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Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study.

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SUMMARY

Background: Ivacaftor is generally safe and effective in patients 2 years and older with cystic fibrosis (CF) and specific *CFTR* mutations. We evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy of ivacaftor in children aged 12 to <24 months.

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CONTRIBUTORS

The study sponsor, Vertex Pharmaceuticals Incorporated, designed the protocol in collaboration with the academic authors. Site investigators collected the data, which were analyzed by the sponsor. MR, JCD, MH, and CM participated in the conception of the ARRIVAL study. MR, JCD, MH, LTW, CM, and DC participated in the study design. MR, CEW, SC, and JCD were responsible for acquisition of data. All authors participated in analysis and interpretation of study data, drafting and critically revising the manuscript for important intellectual content, and final approval of the manuscript for publication.

ARRIVAL Study Group

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Methods: This phase 3, single-arm, two-part, multicenter, multinational study (ARRIVAL) enrolled children 12 to <24 months with a confirmed diagnosis of CF and a *CFTR* gating mutation on at least one allele. Children received oral ivacaftor 50 mg (weight 7 to <14 kg) or 75 mg (weight ≥14 to <25 kg) every 12 hours for 4 days in part A (to assess short-term safety and PK) and 24 weeks in part B (to assess safety and PD and explore efficacy). Primary endpoints were PK (part A) and safety (A and B); analyses included all children who received ≥1 dose of ivacaftor. Secondary endpoints were PK and absolute change from baseline at week 24 in sweat chloride. Tertiary endpoints included absolute change from baseline at week 24 in growth parameters and markers of pancreatic function. Safety analyses in parts A and B were performed on all children dosed; PD and efficacy analyses in part B were performed on all children enrolled and dosed. Final data for children aged 12 to <24 months were collected from August 2016 to November 2017; ARRIVAL is ongoing for those aged <12 months. This study is registered with ClinicalTrials.gov, number NCT02725567.

Findings: Seven children enrolled in part A, all of whom completed the 4-day treatment period and one of whom enrolled in part B. Nineteen children enrolled in part B, 18 of whom completed the 24-week treatment period. All patients received at least one dose of ivacaftor. PK results suggested that ivacaftor exposures were similar to those reported in older children and adults. Most adverse events (AEs) were typical for children with CF. The most common AE in part B was cough (in 14 [73·7%] of 19 children). Two children had four serious AEs; one (constipation) was considered to be possibly related to ivacaftor. Five (27·8%) of 18 children had transaminase elevations >3 × upper limit of normal (ULN) and remained on ivacaftor. Of these, two children had transaminase elevations >8 × ULN; both had concurrent infections and successfully resumed treatment after interruption. No children discontinued because of AEs or any safety findings. At week 24, mean (standard deviation) absolute change from baseline in sweat chloride was −73·5 (17·5) mmol/L. Growth parameters were normal at baseline and were generally maintained during treatment. There was an increase in fecal elastase-1 and a decrease in immunoreactive trypsinogen (IRT). Mean serum lipase and amylase were elevated at baseline and rapidly decreased with ivacaftor

Interpretation: Ivacaftor at doses of 50 mg or 75 mg every 12 hours was generally safe and well tolerated in children 12 to <24 months with CF and a *CFTR* gating mutation for up to 24 weeks. Substantial improvements were observed in sweat chloride, and growth measures were generally well maintained. Reductions in lipase and amylase, a new observation, along with improvements in fecal elastase-1 and IRT, suggest ivacaftor could potentially preserve pancreatic function if initiated early in life.

Funding: Vertex Pharmaceuticals Incorporated.

Keywords

Kalydeco; sweat chloride; fecal elastase-1; lipase; amylase; pancreatic function

INTRODUCTION

Cystic fibrosis (CF) is a progressive, life-shortening, multisystemic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[1] In

patients with CF, lung disease starts early in life, even in the absence of symptoms.[2–4] Infants as young as 3 months of age may exhibit airway infection, inflammation, and structural changes.[2,4–7] Pancreatic damage, which begins in utero,[8] leads to exocrine pancreatic insufficiency, which in turn, is associated with poor nutritional status and growth.[1] Newborn screening for CF is now widely established in North America, Australia and New Zealand, the United Kingdom, and many parts of Europe, providing the opportunity for early therapeutic intervention to improve growth, nutrition, and lung function.[9,10]

The clinical benefits of CFTR modulator therapies have been established in children and adults with CF.[11–14] The CFTR potentiator ivacaftor (Vertex Pharmaceuticals Incorporated, Boston, MA) targets mutations producing dysfunctional but correctly localized CFTR protein, increasing its function. First evaluated in patients with a *CFTR* gating mutation, the drug has been shown to be safe and effective in patients with CF aged 2 years and older with a number of ivacaftor-responsive *CFTR* mutations.[15,16] In the KIWI study, ivacaftor was associated with improvement in markers of pancreatic exocrine function in children aged 2 to 5 years, an organ hitherto considered to be irreversibly damaged in utero, suggesting a potential window of opportunity in early life for improving pancreatic function.[11] Targeting the underlying cause of CF during infancy could potentially help preserve pancreatic and lung function and alter the natural trajectory of CF disease. However, interventions in this vulnerable age group during rapid organ development and growth require careful understanding of appropriate pharmacokinetics (PK) and careful assessment of safety.

The phase 3, two-part, single-arm ARRIVAL study is the first clinical trial of CFTR modulator therapy in children <24 months with CF. It was designed to evaluate the safety, PK, and pharmacodynamics (PD) of ivacaftor in children aged <24 months who have ≥1 *CFTR* gating mutation and explore the efficacy of ivacaftor in this population over 24 weeks.[17] Children completing ARRIVAL are eligible to enroll in an open-label extension trial (NCT03277196). Results for the 12- to <24-month-old ARRIVAL cohort are presented here. ARRIVAL is currently ongoing for infants aged <12 months.

