ivacaftor-treated children in GOAL, height and weight z scores increased significantly from baseline to 6 months (increases of 0.1 [ $P < .05$ ] and 0.26 [ $P < .0001$ ], respectively); height GV increased significantly from 3 to 6 months (2.10-cm/year increase;  $P < .01$ ). In ivacaftor-treated children in ENVISION, height and weight z scores increased significantly from baseline to 48 weeks (increases of 0.17 [ $P < .001$ ] and 0.35 [ $P < .001$ ], respectively). Height and weight GV from baseline to 48 weeks were also significantly higher with ivacaftor than with placebo (differences of 1.08 cm/year [ $P < .05$ ] and 3.11 kg/year [ $P < .001$ ], respectively).

**CONCLUSIONS:** Ivacaftor treatment in prepubescent children may help to address short stature and altered GV in children with CF; results from these analyses support the existence of an intrinsic defect in the growth of children with CF that may be ameliorated by CFTR modulation.



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**WHAT'S KNOWN ON THIS SUBJECT:** Impaired growth is a common complication in patients with cystic fibrosis (CF), both manifesting and contributing to the reduced lung function seen in patients with CF. This poor growth may be mediated by the CF transmembrane conductance regulator (CFTR) protein.

**WHAT THIS STUDY ADDS:** Treatment with ivacaftor, a CFTR potentiator, in prepubescent children with CF and at least 1 copy of the *G551D-CFTR* mutation was associated with improvements in multiple growth variables, including linear growth.

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The life expectancy of patients with cystic fibrosis (CF) continues to increase, leading to clinical challenges not previously encountered in this patient population. With a prevalence of ~1 in 3500 live births, CF is the leading life-limiting genetic disorder in the white population.<sup>1-3</sup> Although CF is a multisystem disorder characterized by recurrent lung and intestinal disease, different constellations of symptoms are associated with different CF mutations, and thus phenotype varies greatly from patient to patient.<sup>4</sup> The disease is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene that lead to deficient or defective *CFTR* protein<sup>5</sup> and reduced anion transport<sup>5</sup> and that are passed on through an autosomal recessive inheritance.<sup>6</sup> There are >2000 different mutations in the *CFTR* gene.<sup>7</sup>

The *CFTR* potentiator ivacaftor has been shown to improve anion transport and *CFTR* function in individuals with CF and a *G551D-CFTR* mutation.<sup>8,9</sup> Ivacaftor functions as a potentiator of the defective gating (class III) of this mutation<sup>5,10</sup> and has been shown to improve lung function in addition to weight and BMI.<sup>11,12</sup> However, studies have yet to report the effects of ivacaftor on linear growth in children with CF.

Although the exact mechanisms of growth restriction are not known, the impact of CF on linear growth and body weight is well documented. Poor growth is both a manifestation of the disease and a contributor to poor lung function through its impact on chest size and lung growth. Because insulin-like growth factor I (IGF-I) signaling is mediated by *CFTR*, *CFTR* dysfunction may directly affect linear growth, adding to indirect effects due to poor nutrition.<sup>13</sup> Optimal BMI during the first 6 years of life is associated with better lung function at ages 6-7,<sup>14,15</sup> and the Cystic Fibrosis Foundation recommends that children and young

adults aged 2 to 20 years maintain a BMI greater than or equal to the 50th percentile.<sup>14</sup> Furthermore, stunting (defined as height-for-age below the fifth percentile based on National Center for Health Statistics criteria) was found to be an independent risk factor for mortality in CF.<sup>16</sup> Konstan et al<sup>17</sup> reported that deficits in linear growth were evident before the detection of significant lung disease in children with CF. At 3 years of age, the children studied were at the 33rd percentile for height relative to National Center for Health Statistics benchmarks. Poor growth at 3 years and relative weight loss over time also predicted lung health at age 6.<sup>17</sup>

