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Original Article

An open-label extension study of ivacaftor in children with CF and a *CFTR* gating mutation initiating treatment at age 2–5 years (KLIMB)[☆]

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ABSTRACT

Background: KIWI (NCT01705145) was a 24-week, single-arm, pharmacokinetics, safety, and efficacy study of ivacaftor in children aged 2 to 5 years with cystic fibrosis (CF) and a *CFTR* gating mutation. Here, we report the results of KLIMB (NCT01946412), an 84-week, open-label extension of KIWI.

Methods: Children received age- and weight-based ivacaftor dosages for 84 weeks. The primary outcome was safety. Other outcomes included sweat chloride, growth parameters, and measures of pancreatic function.

Results: All 33 children who completed KIWI enrolled in KLIMB; 28 completed 84 weeks of treatment. Most adverse events were consistent with those reported during KIWI. Ten (30%) children had transaminase elevations $>3 \times$ upper limit of normal (ULN), leading to 1 discontinuation in a child with alanine aminotransferase $>8 \times$ ULN. Improvements in sweat chloride, weight, and body mass index z scores and fecal elastase-1 observed during KIWI were maintained during KLIMB; there was no further improvement in these parameters.

Conclusions: Ivacaftor was generally well tolerated for up to 108 weeks in children aged 2 to 5 years with CF and a gating mutation, with safety consistent with the KIWI study. Improvements in sweat chloride and growth parameters during the initial 24 weeks of treatment were maintained for up to an additional 84 weeks of treatment. Prevalence of raised transaminases remained stable and did not increase with duration of exposure during the open-label extension.

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Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulator; IRT, immunoreactive trypsinogen; LFT, liver function test; MMRM, mixed-effect model for repeated measures; q12h, every 12 h; SD, standard deviation; SE, standard error; ULN, upper limit of normal.

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1. Introduction

The pathophysiologic effects of cystic fibrosis (CF), including poor nutritional status and structural lung damage, typically begin in the first years of life [1]. Early intervention is known to be clinically beneficial [2,3], and thus treatment with cystic fibrosis transmembrane conductance regulator (CFTR) modulators early in life could potentially improve long-term outcomes. To date, no studies have been conducted on prolonged use of CFTR modulators in children with CF who are younger than 6 years of age.

Ivacaftor, a CFTR potentiator that enhances chloride transport by increasing the channel-open probability of CFTR at the cell surface [4,5], has been shown to be safe and efficacious in patients aged 6 years and older with CF and specific *CFTR* mutations [6–9]. The 24-week, open-label, 2-part, phase 3 KIWI study demonstrated that the pharmacokinetics, safety, and efficacy of ivacaftor in children aged 2 to 5 years with CF and a *CFTR* gating mutation are generally similar to those seen in older patients [10]. Data from KIWI led to the approval of ivacaftor in the United States, European Union, Canada, and Australia for treatment of patients aged 2 years and older with CF and a *CFTR* gating/ivacaftor-responsive mutation.

Here, we report results from KLIMB, an 84-week extension study of ivacaftor in children aged 2 to 5 years with CF and a *CFTR* gating mutation who completed the 24-week KIWI study. The primary outcome was long-term safety. Other outcomes included changes in sweat chloride, growth parameters, and measures of pancreatic function.

2. Methods and materials

2.1. Study design and participants

KLIMB was an open-label extension study (ClinicalTrials.gov, number NCT01946412) in children who completed the 24-week, single-arm, open-label, phase 3 KIWI (part B) study of ivacaftor treatment [10]. Children eligible for KIWI were aged 2 to 5 years (median, 3.0 years), weighed 8 kg or more, and had a confirmed diagnosis of CF [11] and a *CFTR* gating mutation (*G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G970R*, *G1244E*, *S1251N*, *S1255P*, *G1349D*) on at least 1 allele [10]. After completion of the study's design, the *G970R* mutation was discovered to be a class I splice mutation [12]; none of the children in this study had this mutation. There was no interruption of ivacaftor treatment between KIWI and KLIMB. The primary outcome of KLIMB was long-term safety. Other outcomes included change from KIWI and KLIMB study baseline measurements in sweat chloride (assessed at clinic visits at day 1 and weeks 24, 48, 72, and 84) and weight, height, and body mass index (BMI; assessed at day 1 and weeks 12, 24, 36, 48, 60, 72, and 84). Exploratory endpoints included change from KIWI and KLIMB study baseline measurements in fecal elastase-1 (a measure of pancreatic exocrine function [13]), and percent predicted forced expiratory volume in 1 s (ppFEV₁), all assessed at day 1 and weeks 12, 24, 36, 48, 60, 72, and 84. Immunoreactive trypsinogen (IRT; a serum-based marker of pancreatic insult) was assessed at day 1 and weeks 24, 48, 60, 72, and 84 [14]. Neither the site staff nor enrolled children received study-specific training in preschool lung function testing, nor were certification or over-reading conducted for spirometric assessments. Because acceptable spirometric data were only obtained in a small number of children in KIWI, these results are not presented.