METHODS

Study design, participants, and procedures

The ARRIVAL study (VX15-770-124; NCT02725567) is a multicenter, phase 3, single-arm, two-part study of ivacaftor in children aged <24 months with a confirmed diagnosis of CF and ≥1 *CFTR* gating mutation (including the *R117H* mutation [US only]). The study was initiated in August 2016. It consists of two parts (A and B) with sequential decreasing-in-age cohorts (<24 to 12 months, <12 to 6 months, <6 months to birth; Supplementary Figure 1A). Part A evaluates short-term safety and PK of ivacaftor (and ivacaftor metabolites, M1-IVA and M6-IVA), with dosing for 4 days. Part B subsequently evaluates longer-term safety, PK, and PD and explores efficacy of ivacaftor over 24 weeks. Children can participate in part A, part B, or both (if they meet eligibility criteria). Children completing part B are eligible for an open-label extension study (NCT03277196). Final data for children aged 12 to <24 months were collected from August 2016 to November 2017 and are presented here. The analysis for the 12- to <24-month-old cohort in this open-label study was planned,

prespecified, and completed as per the Protocol (Supplementary Appendix). ARRIVAL is ongoing for those aged <12 months.

Children were enrolled in part A at 7 sites (5 US, 1 Australia, 1 UK) and in part B at 13 sites (7 US, 3 UK, 2 Australia, 1 Canada). Data were reviewed by an independent data monitoring committee. The study was conducted with ethics board approval at each participating site. Written informed consent was obtained from each child's parent/legal guardian.

Ivacaftor dose (granule formulation) was based on weight: 50 mg every 12 hours (weight 7 to <14 kg) or 75 mg every 12 hours (weight ≥14 to <25 kg). In part A, oral ivacaftor treatment was administered for 3 days, plus a morning dose on day 4. In part B, treatment was administered for 24 weeks (Supplementary Figure 1B).

Children aged 12 to <24 months with a confirmed diagnosis of CF and a *CFTR* mutation in ≥1 allele of *G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, or *G1349D* were eligible for inclusion; *R117H-CFTR* mutation was permitted at US sites. Exclusion criteria included current or recent (within 4 weeks) acute respiratory infection, changes in therapy (including antibiotics) for pulmonary disease, colonization at screening with organisms associated with a more rapid decline in pulmonary status (eg, *Burkholderia cenocepacia*, *B dolosa*, *Mycobacterium abscessus*), abnormal liver function test (LFT; >2 × upper limit of normal [ULN]), or use of any moderate or strong inducers or inhibitors of cytochrome P450 3A within 2 weeks of study day 1. Eligibility criteria are presented in Supplementary Table 1.

Outcomes

The primary endpoints of part A were safety and PK parameter estimates of ivacaftor, M1-IVA, and M6-IVA after 4 days of treatment. The primary endpoint of part B was safety, assessed by adverse events (AEs; defined using Common Terminology Criteria for Adverse Events, version 4·0), clinical laboratory assessments (including lipase and amylase levels), vital signs, 12-lead electrocardiogram readings, coagulation studies, and physical and ophthalmological examinations. Secondary endpoints in part B were PK parameters and absolute change from baseline in sweat chloride at 24 weeks. Exploratory endpoints across 24 weeks in part B included change from baseline for measures of growth, pulmonary exacerbations (PEx), assessments of pancreatic function (fecal elastase-1, serum immunoreactive trypsinogen [IRT]), qualitative microbiology, intestinal inflammation (fecal calprotectin), and acceptability/palatability of ivacaftor. The following bacteria were assessed in respiratory cultures: *Burkholderia*, *Haemophilus influenza*, methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*–mucoid, *Pseudomonas aeruginosa*–non-mucoid, and *Pseudomonas aeruginosa*–small colony variant. Lung clearance index (LCI) and infant pulmonary function testing (PFT) were optional and performed in one participant at one site. Growth parameters were normalized for age using population growth standards to derive *z* scores[18] to allow any change in growth status to be differentiated from normal growth.[11] Assessments of IRT were performed using an assay that measures all forms of trypsin and trypsinogen with a range of measurement from 0·1 to 1200 ng/mL. Data for exploratory intestinal inflammation marker

(fecal calprotectin) are not shown because of the lack of reference range and difficulty in interpretation.

Statistical analyses

A minimum of five children per cohort in part A and five children per cohort in part B was determined to be appropriate, based on PK analysis considerations and taking into account feasibility for children with CF meeting age and enrollment criteria. The population analysis of PK data for this study was consistent with the approach used in the KIWI study.[11] Population PK analysis of plasma ivacaftor concentrations from parts A and B were estimated using nonlinear mixed-effects modeling software (NONMEM, version 7 [ICON Development Solutions, Hanover, MD]). A previously developed population PK model for ivacaftor in patients aged 2 years and older was used to describe ivacaftor disposition in patients aged 12 to <24 months and to compare exposure with that observed in adult patients with CF from previously completed phase 2 and 3 trials of ivacaftor. Individual AUC and C_{min} values were simulated from empirical Bayesian estimates from the final population PK model. The study was not powered to detect treatment effects, and only descriptive analyses were performed. No formal hypothesis tests were conducted; however, post hoc analyses were performed (95% CI) to supplement descriptive analyses of changes from baseline. All analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

The analyses included all children who received ≥1 dose of study drug. Safety analyses were conducted separately for parts A and B. Pharmacodynamic and exploratory efficacy analyses were applicable to part B only, with continuous data summarized as number of children (n), mean, standard deviation (SD), median, range, and 95% CI (as appropriate) and categorical data as n, percentage, and 95% CI.

This study is registered with ClinicalTrials.gov, number NCT02725567.

Role of the funding source

Vertex Pharmaceuticals Incorporated provided funding for this study and for editorial support in manuscript development. Vertex Pharmaceuticals Incorporated was involved in study design; data collection, analysis, and interpretation; and reviewed and provided feedback on this manuscript. The authors had full editorial control of this manuscript and provided their final approval of all content.

RESULTS

Patient demographics

This study was conducted between 25 August 2016 and 1 November 2017. Seven children were enrolled in and completed part A, with five receiving ivacaftor 50 mg and two receiving ivacaftor 75 mg (Figure 1A). Six children had *G551D* on one allele. One child continued into part B; the other six turned 24 months before start of part B and chose to take commercially available ivacaftor. In part B, 19 children were enrolled and all received ivacaftor 50 mg every 12 hours (Figure 1B). Of these, 16 (84·2%) had *G551D* on one allele (Table 1). Eighteen (94·7%) children completed part B; one withdrew before week 2 because

of difficulty with blood draws. Seventeen (89·5%) children rolled over into the extension study (NCT03277196); one child turned 24 months and chose to take commercially available ivacaftor. All 19 children were included in the safety, PK, and PD and exploratory efficacy analyses. Demographic and baseline characteristics are summarized in Table 1.

