ORIGINAL ARTICLE

A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age with Cystic Fibrosis Homozygous for *F508del-CFTR*

Jonathan H. Rayment[1], Fadi Asfour[2], Margaret Rosenfeld[3], Mark Higgins[4], Lingyun Liu[4], Molly Mascia[4], Hildegarde Paz-Diaz[4], Simon Tian[4], Rachel Zahigian[4], and Susanna A. McColley[5,6]; for the VX16-809-122 Study Group

[1]Division of Respiratory Medicine, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; [2]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; [3]Seattle Children's Hospital, Seattle, Washington; [4]Vertex Pharmaceuticals Incorporated, Boston, Massachusetts; [5]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; and [6]Northwestern University Feinberg School of Medicine, Chicago, Illinois

ORCID IDs: 0000-0003-4955-8876 (J.H.R.); 0000-0001-6317-6845 (F.A.); 0000-0002-5278-1422 (L.L.); 0000-0003-0842-728X (S.A.M.).

Abstract

Rationale: Previous phase 3 trials showed that treatment with lumacaftor/ivacaftor was safe and efficacious in people aged ⩾2 years with cystic fibrosis (CF) homozygous for the *F508del* mutation in *CFTR* (CF transmembrane conductance regulator) (*F*/*F* genotype).

Objectives: To assess the safety, pharmacokinetics, and pharmacodynamics of lumacaftor/ivacaftor in children aged 1 to <2 years with the *F*/*F* genotype.

Methods: This open-label, phase 3 study consisted of two parts (part A [$n = 14$] and part B [$n = 46$]) in which two cohorts were enrolled on the basis of age (cohort 1, 18 to <24 mo; cohort 2, 12 to <18 mo). For the 15-day treatment period in part A, the lumacaftor/ivacaftor dose was based on weight at screening. Pharmacokinetic data from part A were used to determine dose-based weight boundaries for part B (24-wk treatment period).

Measurements and Main Results: The primary endpoint of part A was pharmacokinetics, and the primary endpoint for part B was safety and tolerability. Secondary endpoints for part B were absolute change in sweat chloride concentration from baseline at Week 24 and pharmacokinetics. Analysis of pharmacokinetic data from part A confirmed the appropriateness of part B dosing. In part B, 44 children (95.7%) had adverse events, which for most were either mild (52.2% of children) or moderate (39.1% of children) in severity. The most common adverse events were cough, infective pulmonary exacerbation of CF, pyrexia, and vomiting. At Week 24, mean absolute change from baseline in sweat chloride concentration was −29.1 mmol/L (95% confidence interval, −34.8 to −23.4 mmol/L). Growth parameters (body mass index, weight, length, and associated *z*-scores) were normal at baseline and remained normal during the 24-week treatment period. Improving trends in some biomarkers of pancreatic function and intestinal inflammation, such as fecal elastase-1, serum immunoreactive trypsinogen, and fecal calprotectin, were observed.

Conclusions: Lumacaftor/ivacaftor was generally safe and well tolerated in children aged 1 to <2 years with the *F*/*F* genotype, with a pharmacokinetic profile consistent with studies in older children. Efficacy results, including robust reductions in sweat chloride concentration, suggest the potential for CF disease modification with lumacaftor/ivacaftor treatment. These results support the use of lumacaftor/ivacaftor in this population.

Clinical trial registered with www.clinicaltrials.gov (NCT 03601637).

Keywords: cystic fibrosis; lumacaftor; ivacaftor; children

(Received in original form April 15, 2022; accepted in final form June 29, 2022)

Supported by Vertex Pharmaceuticals Incorporated.

Author Contributions: 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. All authors had full access to the study data. J.H.R., M.H., H.P.-D., and S.A.M. developed the initial draft of the manuscript, with writing assistance from the sponsor. All authors participated in subsequent revisions. All authors approved the final version submitted for publication.

Data sharing statement: Vertex is committed to advancing medical science and improving the health of people with cystic fibrosis. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

Am J Respir Crit Care Med Vol 206, Iss 10, pp 1239–1247, Nov 15, 2022

Originally Published in Press as DOI: 10.1164/rccm.202204-0734OC on June 30, 2022
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Previous phase 3 trials showed that treatment with lumacaftor/ivacaftor is safe and efficacious in people with cystic fibrosis (CF) aged 2 years and older who are homozygous for the *F508del* mutation in *CFTR* (CF transmembrane conductance regulator) (*F*/*F* genotype). As clinical manifestations of CF can begin in infancy, early treatment initiation is critical in altering the course of CF disease progression.

What This Study Adds to the Field: This open-label, phase 3 study was designed to assess the safety, pharmacokinetics, and pharmacodynamics of lumacaftor/ivacaftor treatment in children 1 to <2 years of age with the *F*/*F* genotype, the youngest children to be treated with lumacaftor/ivacaftor to date. Lumacaftor/ivacaftor was generally safe and well tolerated, with a pharmacokinetic profile consistent with studies in older children. Efficacy results, including reductions in sweat chloride concentration, suggest the potential for early CF disease modification. Taken together, these results support use of lumacaftor/ivacaftor in children as young as 1 year of age.

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the *CFTR* (CF transmembrane conductance regulator) gene that affects more than 80,000 people worldwide (1–3). Pathogenic variants in the *CFTR* gene lead to decreases in the quantity and function of the CFTR protein, an anion channel found in various epithelial cells (1, 2, 4).

Clinical manifestations of CF begin early in life. Most infants have elevated sweat chloride concentrations, measurable pulmonary manifestations, and exocrine pancreatic insufficiency with poor growth (5), making early treatment intervention critically important for altering the course of CF. Most newborns with CF have exocrine pancreatic insufficiency from *in utero* pancreatic damage, and impaired lung function and structural airway damage can be measured in infants as young as 3 months of age (6–9). The small airway disease in infants with CF eventually leads to progressively worsening pulmonary dysfunction and advanced lung disease, with pulmonary infection, inflammation, and structural lung disease frequently observed in school-aged children (10, 11).