Clinical strategies for improving growth (both weight gain and linear growth) for patients with CF have predominantly focused on maximizing nutrition (eg, increasing caloric intake and ensuring proper use of pancreatic enzymes).<sup>14</sup> Increasing the anabolic drive to grow (through supplemental growth hormone [GH] therapy) has also been proposed as a potential intervention.<sup>18,19</sup> Appetite stimulants are a mainstay of increased caloric consumption<sup>20</sup> but should be used with caution, because agents such as megestrol acetate are also associated with increasing fat mass to the exclusion of lean body mass.<sup>21,22</sup> GH increases growth and lean body mass<sup>21,23,24</sup> but likely does not address the underlying reasons for poor growth. Until recently, the potential impact on growth outcomes of targeting the *CFTR* defect itself had not been tested. We hypothesized that targeting the biological defect in the *CFTR* protein may affect growth outcomes. Here we present growth outcomes data from an observational study of ivacaftor treatment (*G551D* Observational Study [GOAL]) and from the placebo-controlled, randomized Evaluation of Efficacy and Safety of VX-770 in Children Six to Eleven Years Old with CF (*ENVISION*) trial, both of which

evaluated prepubescent children with 1 copy of the *G551D-CFTR* mutation.

## METHODS

### Study Designs

GOAL was a longitudinal, observational cohort study in children ( $\geq 6$  years) with CF and at least 1 *G551D-CFTR* mutation who were initiating ivacaftor treatment.<sup>25</sup> Data were obtained at baseline and at 1, 3, and 6 months postinitiation. Data before study enrollment were obtained from the Cystic Fibrosis Foundation Patient Registry,<sup>26</sup> which collects information on the health status of people with CF who receive care in an accredited care center in the United States and who agree to participate in the registry to calculate baseline growth velocity (GV).

*ENVISION* (NCT00909727) was a phase 3, randomized, placebo-controlled, double-blind trial evaluating the pharmacokinetics, efficacy, and safety of ivacaftor in children aged 6-11 years with CF who possessed at least 1 copy of the *G551D-CFTR* mutation. Primary results of pulmonary function improvements have previously been published.<sup>12</sup> Other inclusion requirements included a forced expiratory volume in 1 second ( $FEV_{1}$ ) of 40% to 105% of that predicted on the basis of the patient's age, sex, and height, as well as a body weight of  $\geq 15$  kg. After enrollment, patients were evaluated on day 15 and at weeks 8, 16, 24, 32, 40, and 48.

### Participants

For both data sets, we evaluated prepubertal children (aged 6-11 years) to avoid changes in growth due to pubertal influences. Tanner staging as an indicator of pubertal status was not assessed in either study.

**TABLE 1** Study Design and Baseline Characteristics for GOAL and ENVISION Studies

Characteristic	GOAL		ENVISION	
	Ivacaftor (n = 35)	Placebo (n = 25)	Ivacaftor (n = 23)	Placebo (n = 25)
Trial design	Observational		Randomized	
Control	Predrug data		Placebo arm	
Study visits analyzed	Baseline and 3 and 6 months postbaseline		Baseline and 24 and 48 weeks postbaseline	
Sex (male/female), n	19/16		16/9	
Age, y				
Mean (SD)	8.7 (1.6)	8.8 (1.8)	8.5 (1.8)	8.5 (1.8)
Range	6–11	6–11	6–11	6–11
Height, mean (SD), cm	131.1 (11.3)	131.9 (12.0)	133.2 (14.3)	133.2 (14.3)
Height z score, mean (SD)	−0.15 (1.3)	−0.34 (0.9)	0.00 (1.0)	0.00 (1.0)
Weight, mean (SD), kg	29.8 (7.2)	29.6 (7.0)	31.2 (10.3)	31.2 (10.3)
Weight z score, mean (SD)	0.01 (1.2)	−0.16 (0.8)	0.08 (1.0)	0.08 (1.0)
BMI, mean (SD), kg/m <sup>2</sup>	17.1 (2.4)	16.8 (1.8)	17.2 (2.7)	17.2 (2.7)
FEV <sub>1</sub> , mean (SD), % predicted	106.4 (14.6)	83.8 (20.8)	87.3 (14.6)	87.3 (14.6)
<i>Pseudomonas</i> positive, <sup>a</sup> n (%)	15 (42.9)	12 <sup>b</sup> (57.1)	8 <sup>c</sup> (40.0)	8 <sup>c</sup> (40.0)
Sweat chloride, mean (SD), mmol/L	107.3 (9.9)	104.3 (8.7)	104.2 (15.2)	104.2 (15.2)