This study was conducted at 15 sites in the United States, United Kingdom, and Canada from December 2013 to December 2015. Children received weight-based ivacaftor as granules (Vertex Pharmaceuticals Incorporated, Boston, MA) every 12 h (q12h) at a dose of 50 mg q12h (weight < 14 kg) and 75 mg q12h (weight ≥ 14 kg). Children who turned 6 years of age during KLIMB received ivacaftor 150 mg q12h as tablets (Vertex Pharmaceuticals Incorporated, Boston, MA). Dose was adjusted as necessary based on weight at each study visit. Safety assessments consisted of adverse events primarily defined using Common

Terminology Criteria for Adverse Events, version 4.0 [15], clinical laboratory values, vital signs, 12-lead electrocardiogram readings, and physical and ophthalmological examinations. Standardized eye examinations were conducted by a licensed ophthalmologist at baseline and at specified intervals after dosing. Serious adverse events were defined per the International Conference on Harmonisation guidelines [16].

An independent ethics committee or institutional review board for each site approved the study protocol, and an independent data monitoring committee monitored study safety data. Written informed consent was obtained from each child's parent or legal guardian.

2.2. Statistical analyses

Safety and efficacy were assessed among all children who received at least 1 dose of ivacaftor in KLIMB. A mixed-effects model for repeated measures (MMRM) was used to analyze the absolute change from baseline in sweat chloride; height, weight, and BMI z scores; and fecal elastase-1 at each study visit. For IRT, as it was not normally distributed, the Wilcoxon Signed Rank Test was used. There was no adjustment for multiple comparisons in the analyses of absolute change from baseline in study endpoints due to the small sample size. All *P* values are nominal. Additional analyses performed using descriptive statistics and 95% CI for group comparisons are provided. Analyses were performed using SAS[®], version 9.2 (Cary, NC).

3. Results

3.1. Study population

Thirty-four children were enrolled in KIWI part B, and 33 (97%) completed the 24 weeks of treatment (Supplementary Fig. 1). All 33 who completed KIWI enrolled in KLIMB, with 28 (84.8%) completing the

Table 1
Adverse events.

Adverse events (AE), n (%)	Overall (N = 33)	
Children with ≥1 adverse event	33 (100)	
Treatment-emergent adverse events in ≥ 10% of children		
Cough	24 (72.7)	
Pyrexia	13 (39.4)	
Vomiting	13 (39.4)	
Pulmonary exacerbation	10 (30.3)	
Nasal congestion	7 (21.2)	
Increased ALT	7 (21.2)	
Increased AST	6 (18.2)	
Otitis media	6 (18.2)	
Rhinorrhea	6 (18.2)	
Abdominal pain	5 (15.2)	
Sinusitis	5 (15.2)	
Viral upper respiratory tract infection	5 (15.2)	
Viral gastroenteritis	4 (12.1)	
Streptococcal pharyngitis	4 (12.1)	
Rash	4 (12.1)	
Serious adverse events (SAEs)		
Pulmonary exacerbation ^a	6 (18.2)	Patient # 1, 2, 5, 6, 7, 9
ALT >8 × ULN ^b	2 (6.1)	Patient # 10, 11
AST >5 × ULN ^b	2 (6.1)	Patient # 10, 11
Pyrexia ^a	2 (6.1)	Patient # 3, 7
Enterovirus infection ^a	1 (3.0)	Patient # 4
Respiratory syncytial virus infection ^a	1 (3.0)	Patient # 1
Staphylococcal infection ^a	1 (3.0)	Patient # 2
Adenovirus test positive ^a	1 (3.0)	Patient # 3
Dehydration ^a	1 (3.0)	Patient # 3
Anoxic seizure ^a	1 (3.0)	Patient # 8

ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

^a Resulting hospitalization.

^b These were the same 2 children. An episode of transaminase >8 × ULN was observed in a total of 5 children (see Table 2); in only 2 cases did the investigator report the event as an SAE.