Pharmacokinetics

Pharmacokinetic parameters evaluated for ivacaftor include area under the curve (AUC) and minimum plasma drug concentration (C_{min}; Supplementary Table 2). Area under the curve and C_{min} in children aged 12 to <24 months were consistent with those previously observed for ivacaftor in children aged 2 to 5 years and adults.[11] Plasma concentrations of ivacaftor metabolites, M1-IVA and M6-IVA, were summarized by descriptive statistics and were also consistent with those previously observed (data not shown).

Safety

In part A, 3 (42·9%) of 7 children had treatment-emergent AEs (TEAEs); all were mild and considered unlikely to be or not related to ivacaftor. All three children had cough, and one child each had a fall, fatigue, and a head injury. No serious AEs (SAEs), treatment interruptions, or discontinuations occurred. There were no LFT elevations or safety concerns in laboratory, ophthalmological, or electrocardiogram parameters.

In part B, over 24 weeks, 18 (94·7%) of 19 children had TEAEs; the majority were mild or moderate and considered unlikely to be or not related to ivacaftor (Table 2). The most common TEAEs were cough (73·7%; n=14), pyrexia (36·8%; n=7), aspartate aminotransferase (AST) increased (36·8%; n=7), ALT increased (31·6%; n=6), rhinorrhea (31·6%; n=6), otitis media (21·1%; n=4), and upper respiratory tract infection (21·1%; n=4).

Two (10·5%) of 19 children had four SAEs during the study: one child had persistent cough, was hospitalized for 2 weeks, and received intravenous antibiotics; another child was hospitalized for eczema herpeticum and had two additional hospitalizations 1 week apart for distal intestinal obstruction syndrome (DIOS) and constipation. The event of DIOS had been assessed by the investigator as unlikely to be related, but upon recurrence of gastrointestinal symptoms, the second admission for constipation was assessed as possibly related; the other two SAEs were considered unlikely to be related to ivacaftor by the investigator.

Five (27·8%) of 18 children had elevated ALT and/or AST >3 × ULN. Of these, three had elevations >3 to 5 × ULN, and two had elevations >8 × ULN. Ivacaftor treatment was maintained in the three children with transaminases >3 to 5 × ULN. One child returned to normal range and the remaining two had elevations >1 to <3 × ULN at week 24. The two children with transaminase elevations >8 × ULN had concurrent infections, temporarily interrupted ivacaftor, and resumed treatment without further elevations. No elevations in total bilirubin occurred in any child. Supplementary Figure 2 shows the mean (SD) ALT, AST, and bilirubin levels across 24 weeks of ivacaftor treatment.

There were no treatment discontinuations due to AEs or any safety findings; no cataracts were observed and no safety findings from other laboratory, vital sign, or electrocardiogram examinations were reported.

Pharmacodynamics and other outcomes

By week 2, sweat chloride decreased (improved) substantially from a baseline mean (SD) of 104·1 (12·8) mmol/L to 51·8 (25·9) mmol/L (Figure 2A). By week 24, the mean (SD) sweat chloride concentration was 33·8 (10·8) mmol/L, representing a mean absolute change of −73·5 (17·5) mmol/L from baseline (Table 3). Figure 2B shows a waterfall plot for the ten children with paired data at baseline and week 24; individual improvements in sweat chloride ranged from -42·0 to -97·5 mmol/L. At the end of the study, six children (four children with paired data) had sweat chloride concentrations below 30 mmol/L, a value consistent with normal CFTR function.[19] At baseline, mean growth parameters, weight, and length *z* scores were normal for age. Throughout the 24-week study, growth status was generally well maintained, with normal mean growth for age, weight, and length *z* scores (Table 3; Supplementary Figure 3).

Levels of fecal elastase-1 and IRT were measured to evaluate exocrine pancreatic function. Fecal elastase-1 levels <200 μg/g indicate exocrine pancreatic insufficiency. Among the 15 children with measurements at week 24, mean (SD) absolute change (improvement) in fecal elastase-1 was 164·7 (151·9) μg/g. Eleven children were considered pancreatic insufficient at baseline (all 11 had baseline values <50 μg/g). Nine of these children had both baseline and week 24 fecal elastase-1 values; six of these nine children had fecal elastase-1 >200 μg/g at week 24, a value consistent with normal pancreatic function. None of the children who were pancreatic sufficient at baseline (n=8) became pancreatic insufficient after 24 weeks of ivacaftor treatment. Increases in fecal elastase-1 were observed by week 2 and sustained through week 24 (Table 3; Figure 3A; Supplementary Figure 4A). High levels of IRT suggest pancreatic insult or ductal obstruction. Reductions in IRT were observed by week 2 and sustained through week 24. Mean (SD) decrease in IRT was 647·1 (339·3) ng/mL at week 24, a 56% reduction from baseline (Table 3; Figure 3B; Supplementary Figure 4B).

Although levels of serum lipase and amylase were collected as part of safety assessments, the results are relevant to pancreatic function. High levels of lipase and amylase are typically associated with pancreatic inflammation or insult.[20] At baseline (part B), all children had elevated lipase and approximately half had elevated amylase; all were asymptomatic. Marked and rapid reductions in serum lipase and amylase were observed within 4 days of ivacaftor treatment in part A (Supplementary Table 3) and by week 2 in part B (Supplementary Figures 5A–B). Mean (SD) absolute changes from baseline in lipase and amylase at week 24 were −228·4 (263·0) U/L and −54·8 (70·5) U/L, respectively (Table 3; Figure 4). No patients had elevations (increases) in lipase and amylase from baseline to Week 24 with ivacaftor treatment.