<sup>a</sup> Within 12 months of starting the study.

<sup>b</sup> Of 21 patients with available data.

<sup>c</sup> Of 20 patients with available data.

## Study Assessments

In GOAL, height and weight were used to calculate z scores at baseline, 3 months, and 6 months. Height and weight GVs at baseline were calculated by using registry data collected in the previous year. Standard weight and height z scores were compared in ENVISION at baseline, 24 weeks, and 48 weeks. Height z score was calculated by using Centers for Disease Control and Prevention Clinical Growth Charts.<sup>27</sup> Overall GVs for height (cm/year) and weight (kg/year) were assessed for the entire 48 weeks of the study, with GVs calculated by using the following formula: GV (units/year) = (value measured at time 2 – value measured at time 1) / (number of months between time 2 and time 1) × 12. Data on weight change from baseline at 48 weeks for ENVISION have previously been published.<sup>12</sup>

## Statistical Analyses

Each comparison was made for the combined prepubertal group (boys and girls), as well as for boys and girls separately. Data from the GOAL study were analyzed by using analysis of variance, with the last observation carried forward

for missing data. Unless otherwise indicated, results are expressed in means and SEMs. Missing data points were not imputed in the analysis of the ENVISION data. Paired *t* tests were used to analyze change from baseline within each treatment group. Analyses of covariance were used to estimate the treatment effect overall and within each sex. The covariates used in this model were percent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) at day 1 and weight or height z score at day 1, as applicable. This was a post hoc analysis of data collected from previously published studies and was not powered to detect significant treatment effects.

## RESULTS

Study designs and baseline characteristics for patients in GOAL and ENVISION are presented in Table 1. GOAL evaluated 35 prepubertal children with a mean enrollment age of 8.7 years (SD = 1.6 years). ENVISION evaluated 48 prepubertal children (25 in the placebo arm and 23 in the ivacaftor arm) with a mean enrollment age of 8.8 years (SD = 1.8) in the placebo arm and 8.5 years (SD = 1.8 years) in the ivacaftor arm.

## GOAL

### Height and Weight z Scores

At baseline, patients with CF were below average in height z score on the basis of the Centers for Disease Control and Prevention growth curves (Table 2). After ivacaftor use, a significant increase in height z score was observed at 6 months ( $P < .05$ ). Boys and girls exhibited a similar improvement (Supplemental Table 1); however, changes in height z score by sex did not achieve significance, likely because of small sample sizes. At baseline, patients with CF had a weight z score that was similar to the national average (Table 2). Ivacaftor treatment was associated with a statistically significant increase in body weight z score at both 3 and 6 months ( $P < .05$  and  $P < .0001$ , respectively). A significant improvement was observed in boys at 3 and 6 months ( $P < .05$  and  $P < .001$ , respectively; Supplemental Table 3); the improvement seen in girls was not significant.