Table 2
Summary of liver function test elevations during the 84-week KLIMB study.

Maximum on-treatment ALT or AST (U/L), n (%) ^a	N = 33
>3 to ≤5 × ULN	1 (3.0)
>5 to ≤8 × ULN	4 (12.1)
>8 × ULN	5 (15.2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

^a 7 of the 10 total events were reported as AEs; 2 of the 5 events with ALT or AST >8 × ULN were reported as SAEs.

84-week open-label treatment period. Of the 5 children who discontinued study drug before week 84, 2 switched to commercial ivacaftor, 1 had an adverse event (elevated alanine aminotransferase [ALT] >8 × upper limit of normal [ULN] and aspartate aminotransferase [AST] >3 × ULN), 1 had difficulty swallowing the ivacaftor 150-mg tablet, and 1 withdrew because of inability to tolerate further blood tests.

3.2. Primary outcome: safety

Adverse events are summarized in Table 1. All children reported at least 1 adverse event during the 84 weeks. The most common adverse events occurring in ≥30% of children were cough (72.7%), pyrexia (39.4%), vomiting (39.4%), and pulmonary exacerbation (30.3%), events that commonly occur in the pediatric CF population. Twenty-one serious adverse events occurred in 11 children. Serious adverse events considered related to ivacaftor were elevated ALT and AST levels that occurred in 2 children. One child had elevated ALT levels >8 × ULN and elevated AST levels >5 × ULN on the same day. The second had elevated ALT/AST levels >8 × ULN on the same day.

Elevated ALT and/or AST levels >3 × ULN were documented in 10 children (30%) during 84 weeks in KLIMB (Table 2). 4 of these 10 children also had transaminase elevations during KIWI, and a history of liver function test (LFT) elevations before enrollment in KIWI. In KLIMB, LFT elevations were reported as adverse events in 7 of the 10 children. Per protocol, treatment was interrupted in all 5 children who reported ALT and/or AST elevations >8 × ULN. Ivacaftor dosing was successfully resumed in 4 of the 5 children. One child permanently discontinued ivacaftor because of LFT elevations after ivacaftor was reinitiated.

Fig. 1 illustrates the prevalence of transaminase elevations over time during KLIMB. There was no evidence of increased prevalence of elevated transaminases with prolonged exposure to ivacaftor.

No abnormalities were detected on serial electrocardiograms. No meaningful changes in visual acuity from baseline occurred throughout the study. One child with a history of astigmatism developed a lens opacity at week 84 that was considered not visually significant and possibly related to ivacaftor. Drug withdrawal was not recommended.

3.3. Secondary outcomes

3.3.1. Sweat chloride

Ivacaftor treatment during KIWI had led to a significant reduction in sweat chloride that was maintained over 24 weeks of treatment [10]. Continued treatment of these children with ivacaftor in KLIMB maintained this reduction in sweat chloride until the end of the study at week 84 (Fig. 2 and Table 3).

3.3.2. Nutrition

Improvements in weight z score (+0.2 [SD, 0.3]; $P < .0001$) and BMI z score (+0.4 [SD, 0.4]; $P < .001$) were observed during the initial 24-week KIWI study [10]. During the 84-week KLIMB extension, the weight z score from KIWI baseline was unchanged but the BMI z score continued to be significantly better than at KIWI baseline (0.27 [95% CI: 0.04, 0.50]; Table 3).

3.4. Exploratory outcomes

3.4.1. Pancreatic exocrine function

In the KIWI study, mean fecal elastase-1 increased by 99.8 μg/g from baseline (SD, 138.4; $P < .001$). Additionally, 23% ($P = .0504$) had a fecal elastase-1 that improved to >200 μg/g, the cutoff value for pancreatic exocrine insufficiency. Improvements in fecal elastase-1 levels observed during KIWI were maintained during KLIMB (Fig. 2). At week 84, the mean (95% CI) absolute increase in fecal elastase-1 was 128.8 (45.7, 211.9) μg/g from KIWI baseline. During the 84-week open-label extension, fecal elastase-1 continued to increase, but the change from KLIMB baseline was not statistically significant (56.8 μg/g; 95% CI: -22.2, 135.8; Table 3). Seventeen children had paired fecal elastase-1 data at KIWI baseline and week 84 of KLIMB. At the start of the KIWI study, 1 of 17 (6%) children had fecal elastase-1 levels ≥200 μg/g.