Additional exploratory endpoints for this study included LCI (optional), qualitative microbiology cultures, PEx, and acceptability/palatability assessments. Only one child had LCI measured and had an absolute improvement of -0·41 units in $LCI_{2.5}$ from baseline through week 24. The majority of respiratory cultures were negative at baseline and did not change over the course of treatment. Rate of PEx was assessed using two definitions (Supplementary Table 4) because there is no consensus on definition in younger pediatric patients. Eight (42·1%) of 19 children had 13 PEx or, using the alternate definition, 5

(26·3%) of 19 children had 8 PEx. All children accepted and fully consumed the dose of ivacaftor assessed for palatability.

DISCUSSION

This report describes the first clinical trial of a CFTR modulator in children <24 months with CF. Ivacaftor 50 mg or 75 mg every 12 hours was generally safe and well tolerated in children 12 to <24 months with a *CFTR* gating mutation. During the 24-week treatment period, the safety profile of the drug was similar to that reported in older children and adults.[11–15] We observed substantial improvement in sweat chloride, and clinical benefit as shown by maintenance of normal growth and improvement in markers of pancreatic function. The PK parameters of ivacaftor in this age range were consistent with those observed in adults, and by matching exposures to the adults, confirm the appropriateness of these doses in children 12 to <24 months.

The safety profile of ivacaftor in this age group was consistent with that previously reported in children aged 2 to 5 years in the KIWI study.[11] Adverse events were typical for young children with CF. The only SAE determined to be possibly related to study drug was constipation; no child discontinued study drug because of an AE or any safety findings. Elevated LFTs >3 × ULN were observed in five children over the 24-week treatment period. Two had LFTs >8 × ULN, potentially related to concurrent infections. Treatment was temporarily interrupted in these two children and successfully resumed without recurrent elevated LFTs. Interpretation of these results is limited by the small sample size, lack of a comparator group, and the limited understanding of the natural history of LFTs in CF in early childhood.[21] Should ivacaftor be approved for use in this age range, guidance on LFT monitoring will be provided in the approved label.

A large, rapid, and sustained improvement in sweat chloride, a well-described PD marker of CFTR function, was observed, with a mean (SD) absolute decrease of 73·5 (17·5) mmol/L from baseline at week 24. While our small sample size limits the precision of this estimate, the improvement appears at least as large as that observed with ivacaftor in older patients; among the 2- to 5-year-old patients in the KIWI study, the mean (SD) absolute decrease from baseline at week 24 was 46.9 (26.2) mmol/L.[11–13] In the diagnosis of CF, sweat chloride ≥60 mmol/L is diagnostic, 30 to 59 mmol/L is intermediate, and <30 mmol/L suggests CF is unlikely.[19] In our study, mean (SD) sweat chloride at week 24 was 33·8 (10·8) mmol/L, and 9 (47·4%) of 19 children had at least one on-treatment sweat chloride concentration <30 mmol/L. These data demonstrate a robust effect of ivacaftor on *CFTR* function in this age group, which could potentially lead to considerable short- and long-term benefits. Children in general were well nourished at study entry in terms of weight and length *z* scores. Normal growth velocity (for age)[18] was maintained throughout the 24-week study period.

While pancreatic damage in CF begins in utero,[8] exocrine pancreatic insufficiency continues to progress during infancy.[22,23] Therefore, it is possible that CFTR modulators used early in life could alter the natural progression of pancreatic dysfunction. Indeed, in both the KIWI study of ivacaftor in 2- to 5-year-olds and in the ARRIVAL study, there were improvements

in fecal elastase-1, a measure of exocrine pancreatic insufficiency, and of IRT, a nonspecific marker of pancreatic insult.[11] In the ARRIVAL study, pancreatic function was evaluated by changes in fecal elastase-1 and IRT. Additionally, lipase and amylase levels, which were collected as part of safety measures, provided further insight into pancreatic insult. We found rapid and sustained improvements in all four biomarkers. Fecal elastase-1 improved by a mean (SD) of 164·7 (151·9) μg/g from baseline at week 24, consistent with improvements in 2- to 5-year-olds in the KIWI study (100 [138] μg/g).[11] Eleven children had baseline fecal elastase-1 <200 μg/g, diagnostic of pancreatic insufficiency. Nine of these children had paired data at baseline and week 24; six of these nine children had values >200 μg/g at week 24. Serum IRT improved from a mean (SD) 1154·9 (162·6) ng/mL at baseline to 505·4 (303·9) at week 24. It should be noted that the IRT levels reported here are based on a new assay that uses a broader measurement range than the IRT assay used in previous *CFTR* modulator studies[11,24] and commonly used in newborn screening tests, so the results cannot be directly compared with those obtained in KIWI. Given that IRT is expected to decline with age, these results must be interpreted with caution, but the rapid and steep decline with initiation of ivacaftor suggests a treatment effect and supports the hypothesis that a window may exist in which pancreatic function may be impacted. In patients with two mutations resulting in severe CFTR dysfunction, this window may only be in early life. In contrast, patients possessing a residual function mutation often develop symptomatic and biochemical pancreatic disease later in life and thus may have reversible components of pancreatic dysfunction for a longer period; indeed, in a study of ivacaftor and tezacaftor/ivacaftor in patients aged ≥12 years with a residual function mutation, exploratory endpoints of fecal elastase-1 and IRT demonstrated trends toward improvement (the study was not powered for these outcomes).[24]

This is the first report of rapid and substantial decreases in lipase and amylase associated with ivacaftor treatment. All the children in this study had asymptomatic elevations in lipase and approximately half had asymptomatic elevations in amylase at baseline. Overall, 17 (94%) of 18 children had decreased lipase and 16 (89%) of 18 had decreased amylase from baseline at week 24. Notably, reductions were observed after just 4 days of dosing in part A. It has previously been reported that IRT and lipase decrease with age over the first several years of life in children with CF.[25] Fecal elastase-1 tends to remain in the pancreatic insufficient range among those in whom it is low at first assessment.[22] The rapidity of changes in this study in fecal elastase-1, IRT, and lipase and temporal association with ivacaftor suggest a possible treatment effect in the study. Although the clinical significance of these biomarker improvements is unknown, combined improvements in fecal elastase-1, IRT, lipase, and amylase in this cohort, along with data from 2- to 5-year-olds in KIWI,[11] suggest a possible positive and protective effect of ivacaftor on pancreatic exocrine function early in life. Longer-term studies will be needed to test this hypothesis.