CFTR modulators are small-molecule therapeutics designed to treat the underlying causes of CF. Potentiators, such as ivacaftor (IVA), enhance channel gating activity, whereas correctors, such as lumacaftor (LUM), tezacaftor, and elexacaftor, improve CFTR protein processing and trafficking to the cell surface (12–15). The dual-treatment regimen of LUM/IVA has been shown to be safe and efficacious in children aged ⩾2 years and adults with CF homozygous for the *F508del* mutation (*F*/*F* genotype). In adolescents and adults aged ⩾12 years with CF, treatment with LUM/IVA was associated with increased lung function (percentage predicted FEV_1) and decreased rates of pulmonary exacerbations over a 24-week treatment period (16). An open-label extension study showed that these improvements were sustained over 96 weeks (17). Treatment with LUM/IVA has also been shown to be safe and to improve lung function, growth parameters, and health-related quality of life in children aged 6–11 years (18, 19). These results demonstrated that LUM/IVA treatment provides clinically meaningful and durable benefits in people with CF aged ⩾6 years with the *F*/*F* genotype.

Recent studies of LUM/IVA and IVA in children and infants support the clinical benefits of early CFTR modulator treatment initiation. In children aged 2–5 years, treatment with LUM/IVA was associated with decreased sweat chloride concentrations (an indicator of CFTR function), improved biomarkers of pancreatic function (increased fecal elastase-1 concentrations and decreased serum immunoreactive trypsinogen concentrations), and increased growth parameters during a 24-week treatment period (20). Similarly, in infants aged 4 months to <1 year and children aged 1 to <2 years with *CFTR* gating mutations, treatment with IVA was associated with decreased sweat chloride concentrations, improved biomarkers of pancreatic function, and increased stable growth parameters (21, 22). These results suggest that CFTR modulator therapy, if initiated early in life, can improve CFTR function, preserve pancreatic function, and maintain growth measures. Here, we report results from a two-part, open-label, phase 3 trial designed to assess the safety, pharmacokinetic (PK) parameters, and pharmacodynamics of LUM/IVA in children aged 1 to <2 years with the *F*/*F* genotype, the youngest children treated with LUM/IVA to date.

Methods

Participants, Trial Design, and Oversight

In this phase 3, two-part, open-label trial of LUM/IVA, children aged 1 to <2 years with CF homozygous for the *F508del* mutation (*F*/*F* genotype) were enrolled. Part A of the study evaluated PK data and safety over a 15-day treatment period in two cohorts enrolled sequentially: children aged 18 to <24 months (cohort 1) and those aged 12 to <18 months (cohort 2). Part B assessed safety, tolerability, pharmacodynamics, and PK parameters over a 24-week treatment period. Additional details on study design (*see* Figure E1 in the online supplement) and eligibility criteria are provided in the online supplement.

Dosing for part A and part B was based on weight at screening. Initial simulations for children 1 to <2 years of age were used to select LUM/IVA doses for part A that would yield exposures comparable to those of adults with CF. These initial simulations were based on population PK models incorporating data from children 2–11 years of age, noting that PK data from children 1 to <2 years of age were incorporated as they became available to inform dose selections for subsequent

Correspondence and requests for reprints should be addressed to Susanna A. McColley, M.D., Stanley Manne Children's Research Institute, 303 E. Superior Street, #205, Chicago, IL 60611. E-mail: smccolley@luriechildrens.org.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

cohorts and parts of the study. For part A, children in cohort 1 weighing 10 to <14 kg received LUM 100 mg/IVA 125 mg every 12 hours (q12h), and those weighing ≥14 kg received LUM 150 mg/IVA 188 mg q12h. For cohort 2, children weighing 7 to <10 kg received LUM 75 mg/IVA 94 mg q12h, those weighing 10 to <14 kg received LUM 100 mg/IVA 125 mg q12h, and those weighing ≥14 kg received LUM 150 mg/IVA 188 mg q12h. Dosing for part B was based on updated PK modeling, such that children weighing 7 to <9 kg received LUM 75 mg/IVA 94 mg q12h, those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h, and those weighing ≥14 kg received LUM 150 mg/IVA 188 mg q12h.

The study was designed by Vertex Pharmaceuticals Incorporated. Data collection and analysis were performed by Vertex in collaboration with the authors and the VX16-809-122 Study Group. For each enrolled child, informed consent was provided by a parent or legal guardian in accordance with local requirements. Safety was monitored by an independent data and safety monitoring committee. All authors had full access to the trial data after final database lock and critically reviewed and approved the manuscript for submission. The investigators vouch for the accuracy and completeness of the data generated at their respective sites, and the investigators and Vertex vouch for the fidelity of the trial to the study protocol. Confidentiality agreements were in place between the sponsor and each investigative site during the trial.

During this trial, a global protocol addendum that enabled in-home assessments was implemented to address travel restrictions and limitations of onsite research procedures on the basis of governmental and institutional mandates resulting from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Access to study drug therapy and the collection of safety data were prioritized. Implemented measures included remote consent, shipment of study drug to patients' homes, in-home or teleconference visits by qualified personnel, in-home blood collection and analysis at central or local laboratories, and remote monitoring. The clinical trial protocol, SARS-CoV-2–related protocol addendum, and informed-consent forms were approved by independent ethics committees as required by local regulations.