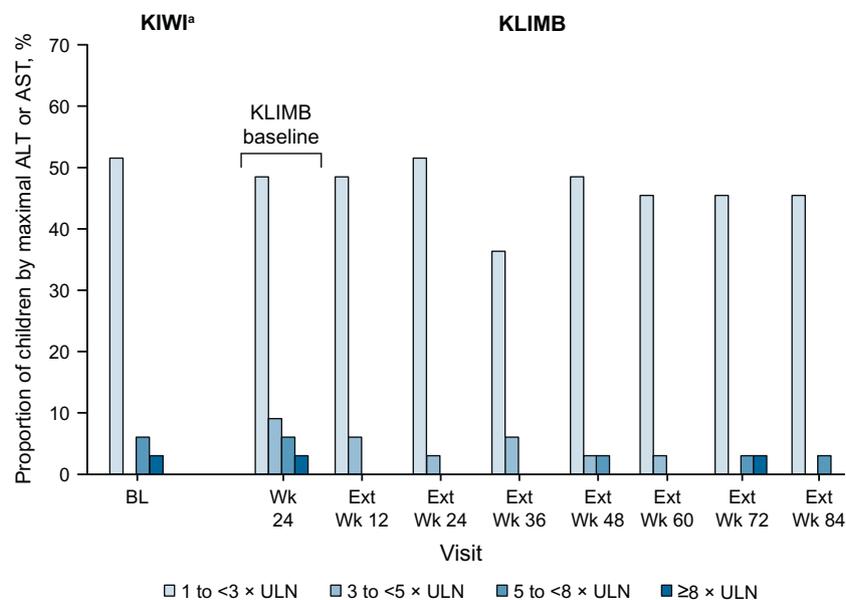


Fig. 1. Prevalence of elevated transaminase measurements over time in KLIMB, including proportion of children with ALT or AST elevations 3 × ULN and greater during the 84-week study. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; Ext, extension; ULN, upper limit of normal. ^a Data shown for children who enrolled in KLIMB.

By week 84 of KLIMB, 6 of 17 (35%) children had fecal elastase-1 ≥ 200 $\mu\text{g/g}$.

In KIWI, IRT levels decreased from baseline to week 24 by a mean of 20.7 ng/mL (SD, 24), suggesting reduced pancreatic inflammation/stress from KIWI study entry [10]. This decrease was maintained in KLIMB: at week 84, the mean (SD) absolute decrease from KIWI baseline was -15.9 (25.2) ng/mL. The median (range) absolute decrease

from KIWI baseline was -8.1 ng/mL ($-71.1, 21.9$), with no significant change during the KLIMB extension (1.0 ng/mL; $-16.4, 35.6$).

4. Discussion

The results of this open-label extension study suggest that ivacaftor is generally well tolerated in children aged 2 to 5 years with CF and a gating mutation for up to 108 weeks. The safety profile was consistent