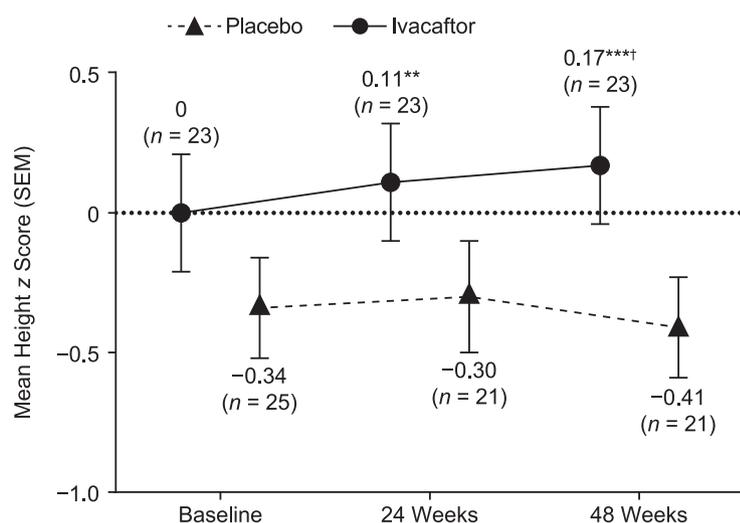
### Height and Weight GVs

A significant increase in height GV was observed between 3 and 6 months for the full population ( $P < .01$ ; Table 2). Height GV improved

**TABLE 2** Weight and Height Outcomes From the GOAL Study

Outcome	Mean (SEM)	P (Compared With Baseline)
<b>Height z score</b>		
Baseline	-0.15 (0.21)	—
3 months	-0.12 (0.21)	NS
6 months	-0.05 (0.22)	<.05
<b>Weight z score</b>		
Baseline	0.01 (0.20)	—
3 months	0.14 (0.19)	<.05
6 months	0.27 (0.20)	<.0001
<b>Height GV, cm/y</b>		
Before baseline	5.44 (0.31)	—
Baseline to 3 months	6.27 (0.57)	NS <sup>a</sup>
3 to 6 months	7.54 (0.66)	<.01 <sup>a</sup>
<b>Weight GV, kg/y</b>		
Before baseline	2.61 (0.43)	—
Baseline to 6 months	7.15 (0.98)	<.0001 <sup>a</sup>

NS, not significant; —, not applicable.

<sup>a</sup> Calculated GV was compared with mean GV before baseline.**FIGURE 1**Height z scores over time in ENVISION. *n* indicates number of patients at each time point. \*\**P* < .01 versus baseline; \*\*\*\**P* < .001 versus baseline; †*P* < .05 versus placebo.

significantly in girls from 3 to 6 months (*P* < .05) but not in boys (Supplemental Table 3). After 6 months of ivacaftor treatment, weight GV was improved compared with the results seen before enrollment (*P* < .0001; Table 2). This improvement in weight GV was observed in boys and girls (*P* < .001 and *P* < .05 respectively; Supplemental Table 3).

## ENVISION

### Height z Scores

At baseline, height z score was average in the ivacaftor arm and

below average in the placebo arm (Fig 1). In the ivacaftor arm, height z score increased significantly from baseline at 24 and 48 weeks (*P* < .01 and *P* < .001, respectively). A significant improvement was seen in boys at 24 and 48 weeks (*P* < .05 and *P* < .01, respectively) and in girls at 48 weeks (*P* < .01; Supplemental Fig 4). In the placebo arm, the change from baseline in height z score was slightly positive but nonsignificant at 24 weeks and was slightly negative but nonsignificant at 48 weeks (Fig 1). Boys and girls exhibited similar nonsignificant changes

(Supplemental Fig 4). In the overall group, change from baseline in height z score was significantly higher in the ivacaftor arm than in the placebo arm at 48 weeks (*P* < .05).