Limitations of this study include a small sample size, reflecting the rarity of this patient population. The single-arm design without a comparator group limits the interpretation of safety and efficacy endpoints, particularly the biomarkers of pancreatic function for which the progression over time in infants with CF is poorly understood. Finally, aside from the measurement of $LCI_{2·5}$ in one child, there was no other assessment of lung function. An extension study is ongoing and will provide data on longer-term safety and durability of

ivacaftor effects in children in this age group (NCT03277196). ARRIVAL is currently ongoing for infants aged <12 months.

In summary, ivacaftor treatment in children aged 12 to <24 months with a *CFTR* gating mutation was well tolerated at both doses tested, with no new safety signals in this single-arm phase 3 study. Transaminase elevations in children of very young age are common and were observed in this study; as the role of ivacaftor is uncertain, monitoring of LFTs is recommended. Substantial improvements were observed in sweat chloride, a marker of CFTR function, and growth measures were well maintained throughout the 24 weeks of ivacaftor treatment. For the first time, we demonstrated rapid reduction in asymptomatic raised baseline lipase and amylase with ivacaftor. These findings, along with improvements in fecal elastase-1 and IRT, support the potential of ivacaftor to protect against progressive exocrine pancreatic dysfunction. The premise of CF newborn screening is to diagnose CF in the presymptomatic period and intervene before irreversible organ damage. Ivacaftor, if initiated in infancy, could potentially delay or minimize pancreatic and airway damage. Evaluation of a larger number of children for longer periods of time will be required to test this hypothesis in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DECLARATION OF INTERESTS

MR has received research grants and served as a consultant for Vertex Pharmaceuticals Incorporated, for which her institution received payment. CEW has received income on a per-patient basis derived from pharmaceutical studies sponsored by Vertex Pharmaceuticals and Boehringer-Ingelheim; has received a research grant from Novo Nordisk; has received honoraria for participation in advisory boards, symposia, and meetings from Vertex Pharmaceuticals Incorporated, Novartis Pharmaceuticals, DKBmed LLC, and University of Miami; and has received honoraria from *Thorax* for serving as the associate editor, from *BMJ* for serving as a consultant, and from DKBmed LLC for participation in the eCF Review issue. CEW has also received travel support from Vertex Pharmaceuticals Incorporated for meetings and consultancy work and currently serves on the International Advisory Board for Vertex Pharmaceuticals Incorporated and as the associate editor of *Thorax* and *Respirology*. MH, LTW, CM, DC, ST, and JS are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. SC has participated in the CF Trust Pharmacovigilance Program and the University of Edinburgh has received fees from the UK Cystic Fibrosis Trust for his contributions. JCD has performed advisory, clinical trial leadership, or clinical trial design assistance roles for AlgiPharma, Bayer AG, Boehringer-Ingelheim Pharma GmbH and Co. KG, Enterprise, Flatley, Galapagos NV, ImevaX GmbH, Nivalis Therapeutics Inc, Novartis, ProQR Therapeutics III BV, Proteostasis Therapeutics Inc, PTC Therapeutics International Limited, Pulmocide, Raptor Pharmaceuticals Inc, and Vertex Pharmaceuticals Incorporated; has received grants from the Cystic Fibrosis Trust; and has undertaken educational activities for Teva.

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RESEARCH IN CONTEXT

Evidence before this study

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Treatments that help improve the function of CFTR protein target the underlying cause of CF. Ivacaftor is a first-in-class CFTR potentiator that increases the channel-open probability of CFTR to enhance chloride transport and was the first CFTR modulator to show improvement in CFTR function, with clinical benefits in patients with CF. Ivacaftor is indicated for the treatment of CF in patients 2 years and older who have at least one ivacaftor-responsive *CFTR* mutation (approved mutations vary by country). In trials and clinical practice, ivacaftor has been found to be generally safe and well tolerated and has demonstrated marked efficacy with substantial evidence that it modifies the course of long-term disease. In children aged 2 to 5 years, exploratory analyses suggested that ivacaftor may partially restore exocrine function of the pancreas, an organ hitherto considered to be irreversibly damaged, suggesting a window of opportunity in early life for improving pancreatic function. We performed a PubMed search in February 2018 for studies on ivacaftor using the terms “ivacaftor,” “Kalydeco,” “gating,” “infant,” and “child,” without any restrictions on publication date or language and found no studies that evaluated the effect of ivacaftor in children aged <24 months.

Added value of this study

To our knowledge, this study is the first to evaluate the safety, dose, and therapeutic benefit of ivacaftor in children aged 12 to <24 months with CF who have a *CFTR* gating mutation. Ivacaftor was well tolerated with a safety profile consistent with studies in patients 2 years and older; exposures of ivacaftor and metabolites were similar to those in older populations. There were substantial improvements in sweat chloride, a marker of CFTR activity. Ivacaftor showed therapeutic benefit, with improvements in markers of exocrine pancreatic function (fecal elastase-1) and pancreatic insult (immunoreactive trypsinogen [IRT], lipase, and amylase). In addition, growth parameters were normal at study baseline and generally maintained during treatment.

Implications of all the available evidence

The findings from this study establish the safety, appropriate dose, and therapeutic benefit of ivacaftor in children aged 12 to <24 months. Our data suggest the potential of ivacaftor to protect the pancreas and preserve its function when treating at this early age. The results of this study support use of ivacaftor therapy in children aged 12 to <24 months with CF and an ivacaftor-responsive mutation.