Outcome Measures

The primary endpoint for part A was PK parameters of LUM and IVA. The primary endpoint for part B was safety and tolerability as assessed by adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations. Secondary endpoints for part B were absolute change in sweat chloride concentration from baseline at Week 24 and PK parameters of LUM, IVA, and their respective metabolites. Additional endpoints in part B included absolute change from baseline at Week 24 in weight-for-length *z*-score, body mass index (BMI)-for-age *z*-score, BMI, weight-for-age *z*-score, weight, length-for-age *z*-score, length, fecal elastase-1 concentration, serum immunoreactive trypsin and trypsinogen (IRT) concentration, and fecal calprotectin concentration, together with number of pulmonary exacerbations and number of CF-related hospitalizations through Week 24. Further details are provided in the online supplement.

Statistical Analysis

Analyses of PK parameters, safety, and pharmacodynamic/efficacy-related endpoints included all children who received at least one dose of LUM/IVA. Approximately 10 children were planned for enrollment in part A (considered sufficient to achieve the PK objectives in part A) and 30 children in part B (considered sufficient to achieve the primary safety objective in part B). No formal sample size calculations were performed. Assuming a 10% dropout rate in part B, 27 children would complete the study. A total sample size of 27 children would give a 75% chance of observing an AE in at least one child if the true incidence rate is 5% and a 94.2% chance of observing an AE in at least one child if the true incidence rate is 10%. Baseline was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before administration of the first dose of LUM/IVA. No adjustments for multiplicity were performed and there was no hypothesis testing. Data were analyzed using SAS version 9.4 or higher (SAS Institute Inc.).

Results

Population

The trial was conducted at 23 sites in the United States and Canada from September 7, 2018 to October 29, 2021. Fourteen children were enrolled and received at least one dose of LUM/IVA in part A (7 in cohort 1 and 7 in cohort 2) (*see* Figure E2). One child in cohort 1 discontinued treatment because of an AE of rash. Additional details on part A enrollment and demographics and clinical characteristics at baseline are provided in Table E1. In part B, 46 children were enrolled and received at least one dose of LUM/IVA; 45 children (97.8%) completed treatment (Figure 1). One child discontinued treatment because of AEs of increased alanine aminotransferase and aspartate aminotransferase concentrations. Part B demographics and clinical characteristics at baseline are provided in Table 1.

Safety and PK Data

Assessments of safety and tolerability for part A are included in the online supplement. In part B, safety and tolerability were the primary endpoint. Overall, 44 children (95.7%) in part B had AEs, which for most were mild (52.2%) or moderate (39.1%) in severity and generally consistent with manifestations of CF (Table 2). The most common AEs (≥15% of children) were cough (34.8%), infective pulmonary exacerbation of CF (21.7%), pyrexia (21.7%), and vomiting (17.4%). Five children (10.9%) had serious AEs (infective pulmonary exacerbation of CF [$n = 3$], post-procedural fever [$n = 1$], and distal intestinal obstruction syndrome [$n = 1$]), all of which were considered by study investigators to be mild or moderate in severity. The only serious AE considered possibly related to study drug was distal intestinal obstruction syndrome.

Elevated concentrations of alanine aminotransferase and/or aspartate aminotransferase that were >3 times the upper limit of normal occurred in five children (10.9%), two of whom had elevations >5 times the upper limit of normal and one of whom had an elevation >8 times the upper limit of normal (*see* Table E3). No children had total bilirubin >2 times the upper limit of normal. Four children (8.7%) had AEs of elevated transaminases, most of which were mild or moderate in severity. One child (2.2%) had AEs of increased alanine aminotransferase and aspartate aminotransferase concentrations that were considered by study investigators to be severe and related to study drug and that led to treatment discontinuation. One child (2.2%) had an AE of dyspnea that occurred on Day 1, which

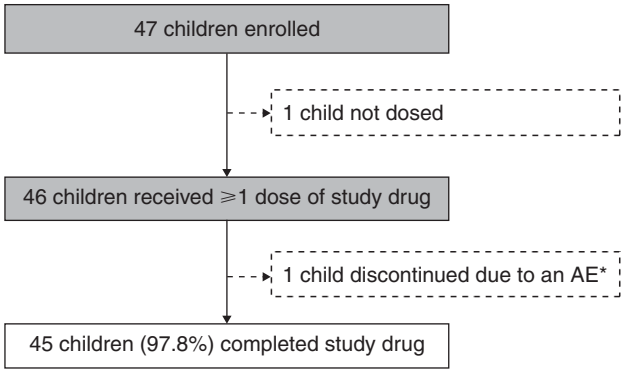

Figure 1. Participant disposition diagram for part B. *This child had an AE of increased alanine aminotransferase and aspartate aminotransferase concentrations that led to treatment discontinuation. AE = adverse event.

was considered possibly related to study drug and led to interruption of the Day 1 evening dose. LUM/IVA treatment was resumed the next day and the event did not recur. There were no relevant safety findings in other clinical or laboratory assessments.

Analysis of PK data from part A confirmed the appropriateness of the dosing regimen in part B. PK analysis incorporating data from part B indicated that body weight was the only covariate found to have a clinically meaningful impact on LUM and IVA disposition in patients ⩾1 year of age; no age-related effects were observed. For part B, the plots of area under the curve versus time for both LUM and IVA were within the ranges of exposures previously shown to be safe and efficacious in adults (Figures 2A and 2B). The median area under the curve for LUM was close to the adult median. The median exposure of IVA was modestly higher than the median in adults but was comparable to other pediatric age groups (*see* Table E4).