### Weight z Scores

At baseline, weight z score was average in the ivacaftor arm and below average in the placebo arm (Fig 2). Ivacaftor treatment was associated with a statistically significant increase in weight z score at 24 and 48 weeks (*P* < .001 for both). Similar results were observed in girls (*P* < .001 for 24 weeks and *P* < .01 for 48 weeks) and boys (*P* < .05 for both time points) (Supplemental Fig 5). Treatment with placebo was associated with a statistically significant decrease in weight z score at 48 weeks compared with baseline (*P* < .05; Fig 2); boys and girls exhibited similar findings as the combined population, but differences in weight z score did not achieve significance in these subgroups (Supplemental Fig 5). The change from baseline in weight z score was significantly higher in the ivacaftor arm than in the placebo arm at 24 and 48 weeks (*P* < .001 for both). The change from baseline in weight z score was significantly higher in the ivacaftor arm than in the placebo arm in boys at 24 and 48 weeks (*P* < .05 and *P* < .01, respectively); the change from baseline in weight z score was also significantly higher in the ivacaftor arm than in the placebo arm in girls at 24 and 48 weeks (*P* < .01 for both).

### Height and Weight GVs

Patients had a significantly greater height GV in the ivacaftor arm than in the placebo arm (*P* < .05; Fig 3). Both boys and girls exhibited nonsignificant improvements compared with the placebo arm (Supplemental Fig 6). Patients also had a significantly higher weight GV in the ivacaftor arm than in

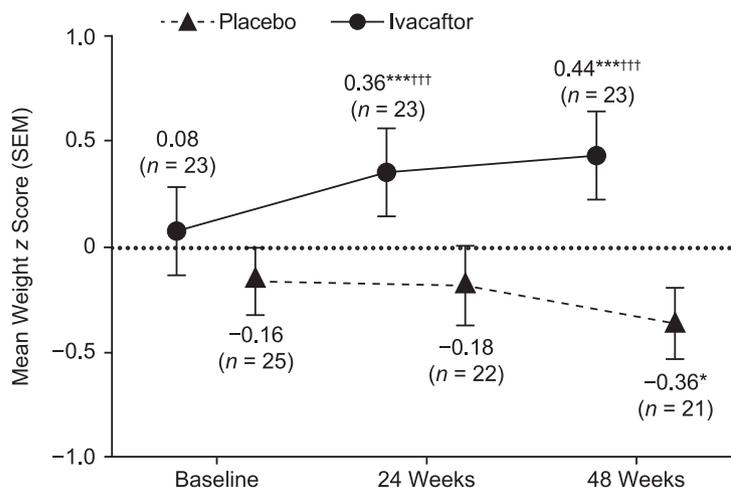
the placebo arm ( $P < .001$ ; Fig 3). Boys and girls exhibited similar statistically significant improvements compared with placebo ( $P < .05$  for both; Supplemental Fig 6).

## DISCUSSION

For many years, the treatment of growth restriction in CF has focused on increasing oral intake of a high-calorie, high-protein diet, partially through appetite stimulation, and on optimizing pancreatic enzyme replacement therapy. Multiple clinical trials have also reported improvements in growth through the use of anabolic stimulants, primarily GH.<sup>18,23</sup> However, neither of these approaches targets the basic molecular defect in CF. Our study presents the first evidence that correction of the abnormally functioning CFTR channel is associated with improved linear growth and supports the hypothesis that defective CFTR function directly contributes to impaired linear growth in CF.