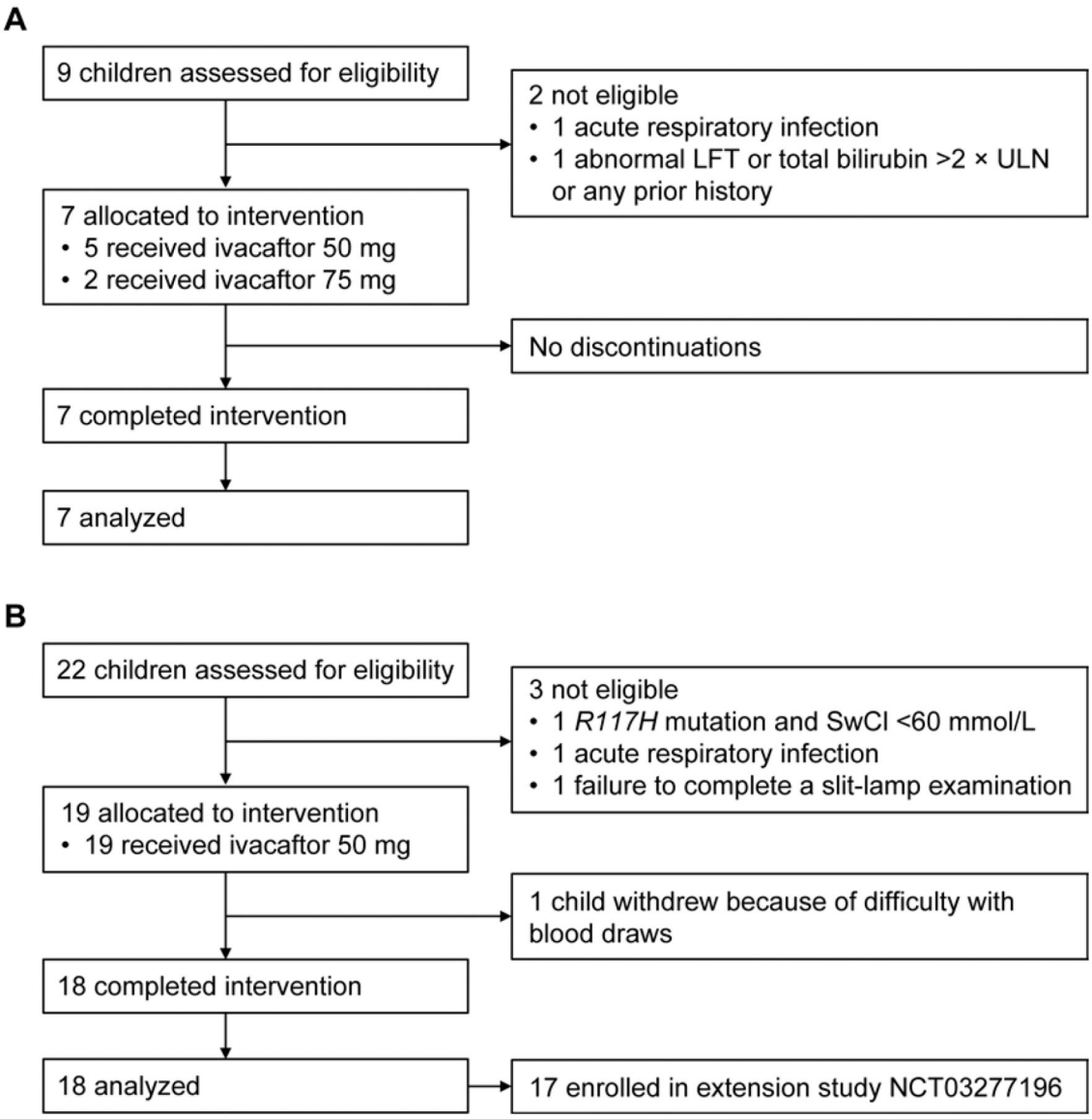

Figure 1.

CONSORT diagrams for **(A)** part A and **(B)** part B. LFT, liver function test; SwCl, sweat chloride; ULN, upper limit of normal.