Table 1. Demographics and Clinical Characteristics of the Participants in Part B at Baseline*

Baseline Parameter	LUM/IVA ($n = 46$)†
Female sex, *n* (%)	24 (52.2)
Age at baseline, mo, mean (SD)	18.1 (3.50)
Race, *n* (%)‡	
White	36 (78.3)
Black or African American	1 (2.2)
Asian	1 (2.2)
American Indian or Alaska Native	3 (6.5)
Native Hawaiian or other Pacific Islander	1 (2.2)
Other	1 (2.2)
Not collected per local regulations	7 (15.2)
Dosing group at enrollment, *n* (%)	
LUM 75 mg/IVA 94 mg q12h	1 (2.2)
LUM 100 mg/IVA 125 mg q12h	44 (95.7)
LUM 150 mg/IVA 188 mg q12h	1 (2.2)
Weight, kg, mean (SD)	11.3 (1.30)
Weight-for-age *z*-score, mean (SD)	0.46 (0.79)
Length, cm, mean (SD)	81.1 (4.1)
Length-for-age *z*-score, mean (SD)	−0.25 (0.97)
BMI kg/m^2, mean (SD)	17.17 (1.22)
BMI-for-age *z*-score, mean (SD)	0.86 (0.77)
Weight-for-length-for-age *z*-score, mean (SD)	0.79 (0.77)
Sweat chloride concentration, mmol/L, mean (SD)	104.2 (7.70)

Definition of abbreviations: BMI = body mass index; IVA = ivacaftor; LUM = lumacaftor; q12h = every 12 hours.
*Baseline was defined as the most recent nonmissing measurement before administration of the first dose of study drug.
†All patients in the safety set received at least one dose of study drug in part B.
‡The race categories may sum to >100% because each patient was able to indicate more than one race.

Pharmacodynamic Results

Treatment with LUM/IVA led to a mean absolute change from baseline in sweat chloride concentration of −29.1 mmol/L (95% confidence interval [CI], −34.80 to −23.40 mmol/L) at Week 24 (Table 3). Reductions in sweat chloride were seen by Week 4 and maintained over the 24-week treatment period (Figure 3). In an additional prespecified analysis, the absolute change from baseline in sweat chloride through Week 24 (defined as the average of sweat chloride measurements at Weeks 4, 12, and 24) was −31.3 mmol/L (95% CI, −35.8 to −26.9 mmol/L), similar to the observed change from baseline at Week 24 and indicating consistency in LUM/IVA treatment effect across the study period. At baseline, mean BMI-for-age *z*-score (0.86; 95% CI, 0.63 to 1.09), weight-for-length *z*-score (0.79; 95% CI, 0.56 to 1.01), weight-for-age *z*-score (0.46; 95% CI, 0.23 to 0.70), and length-for-age *z*-score (−0.25; 95% CI, −0.54 to 0.03) were all within normal ranges (Table 3). Mean absolute change from baseline at Week 24 in BMI-for-age *z*-score was 0.04 (95% CI, −0.14 to 0.22), in weight-for-length *z*-score was 0.04 (95% CI, −0.13 to 0.22), in weight-for-age *z*-score was 0.06 (95% CI, −0.05 to 0.17), and in length-for-age *z*-score was 0.07 (95% CI, −0.11 to 0.24) (Table 3). Markers of pancreatic function and intestinal inflammation showed trends toward improvement with LUM/IVA treatment. The mean absolute change from baseline at Week 24 in fecal elastase-1 concentrations was 73.1 μg/g (95% CI, 29.40 to 116.80 μg/g), in serum IRT was −295.50 μg/L (95% CI, −416.60 to −174.50 μg/L), and in fecal calprotectin was −106.63 mg/kg (95% CI, −180.60 to −32.66 mg/kg) (Table 3 and Figures 4A–4C). At baseline, all children had fecal elastase-1 values <200 μg/g, indicative of exocrine pancreatic insufficiency. At Week 24, 4 of 28 children (14.3%) with both baseline and Week 24 values had fecal elastase-1 concentrations ⩾200 μg/g (Figure 4D). After Week 24, fecal elastase-1, serum IRT, and fecal calprotectin concentrations showed a rapid reversal during the 2-week washout period (Figures 4A–4C). Through Week 24, nine children (19.6%) experienced pulmonary

Table 2. Adverse Events in Part B

	LUM/IVA ($n = 46$)
Any AE	44 (95.7)
AE by maximum relatedness*	
Not related	15 (32.6)
Unlikely related	13 (28.3)
Possibly related	14 (30.4)
Related	2 (4.3)
AE by maximum severity	
Mild	24 (52.2)
Moderate	18 (39.1)
Severe	2 (4.3)
Serious AE†	5 (10.9)
AE leading to death	0
AE leading to discontinuation	1 (2.2)
AE leading to interruption	2 (4.3)
Most common AEs‡	
Cough	16 (34.8)
Infective pulmonary exacerbation of CF	10 (21.7)
Pyrexia	10 (21.7)
Vomiting	8 (17.4)
Upper respiratory tract infection	6 (13.0)
Constipation	5 (10.9)
Ear infection	5 (10.9)
Positive *Pseudomonas* test result	5 (10.9)
Rhinorrhea	5 (10.9)
Viral upper respiratory tract infection	5 (10.9)

Definition of abbreviations: AE = adverse event; CF = cystic fibrosis; IVA = ivacaftor; LUM = lumacaftor.
Data are expressed as *n* (%). All events in the table are treatment-emergent AEs.
*Relatedness to the trial regimen is as determined by the investigator observing the event.
†Serious AEs were infective pulmonary exacerbation of CF ($n = 3$), post-procedural fever ($n = 1$), and distal intestinal obstruction syndrome ($n = 1$).
‡Only AEs that occurred in ⩾10% of the patients are presented; the table is according to the Medical Dictionary of Regulatory Activities Version 24.1 and preferred term.

exacerbations; the mean rate of pulmonary exacerbations among all participants in part B was 0.6 (SD = 1.5) per patient-year (*see* Table E5). Through Week 24, three children (6.5%) had CF-related hospitalizations; the mean rate of CF-related hospitalizations was 0.2 (SD = 0.7) per patient-year (*see* Table E6). There were no notable changes in respiratory microbiology observed between baseline and Week 24.