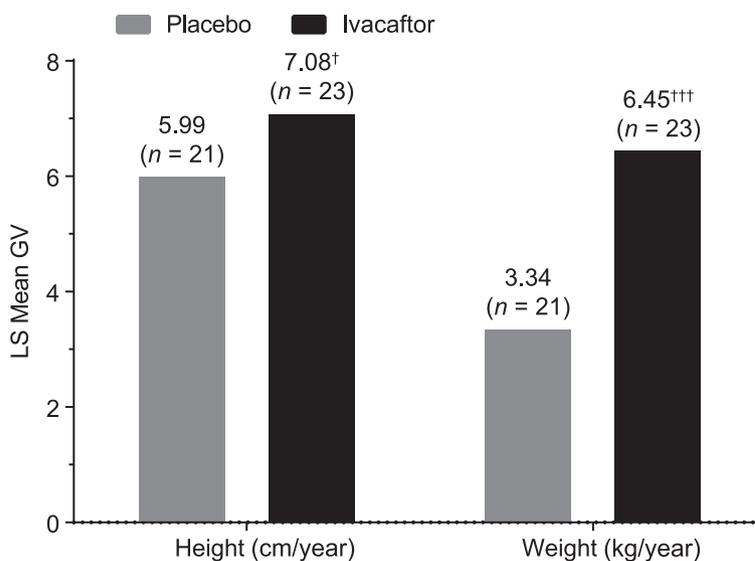
Caloric intake is needed for adequate growth, and meeting increased energy and nutrient needs can undeniably help growth in CF. Individuals with CF have caloric requirements 1.5 to 2 times those of average individuals.<sup>14</sup> Thus, the intake necessary to sustain good linear growth may not be met. Evidence to support the impact of nutritional intake can be ascertained from the use of newborn screens. Children and young adults with CF identified at birth show improved linear growth and final adult height, findings that are attributed to earlier interventions with nutritional intake and improved growth in the early years of life.<sup>28,29</sup>

Lung disease severity has been shown to correlate with prepubertal growth.<sup>30</sup> We did not assess the correlation between linear growth and improved lung function here due



**FIGURE 2**

Weight z scores over time in ENVISION. *n* indicates number of patients at each time point. \* $P < .05$  versus baseline; \*\*\*\* $P < .001$  versus baseline; ††† $P < .001$  versus placebo.



**FIGURE 3**

Height and weight GV from baseline to 48 weeks in ENVISION. *n* indicates number of patients with measurements at baseline and 48 weeks. † $P < .05$  versus placebo; ††† $P < .001$  versus placebo. LS, least squares.

to the small sample size. However, patients enrolled in GOAL showed a statistically significant improvement in ppFEV<sub>1</sub> from baseline to 6 months ( $P < .001$ ),<sup>25</sup> and ivacaftor-treated patients in ENVISION showed a statistically significant improvement in ppFEV<sub>1</sub> compared with placebo-treated patients at 48 weeks ( $P < .001$ ).<sup>12</sup>

In animal models of CF, the absence of clinical confounders such as

pancreatic insufficiency and lung disease does not translate into normalized growth. The mouse CF model does not develop human-analog CF-type diseases of the lung or pancreas<sup>31</sup>; however, affected animals show reduced growth (length and weight) relative to wild-type animals.<sup>32</sup> Although it has been argued that these differences reflect inadequate nutritional intake in the mouse model, newborn CF piglets also have shorter humeral lengths

than their wild-type littermates, before the contribution of altered nutritional intake.<sup>13</sup> Because all piglets would have had the same nutritional intake in utero, this finding implies that CFTR deficiency has an intrinsic and early impact on linear growth.

How might CFTR modulation improve growth in CF through a CFTR-dependent pathway? One proposed mechanism for growth restriction in CF is decreased levels of IGF-I, an effector agent of GH.<sup>13</sup> Increasing IGF-I concentrations with exogenous GH likely contributes to the improved growth seen in clinical trials, because it has been established that IGF-I concentration is an indicator of nutritional status.<sup>33</sup> IGF-I has both endocrine and autocrine/paracrine functions and effects on growth. Measurable levels of IGF-I in the serum are produced primarily in the liver, and production is reduced by nutritional as well as insulin deficiency, 2 problems often seen in CF. It is IGF-I produced at the target tissues that has autocrine/paracrine effects, and multiple studies in CF showed reduced concentrations of IGF-I in both humans and animal models.<sup>13,32,34</sup> Interestingly, decreased IGF-I concentrations can be detected despite controlling for nutritional differences or malnutrition. This finding is evident, for example, in newborn CF pigs, whose nutritional intake is dependent on maternal nutrient transfer in utero. Newborn CF pigs have reduced IGF-I concentrations,<sup>13</sup> implying an intrinsic effect of CFTR deficiency on IGF-I production and potentially a direct influence on bone growth. Together, these results suggest that correction of the underlying defect in CFTR could increase IGF-I levels, resulting in improved nutritional status.