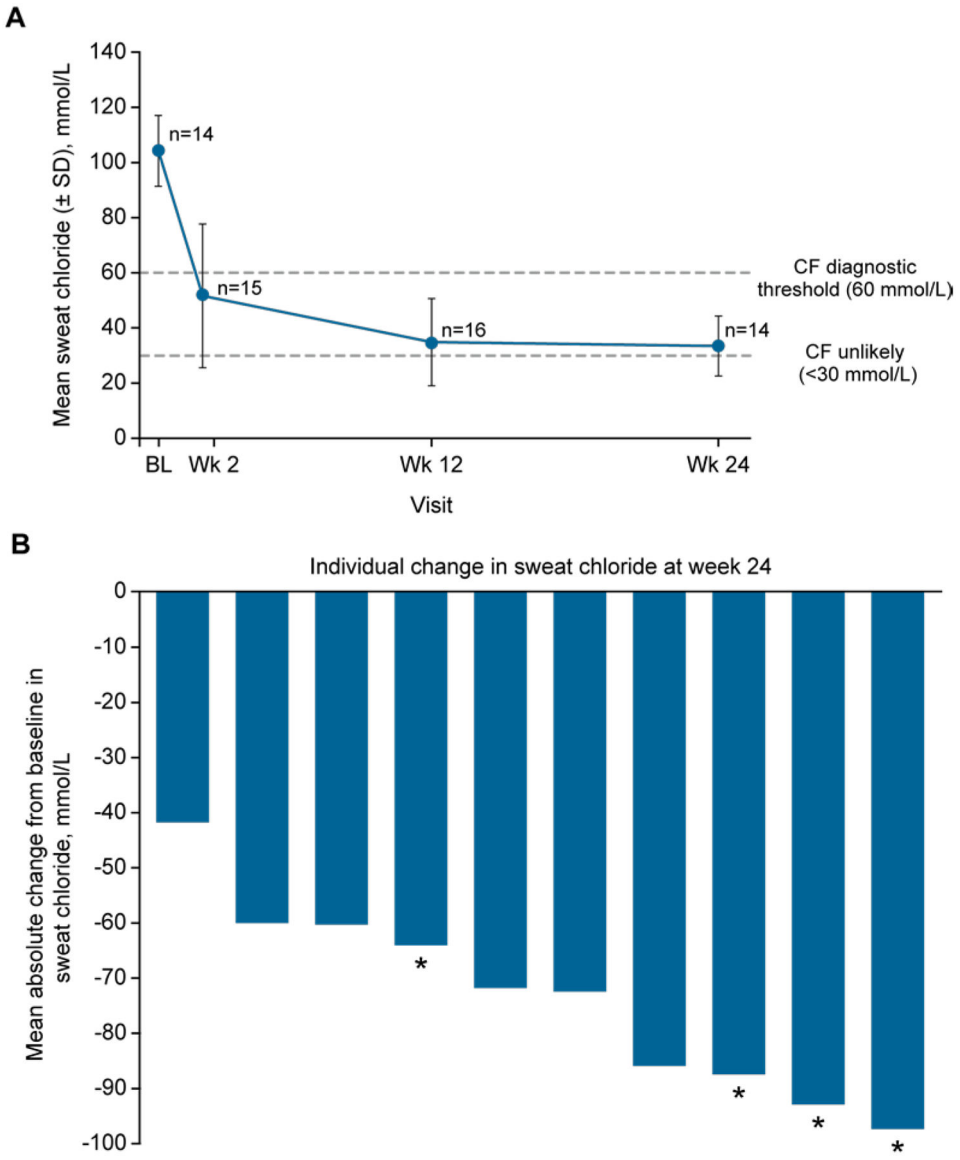

Figure 2.

Sweat chloride concentrations. **(A)** Mean sweat chloride concentration by visit. Means were calculated for each visit from the number of children contributing data at that time point. **(B)** Mean absolute change from baseline at week 24 for individual children with paired data at BL and 24 weeks. BL, baseline; CF, cystic fibrosis; SD, standard deviation. *Children with paired data at baseline and week 24 for whom sweat chloride concentrations were <30 mmol/L at week 24.

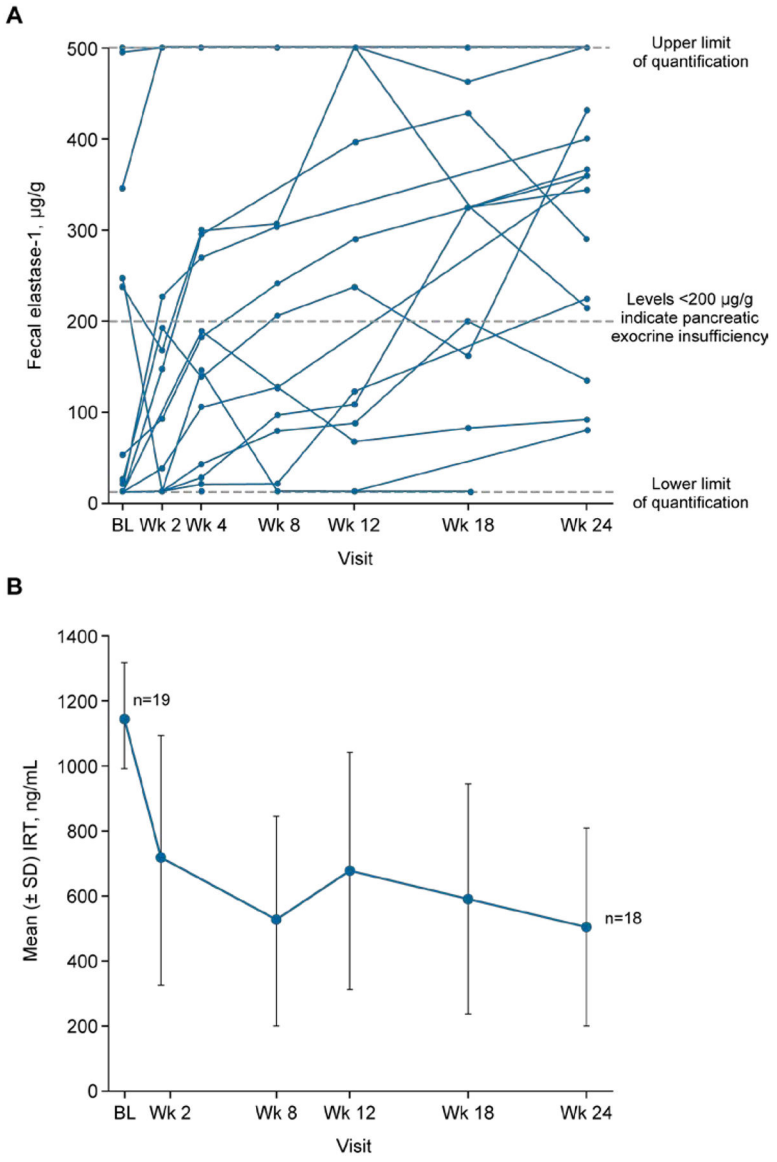

Figure 3.

Exploratory efficacy outcomes. **(A)** Fecal elastase-1 levels in each child with available data (n=18). **(B)** Mean IRT levels by visit during the 24-week ivacaftor treatment period. Means were calculated for each visit from the number of children contributing data at that time point. BL, baseline; IRT, immunoreactive trypsinogen; SD, standard deviation.