Discussion

Here, we report results from a phase 3, open-label trial of LUM/IVA in children aged 1 to <2 years with CF homozygous for *F508del*, the youngest patient population to be treated with LUM/IVA to date. Treatment with LUM/IVA was generally safe and well tolerated, with most AEs mild or moderate in severity. Overall, the safety profile was consistent with the established profile of LUM/IVA in older children, adolescents, and adults. Analysis of PK data showed that the exposure of LUM/IVA in these children was comparable to that in adult patients. LUM/IVA treatment resulted in robust and clinically meaningful decreases in sweat chloride concentration and improvements in biochemical measures of exocrine pancreatic function and intestinal inflammation. Growth parameters, which were on average

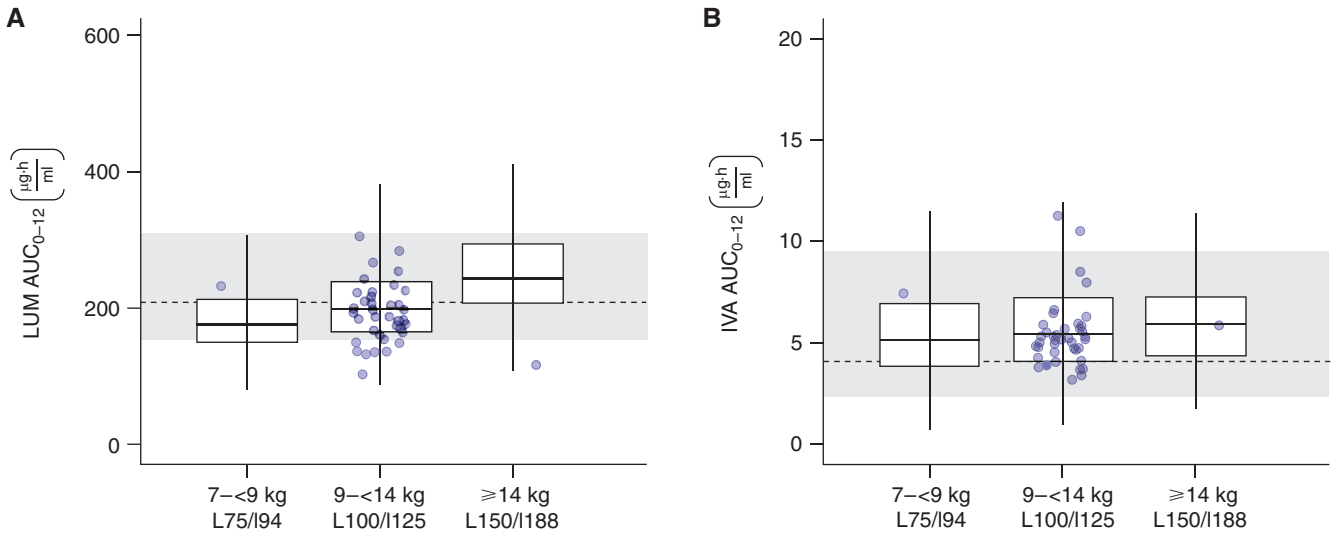

Figure 2. Predicted areas under the curve (AUCs) for LUM (*A*) and IVA (*B*) at steady state for children in part B. In each boxplot, the median is represented by the horizontal line and the box represents the interquartile range. The whiskers represent the largest and smallest values within 1.5 times the interquartile range. Gray bars represent the adult dose exposure, with the upper line of the gray box indicating the 95th percentile of adult AUC values and the lower line of the gray box indicating the 5th percentile. The horizontal dotted lines represent the adult median AUC. Blue dots represent AUC values from individual patients. IVA = ivacaftor; L75/I94 = lumacaftor 75 mg/ivacaftor 94 mg; L100/I125 = lumacaftor 100 mg/ivacaftor 125 mg; L150/I188 = lumacaftor 150 mg/ivacaftor 188 mg; LUM = lumacaftor.

Table 3. Secondary and Other Pharmacodynamic Endpoints from Part B

	Baseline,* Mean (SD)	Mean Absolute Change at Week 24 (SD; 95% CI)
Secondary endpoint		
Sweat chloride concentration, mmol/L	104.20 (7.70); *n* = 35	−29.10 (13.50; −34.80 to −23.40); *n* = 24
Other endpoints		
Weight, kg	11.30 (1.3); *n* = 46	1.30 (0.60; 1.10 to 1.50); *n* = 38
Length, cm	81.10 (4.1); *n* = 46	5.10 (1.70; 4.50 to 5.70); *n* = 38
BMI, kg/m^2	17.17 (1.22); *n* = 46	−0.20 (0.84; −0.47 to 0.08); *n* = 38
Weight-for-age *z*-score	0.46 (0.79); *n* = 46	0.06 (0.33; −0.05 to 0.17); *n* = 38
Weight-for-length *z*-score	0.79 (0.77); *n* = 46	0.04 (0.53; −0.13 to 0.22); *n* = 38
BMI-for-age *z*-score	0.86 (0.77); *n* = 46	0.04 (0.55; −0.14 to 0.22); *n* = 38
Length-for-age *z*-score	−0.25 (0.97); *n* = 46	0.07 (0.52; −0.11 to 0.24); *n* = 38
Fecal elastase-1 concentration, μg/g (normal range ⩾200 μg/g)	9.70 (8.10); *n* = 45	73.1 (112.60; 29.40 to 116.80); *n* = 28
Serum IRT concentration, μg/L (normal range 115–350 μg/L)	647.50 (452.60); *n* = 42	−295.50 (329.90; −416.60 to −174.50); *n* = 31
Fecal calprotectin concentration, mg/kg (normal range 0–162.9 mg/kg)	226.06 (279.26); *n* = 45	−106.63 (186.98; −180.60 to −32.66); *n* = 27

Definition of abbreviations: BMI = body mass index; CI = confidence interval; IRT = immunoreactive trypsinogen.
*Baseline was defined as the most recent nonmissing measurement before administration of the first dose of study drug.

normal at baseline, remained normal over the 24-week treatment period.