Another mechanism potentially contributing to poor growth in the setting of CFTR impairment is the Wnt signal transduction cascade.

Linear growth of long bones results from endochondral bone formation, in which cartilaginous growth is replaced by ossified bone at the growth plate. This process is governed by a complex set of interactions among GH, IGF-I,<sup>35</sup> thyroid hormone,<sup>35</sup> sex steroids,<sup>36</sup> and glucocorticoids, as well as promotion by Wnt signaling.<sup>37</sup> Our laboratory recently reported decreased canonical Wnt signaling in *CFTR*<sup>-/-</sup> murine osteoblasts,<sup>38</sup> suggesting another intrinsic mechanism for poor growth and osteopenia in CF.

Data presented here from both observational and placebo-controlled studies provide evidence that improvements in linear growth and GV are seen after therapeutic intervention with ivacaftor in children with the *G551D-CFTR* mutation. However, these studies were not specifically designed or powered to address the association between ivacaftor and linear growth/GV. We also recognize that these improvements are seen in conjunction with weight gain, as well as improved pulmonary function, which could confound the influence of CFTR on linear growth; nevertheless, the consistency of the data and the strength of preclinical data indicating a role for CFTR suggest that a CFTR-mediated pathway likely has at least some impact. Given the complexity of growth, it may be difficult to prove this definitively in the clinic.

One possible weakness of this analysis is that we did not include an assessment of puberty by Tanner staging or another method as a criterion for inclusion, but used age-based inclusion criteria instead. The literature on pubertal development/progression and pubertal peak height velocity suggests a significant delay in children with CF.<sup>39,40</sup> Similar delays are reported in CF mice.<sup>41</sup> By using the upper limit of age 11, we believe we selected for prepubertal

children with CF with comparable mean ages. However, it is possible that some of the older girls included may have entered puberty during the study. The ratios of boys to girls in the ivacaftor and placebo arms of ENVISION were skewed, and although one would expect the treatment effects to be similar in prepubertal boys and girls, this discrepancy could have affected the results.

Another weakness is the inconsistency of height/weight data before enrollment in the clinical trials. To control for this weakness, we used the placebo group in the ENVISION study and used pre-enrollment data at least 3 months before baseline for the GOAL study. The GOAL study is limited because it was an observational study without a placebo arm; therefore, we can only compare results before and after treatment. We examined the placebo-controlled ENVISION study to account for this limitation. Because of the small sample size in ENVISION, there were discrepancies in height and weight z scores between the ivacaftor and placebo groups; however, these differences were not statistically significant (data not shown). Height and weight z scores at baseline were used as covariates in the analysis of corresponding GV; therefore, differences in growth between placebo and ivacaftor arms were not due to these differences at baseline.

## CONCLUSIONS

In this post hoc analysis of results from the GOAL and ENVISION studies, treatment with ivacaftor significantly improved multiple growth variables (including height and weight z scores) compared with placebo in prepubescent children with CF and the *G551D-CFTR* mutation. These results suggest that ivacaftor may help to address short stature and altered GV in children

with CF, and they support the existence of an intrinsic defect in the growth of children with CF that may be ameliorated by CFTR modulation, which raises further questions for research study. Improving growth with CFTR potentiator therapy, either directly or indirectly, should be a goal of all CF health care providers, which reinforces the need for early initiation of CFTR restoration therapy when possible.

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## ABBREVIATIONS

CF: cystic fibrosis  
CFTR: CF transmembrane conductance regulator  
ENVISION: Evaluation of Efficacy and Safety of VX-770 in Children Six to Eleven Years Old with CF  
GH: growth hormone  
GOAL: G551D Observational Study  
GV: growth velocity  
IGF-I: insulin-like growth factor I  
ppFEV<sub>1</sub>: percent predicted forced expiratory volume in 1 second

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