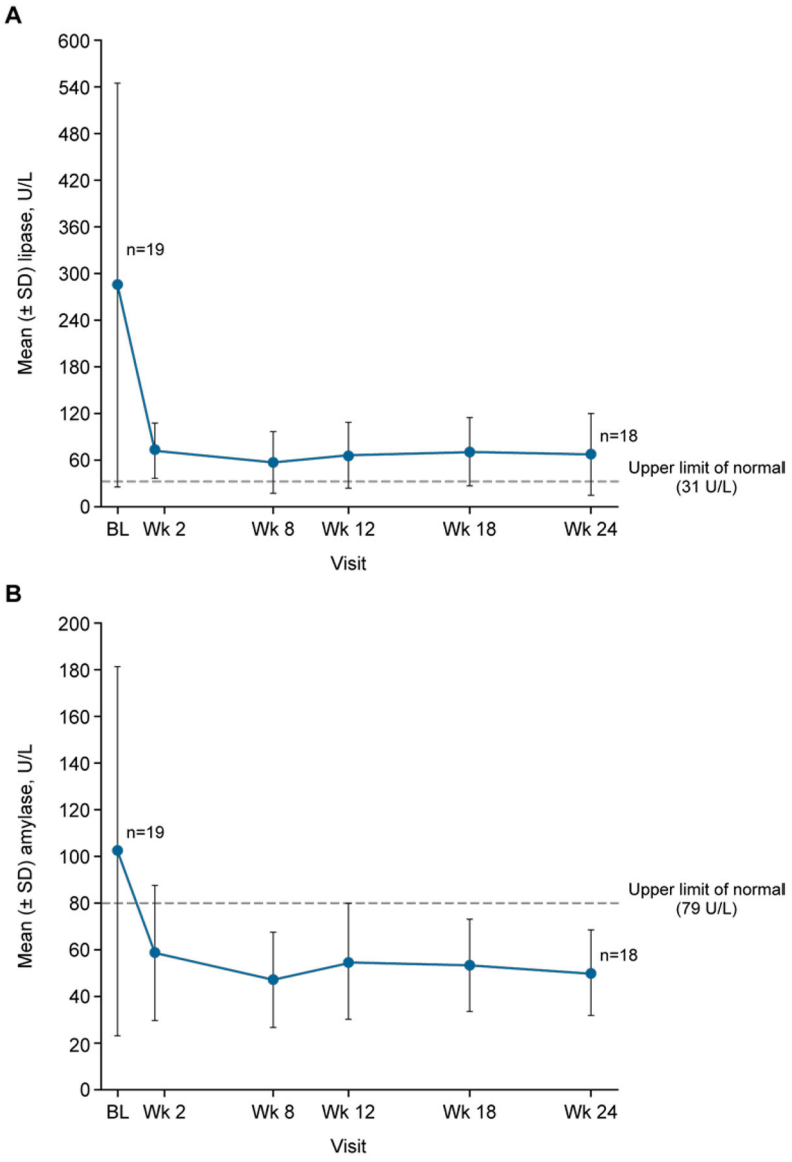

Figure 4.

Additional safety assessments. **(A)** Mean lipase and **(B)** mean amylase levels by visit during the 24-week ivacaftor treatment period. Means were calculated for each visit from the number of children contributing data at that time point. BL, baseline; SD, standard deviation.

Table 1.

Demographics and Baseline Characteristics for Children in Part B of the Study

Parameter	Ivacaftor 50 mg (N=19)
Age, mean (SD), months	15·2 (3·6)
Male, n (%)	11 (57·9)
Weight, mean (SD), kg	10·5 (1·3)
Genotype, n (%)	
G551D/F508del	11 (57·9)
G551D/2789+5G>A	1 (5·3)
G551D/DELTA 1507	1 (5·3)
G551D/G551D	1 (5·3)
G551D/UNKNOWN	1 (5·3)
G551D/V392G	1 (5·3)
S549N/F508del	2 (10·5)
G178R/F508del	1 (5·3)

SD, standard deviation.

Table 2.

Adverse Events in Part B of the Study

Preferred term, n (%)	Ivacaftor 50 mg (N=19)
Children with at least one adverse event[a]	18 (94·7)
Serious adverse events[b]	
Constipation	1 (5·3)
Distal intestinal obstruction syndrome	1 (5·3)
Eczema herpeticum	1 (5·3)
Cough	1 (5·3)
Treatment-emergent adverse events in ≥10% of children	
Cough	14 (73·7)
Pyrexia	7 (36·8)
Aspartate aminotransferase increased[c]	7 (36·8)
Alanine aminotransferase increased[c]	6 (31·6)
Rhinorrhea	6 (31·6)
Otitis media	4 (21·1)
Upper respiratory tract infection	4 (21·1)
Blood pressure increased[d]	3 (15·8)
Constipation	3 (15·8)
Gamma-glutamyltransferase increased	3 (15·8)
Pseudomonas test positive	3 (15·8)
Vomiting	3 (15·8)
Blood lactate dehydrogenase increased	2 (10·5)
Conjunctivitis	2 (10·5)
Dehydration	2 (10·5)
Rhinitis	2 (10·5)

PT, preferred term; SOC, system organ class; ULN, upper limit of normal.

Data in each row are number of patients with each event (percentage of patients). Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4·0.

aA child with multiple events within a category (any, SOC, or PT) was counted only once in that category.

bThe first three events occurred in one child and the cough in another child.

cAny elevation exceeding ULN.

dOf the three children with elevated blood pressure, two had mild elevated blood pressure that was similar before and after treatment, and one child was uncooperative and agitated during blood pressure assessments.

Table 3.

Outcomes: Mean Absolute Change From Baseline at Week 24 in Part B of the St**udy**

Endpoint	Baseline, mean (SD)	Week 24, mean (SD)	Absolute change, mean (SD),[a] 95% CI
Secondary endpoints			
Sweat chloride, mmol/L (normal range, <30 mmol/L)	104·1 (12·8) n=14	33·8 (10·8) n=14	−73·5 (17·5) −86·0, −61·0 n=10
Tertiary endpoints			
Weight-for-age *z* score	0·31 (0·74) n=19	0·48 (0·83) n=18	0·15 (0·42) −0·05, 0·36 n=18
Length-for-age *z* score	−0·30 (0·82) n=19	0·03 (0·91) n=17	0·28 (0·60) −0·03, 0·58 n=17
Weight-for-length-for-age *z* score	0·61 (0·90) n=19	0·69 (0·98) n=17	0·07 (0·65) −0·26, 0·40 n=17
Fecal elastase-1, µg/g[b] (normal range, >200 µg/g)	182·2 (217·1) n=19	326·9 (152·1) n=15	164·7 (151·9) 80·6, 248·8 n=15
IRT, ng/mL[c] (reference range not established)	1154·9 (162·6) n=19	505·4 (303·9) n=18	−647·1 (339·3) −815·8, −478·3 n=18
Safety assessments			
Lipase, U/L (normal range, >4 to <31 U/L)	285·3 (259·7) n=19	67·4 (52·5) n=18	−228·4 (263·0) −359·2, −97·6 n=18
Amylase, U/L (normal range, >8 to <79 U/L)	102·2 (79·5) n=19	49·8 (18·4) n=18	−54·8 (70·5) −89·9, −19·7 n=18

IRT, immunoreactive trypsinogen; SD, standard deviation.

aCalculated from the children with data available at both time points.

bEleven children had baseline fecal elastase-1 values <200 µg/g. Nine of these children had paired data at baseline and week 24; six of these nine children had fecal elastase-1 >200 µg/g at week 24.

cReduction means improvement.