Children in this study had AEs that were generally consistent with manifestations of CF observed in this age group. The incidence of transaminase elevations in this population was consistent with the incidence observed in older children and adults (16, 19, 20). One child discontinued LUM/IVA because of AEs of increased alanine aminotransferase and aspartate aminotransferase concentrations. Respiratory AEs were uncommon (2.2%), with a lower incidence than that reported in children aged 2–5 years (10%), children aged 6–11 years (18%), and adolescents and adults aged >12 years (26%) (16, 19, 20).

Analysis of PK data across age groups showed that the ranges of LUM and IVA exposure in children 1 to <2 years of age were consistent with exposure concentrations previously shown to be safe and efficacious in adults with CF taking LUM/IVA. Although the median IVA exposure was higher than in adults, it was comparable to other pediatric groups and was lower than IVA exposure in children 1 to <2 years of age receiving IVA monotherapy. It is acknowledged that part B included only one child in the 7 to <9 kg weight group and one child in the ⩾14 kg weight group. However, exposures for these weight groups were further supported by two children in part A weighing 7 to <9 kg as well as in a prior study conducted in children 2–5 years of age weighing ⩾14 kg (20), noting that no age-related effects affected the PK parameters. Taken together, these results confirm the appropriateness of the weight-based dose selection used in this study.

Sweat chloride concentration is a clinical indicator of CFTR function that is directly related to CF disease severity (23, 24). Children in this study had a mean reduction in sweat chloride concentration of 29.1 mmol/L, from a mean baseline value of 104.2 mmol/L to a mean value of 73.1 mmol/L at Week 24. This decrease in sweat chloride concentration with LUM/IVA treatment is consistent with the decrease reported in children aged 2–5 years (31.7 mmol/L) and is larger than the decreases reported in placebo-controlled and

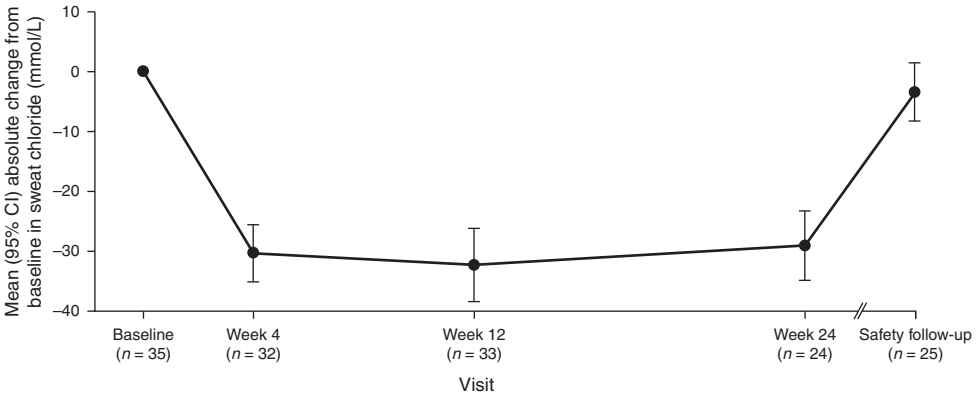

Figure 3. Mean absolute change from baseline in sweat chloride concentration by study visit in part B. Mean absolute changes from baseline are presented with 95% CIs, with numbers of children assessed at each study visit indicated on the *x*-axis. After the 2-week washout period (Weeks 24–26), mean sweat chloride concentrations returned to baseline at safety follow-up visits. CI = confidence interval.