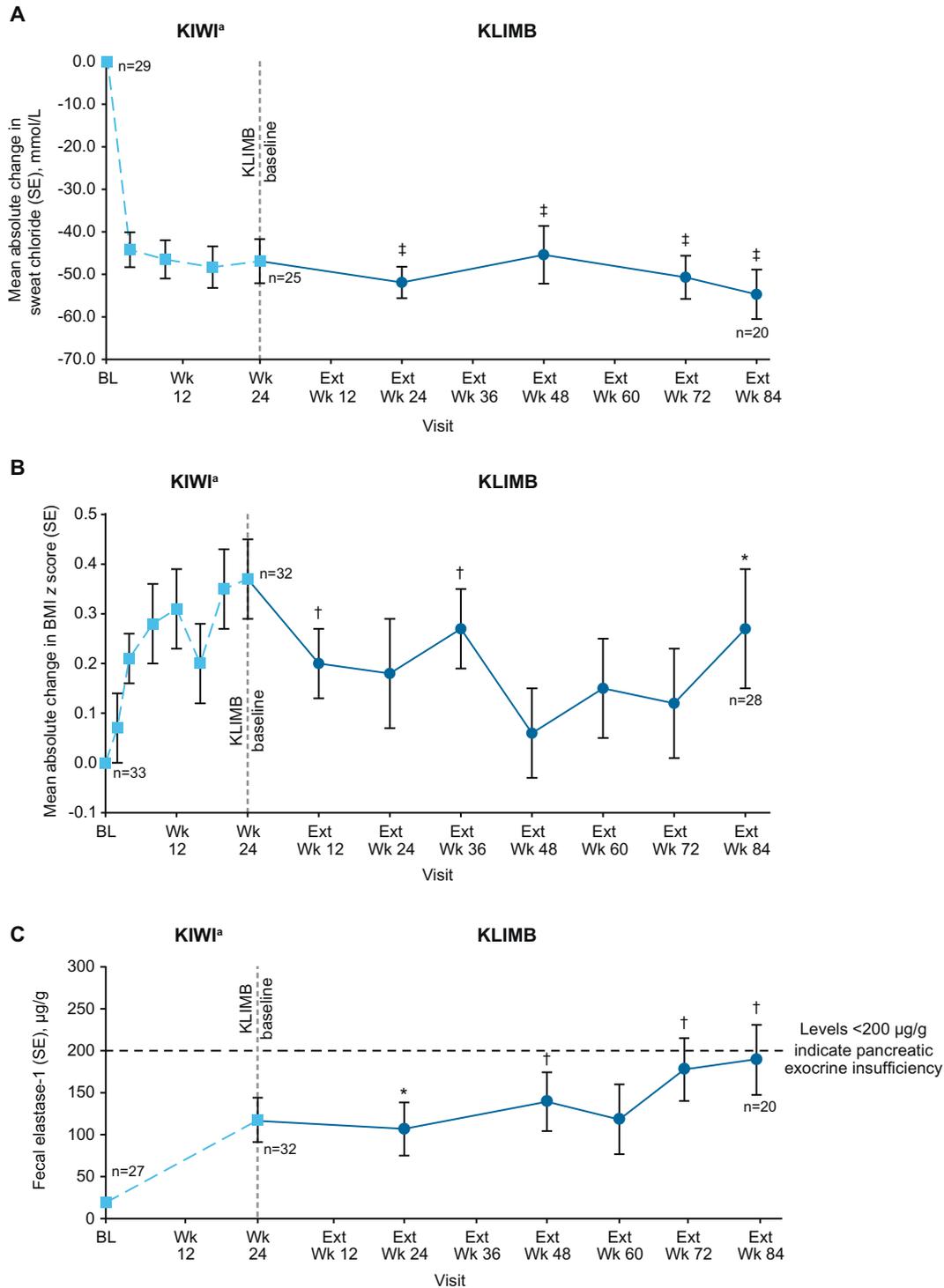


Fig. 2. Mean absolute change from KIWI baseline in (A) sweat chloride and (B) BMI z score and mean values for (C) fecal elastase-1 levels by visit. Means were calculated for each visit from the number of children contributing data at that time point. BL, baseline; Ext, extension; SE, standard error. ^a Data shown for all children who enrolled in KLIMB. Data for intermediate visits from KIWI are not shown for fecal elastase-1. * $P < .05$. † $P < .01$. ‡ $P < .0001$. All P values are for absolute change from KIWI baseline.

Table 3
Absolute change in secondary and tertiary endpoints at extension week 84.

Endpoints	Mean absolute change at extension week 84 (95% CI)		P value for mean absolute change from KIWI baseline ^a
	From KIWI baseline	From KLIMB baseline	
Secondary endpoints			
Sweat chloride, mmol/L	−54.7 (−65.4, −43.9)	−8.5 (−18.9, 1.8)	<.0001
Tertiary endpoints			
BMI z score	0.27 (0.04, 0.50)	−0.08 (−0.31, 0.15)	.0229
Weight z score	0.20 (−0.05, 0.44)	0.00 (−0.20, 0.20)	.1119
Height z score	0.12 (−0.06, 0.29)	0.14 (0.00, 0.29)	.1800
Fecal elastase-1, µg/g	128.8 (45.7, 211.9)	56.8 (−22.2, 135.8)	.0050
Median absolute change (min,max) at extension week 84			
IRT, ng/mL	−8.1 (−71.1, 21.9)	1.0 (−16.4, 35.6)	.0103 ^b

BMI, body mass index; IRT, immunoreactive trypsinogen.

^a All P values are nominal.

^b From a Wilcoxon Signed Rank Test.

with previous clinical trials of ivacaftor in children and adults. There were no clinical safety concerns identified in assessments of hematology laboratory parameters, vital signs, or electrocardiograms in this small sample.