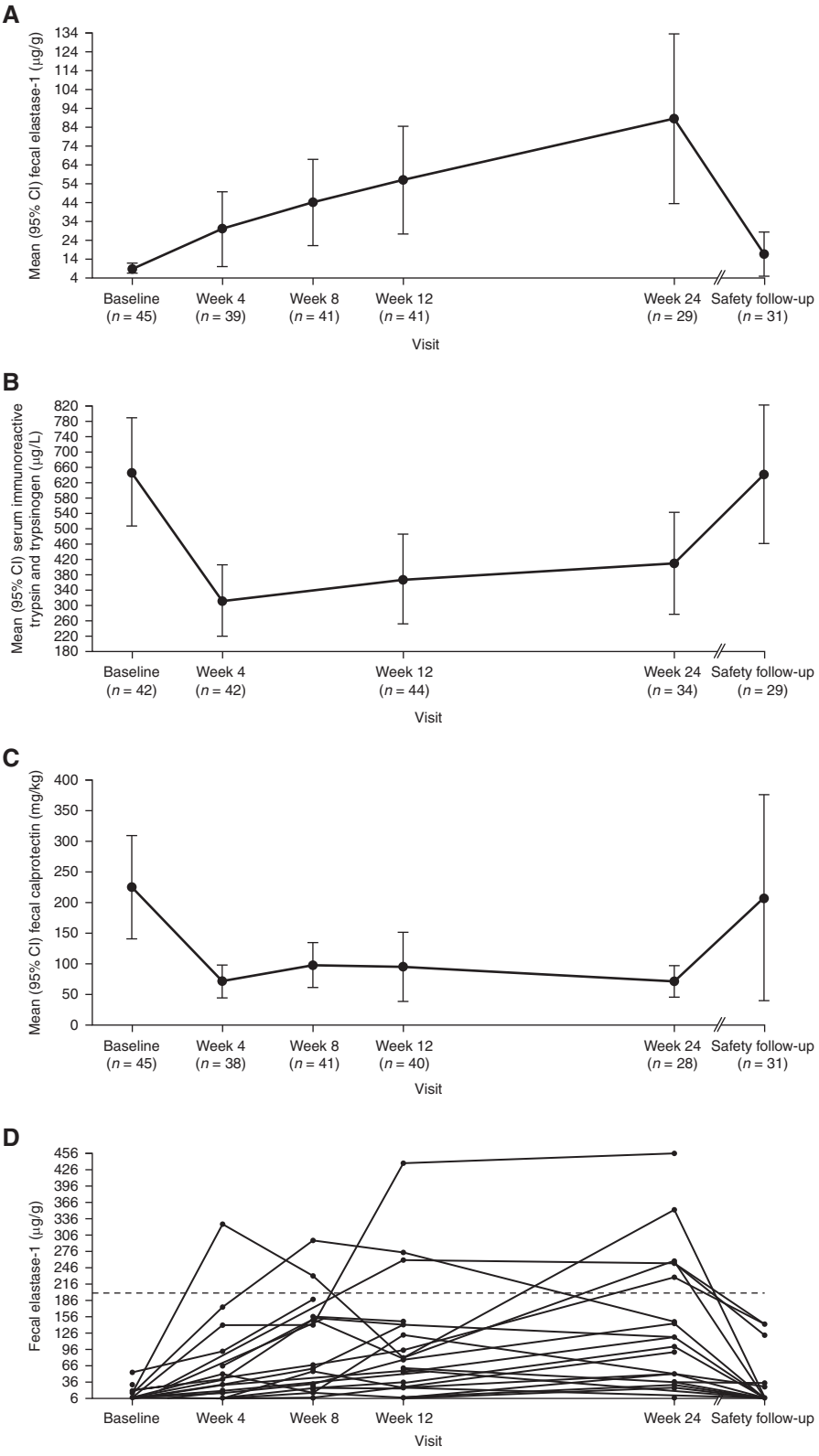

Figure 4. Changes in biomarkers of pancreatic function and intestinal inflammation by study visit in part B. Mean concentrations of fecal elastase-1 (*A*), serum immunoreactive trypsinogen (*B*), and fecal calprotectin (*C*) are shown by study visit. Mean values are presented with 95% CIs, with number of children assessed at each visit indicated on the *x*-axis. (*D*) Fecal elastase-1 concentrations in each child ($n = 46$) at each study visit. Four children who were pancreatic insufficient at baseline (<200 μg/g) had fecal elastase-1 concentrations ⩾200 μg/g at Week 24; 200 μg/g is represented by the horizontal dotted line. CI = confidence interval.

open-label studies in children aged 6–11 years (21.7 and 24.8 mmol/L, respectively) (18–20). The reduction in sweat chloride concentration occurred by Week 4, was sustained through Week 24, and was reversed after a 2-week washout period without LUM/IVA treatment. These results show that treatment with LUM/IVA improves CFTR function in people with CF and the *F*/*F* genotype as young as 1 year of age.

Poor growth has been associated with CF disease progression in children; however, studies have shown that early intervention aimed at improving or maintaining normal growth can positively affect later pulmonary function (25, 26). In a previous clinical trial in children aged 2–5 years with CF, normal growth was maintained during a 24-week LUM/IVA treatment period (20). In the present study, children on average had normal BMI, weight, and length *z*-scores at baseline. After 24 weeks of LUM/IVA treatment, no *z*-scores were found to increase or decrease, a result that is consistent with the result seen in older children and that suggests that normal growth was maintained during the treatment period.

The impaired growth associated with CF is explained in part by early development of exocrine pancreatic insufficiency in infants and children, with subsequent macronutrient malabsorption and continued poor growth (26). Most children who have the *F*/*F* genotype are pancreatic insufficient at diagnosis (27). In the present study, all children had abnormal exocrine pancreatic function at baseline, as indicated by low mean fecal elastase-1. Improvements in fecal elastase-1 concentrations were seen across 24 weeks of LUM/IVA treatment, with a mean absolute increase of 73.1 μg/g. Notably, four children (14.3%) who were pancreatic insufficient at baseline had fecal elastase-1 concentrations in the normal range (≥200 μg/g) at Week 24. This increase in fecal elastase-1 concentration at Week 24 is larger than the increase reported in children aged 2–5 years after receiving 24 weeks of LUM/IVA treatment (52.6 μg/g) (20), suggesting that earlier intervention could lead to improved pancreatic function. This hypothesis of improved pancreatic outcomes with early CFTR modulator intervention is further supported by studies that looked at increases in fecal elastase-1 concentration with IVA treatment in infants aged 4 months to <1 year (166 μg/g) and in children aged 1 to <2 years (164.7 μg/g) and 2–5 years (99.8 μg/g) (21, 22, 28). Improvements were also seen in serum IRT concentrations in the present study, with a mean absolute decrease in serum IRT concentration of 295.5 μg/L at Week 24. Lipase and amylase concentrations were collected as part of safety assessments and are indicators of pancreatic inflammation and injury. Lipase concentrations, which were elevated at baseline, showed a mean absolute change from baseline at Week 24 of −26.77 (SD = 53.92) U/L. Total amylase and pancreatic amylase concentrations were generally stable during the 24 weeks of LUM/IVA treatment (mean absolute change from baseline −4.6 [SD = 27.5] U/L and −2.1 [SD = 5.3] U/L at Week 24, respectively). Markers of intestinal inflammation, such as fecal calprotectin, also improved during the 24 weeks of LUM/IVA treatment. These results suggest that LUM/IVA treatment can improve pancreatic function in children with CF as young as 1 year of age who may already have substantial pancreatic damage.