While there are limited data on the prevalence of LFT elevations in children with CF, studies indicate a natural propensity for transaminase elevations in children with CF in the first 2 to 3 years of life [17,18]. Our findings on transaminase elevations seem to be consistent with the published data. Thirty percent of children aged 2 to 5 years in KLIMB had transaminase elevations $>3 \times$ ULN on at least 1 occasion across 84 weeks. Transaminase elevations were generally asymptomatic, did not require permanent treatment discontinuation except in 1 child, and occurred more often in children with a history of transaminase elevations prior to ivacaftor exposure and in KIWI. The lack of a placebo arm in this study makes interpretation of our results difficult, with uncertainty as to whether the prevalence of elevated transaminases reflects an effect of ivacaftor, ascertainment bias due to increased monitoring during a clinical trial, or the natural history of LFT elevations in this age group. This long-term extension study is important in demonstrating that the prevalence of LFT elevations did not appear to increase with the length of exposure to ivacaftor. However, it is recommended that LFTs be assessed before initiation of ivacaftor and monitored during treatment, particularly in children with a history of elevated transaminases.

It is difficult to interpret the potential risk of the non-visually significant lens opacity seen in 1 patient at week 84 in association with astigmatism. Baseline assessment for lens opacities and periodic monitoring while on therapy is recommended.

The improvements observed in sweat chloride concentrations during the 24-week KIWI study were maintained during this 84-week extension trial, demonstrating maintenance of improved CFTR function. Similarly, improvements in BMI z scores observed in KIWI were generally maintained in KLIMB, although without further improvement.

The changes in the exploratory endpoints of fecal elastase-1 and serum IRT observed during KIWI were maintained during KLIMB, suggesting that early, effective CFTR modulation has the potential to delay deterioration in pancreatic function. Further support is lent to this hypothesis by the improvements in markers of pancreatic exocrine function (fecal elastase-1) and pancreatic insult (IRT, amylase, and lipase) reported recently in children 12 to <24 months treated with ivacaftor [19]. The mechanism by which ivacaftor might improve exocrine pancreatic function is unclear. In a recent study employing mouse models of Sjogren's syndrome and autoimmune pancreatitis, both of which involve decreased expression and mislocalization of CFTR in the pancreatic ducts, treatment with ivacaftor and a CFTR corrector rescued CFTR expression and localization, resulting in decreased acinar inflammation, fibrosis, and tissue damage [20]. These results (albeit not from a CF model) suggest that the effect of ivacaftor on the pancreas in infants and toddlers with CF may be mediated through restoration of ductal function, in turn improving acinar cell function and

allowing some normalization of pancreatic secretions (enzymes, bicarbonate, fluid). In older children and adults, in whom ivacaftor does not improve fecal elastase, the improved nutritional status associated with ivacaftor appears to be the result of normalization of intestinal pH and CFTR-mediated bicarbonate secretion [21] as well as decreased intestinal inflammation, resulting in improved absorption of fat [22].

The current study had several limitations. The age of the population and relative rarity of the *CFTR* gating mutations led to the decision to perform the original KIWI study as an open-label rather than a placebo-controlled trial. Because KLIMB was designed as a single-arm extension of this safety and pharmacokinetic trial, there was no placebo group. The lack of a control group limits our interpretation of both safety and therapeutic benefit. In addition, most participants had at least 1 *G551D* mutation, limiting our ability to assess the effects of ivacaftor treatment in persons with rarer gating mutations. The small sample size also limited our ability to detect rare adverse events. Finally, because of the challenge of obtaining accurate spirometry data from children aged 2 to 5 years [23], very little acceptable spirometry data were collected, precluding our ability to analyze those data. Alternative lung function measures such as the lung clearance index from multiple-breath washout may also be considered in the future [24].

5. Conclusions

This is the first study reporting long-term safety and efficacy of ivacaftor in children aged 2 to 5 years with a *CFTR* gating mutation. Ivacaftor was generally safe and well tolerated for up to 108 weeks. Increases in transaminases did not become more frequent with prolonged exposure to the drug. The reduction in sweat chloride concentration, growth benefits, and improvements in markers of pancreatic exocrine function observed during 24 weeks in KIWI were maintained for an additional 84 weeks in KLIMB.

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Declaration of interest

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served as site principal investigators for trials, institutions received fees from Vertex Pharmaceuticals Incorporated. GSS has received consulting fees from Vertex Pharmaceuticals Incorporated and his institution has received financial support from Vertex Pharmaceuticals Incorporated, Gilead Sciences, and Genentech. MH and ST are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. JC is a former employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. JCD has served on advisory boards, undertaken educational activities, and served as a national/site principal investigator for trials, for which her institution received fees from Vertex Pharmaceuticals Incorporated. AL and KWS have no declarations of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcf.2019.03.009>.

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