In the present study, children aged 1 to <2 years treated with LUM/IVA had a rate of pulmonary exacerbations of 0.6 per patient-year and a rate of CF-related hospitalizations of 0.2 per patient-year. These results are consistent with, or lower than, previous observations in children aged 2–5 years treated with LUM/IVA, who had rates of pulmonary exacerbations of 0.9 per patient-year and CF-related hospitalizations of 0.2 per patient-year (20).

A limitation of this study is the lack of a direct comparator group, together with the small sample size, which limits the interpretation of safety and efficacy data. It is important to note, however, that the safety profile of LUM/IVA in the present trial is generally consistent with the safety profile reported in other randomized controlled trials of LUM/IVA treatment in adolescents and adults (29). In addition, the PK exposure of LUM/IVA in these children was consistent with patients aged ≥12 years, suggesting that efficacy in this population may be extrapolated from placebo-controlled studies in patients with CF ≥12 years old that showed improvements in lung function and CFTR function and decreases in pulmonary exacerbations. Consistent with this, children in the present study had improvements in sweat chloride concentration together with improving trends in markers of pancreatic function and intestinal inflammation (fecal elastase-1, serum IRT, and fecal calprotectin), both of which showed rapid reversals during the 2-week washout period after the LUM/IVA treatment period, returning to baseline or near baseline concentrations. Finally, it should be noted that parts of the present study occurred during the SARS-CoV-2 pandemic, when the enforcement of mask wearing and social distancing and restrictions on social interactions might have resulted in decreases in the rate of pulmonary exacerbations in children with CF (30).

Conclusions

LUM/IVA treatment was generally safe and well tolerated in children aged 1 to <2 years with the *F*/*F* genotype, with a PK profile consistent with that of children aged ≥2 years. Robust decreases in sweat chloride concentration together with improving trends in biomarkers of pancreatic function and *z*-scores suggestive of normal growth being maintained were seen during the treatment period. These results support the use of LUM/IVA in this pediatric population and suggest the potential for LUM/IVA to modify CF disease progression in children as young as 1 year of age. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the patients and their families for participating in this trial and the study investigators and coordinators for their contributions to the study. Editorial coordination and support were provided by Wayne Dunlap, and medical writing and editorial support were provided by Nathan Blow, under the guidance of the authors. Both individuals are employees of Vertex Pharmaceuticals Incorporated and might own stock or options in the company. Editorial support was provided by Nicholas Strange of Complete HealthVizion, funded by Vertex Pharmaceuticals Incorporated.

References

1. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, *et al.* The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020;8:65–124.
2. Elborn JS. Cystic fibrosis. *Lancet* 2016;388:2519–2531.
3. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, *et al.* Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245: 1066–1073.
4. Anderson MP, Gregory RJ, Thompson S, Souza DW, Paul S, Mulligan RC, *et al.* Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. *Science* 1991;253:202–205.
5. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. *J Cyst Fibros* 2016;15: 147–157.
6. Nguyen TT, Thia LP, Hoo AF, Bush A, Aurora P, Wade A, *et al.*; London Cystic Fibrosis Collaboration (LCFC). Evolution of lung function during the first year of life in newborn screened cystic fibrosis infants. *Thorax* 2014;69:910–917.
7. Hoo AF, Thia LP, Nguyen TT, Bush A, Chudleigh J, Lum S, *et al.*; London Cystic Fibrosis Collaboration. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. *Thorax* 2012;67:874–881.
8. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet* 2009;373: 1891–1904.
9. Abu-El-Haija M, Ramachandran S, Meyerholz DK, Abu-El-Haija M, Griffin M, Giriyappa RL, *et al.* Pancreatic damage in fetal and newborn cystic fibrosis pigs involves the activation of inflammatory and remodeling pathways. *Am J Pathol* 2012;181:499–507.
10. Stahl M, Steinke E, Graeber SY, Joachim C, Seitz C, Kauczor HU, *et al.* Magnetic resonance imaging detects progression of lung disease and impact of newborn screening in preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2021;204:943–953.
11. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Early lung disease in infants and preschool children with cystic fibrosis: what have we learned and what should we do about it? *Am J Respir Crit Care Med* 2017;195:1567–1575.
12. Van Goor F, Hadida S, Grootenhuis PD, Burton B, Cao D, Neuberger T, *et al.* Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A* 2009;106: 18825–18830.
13. Mall MA, Mayer-Hamblett N, Rowe SM. Cystic fibrosis: emergence of highly effective targeted therapeutics and potential clinical implications. *Am J Respir Crit Care Med* 2020;201:1193–1208.
14. Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med* 2013;1: 158–163.
15. Van Goor F, Straley KS, Cao D, González J, Hadida S, Hazlewood A, *et al.* Rescue of ΔF508-CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. *Am J Physiol Lung Cell Mol Physiol* 2006;290:L1117–L1130.
16. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:1783–1784.
17. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, *et al.* Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017;5:107–118.
18. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, *et al.*; VX14-809-109 investigator group. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2017;5:557–567.
19. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M; VX13-809-011 Part B Investigator Group *. Lumacaftor/ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2017;195:912–920.
20. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, *et al.* Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2–5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med* 2019;7:325–335.
21. Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, *et al.*; ARRIVAL study group. 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. *Lancet Respir Med* 2018;6: 545–553.
22. Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, *et al.* Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation: results of a two-part phase 3 clinical trial. *Am J Respir Crit Care Med* 2021;203:585–593.
23. Accurso FJ, Van Goor F, Zha J, Stone AJ, Dong Q, Ordonez CL, *et al.* Sweat chloride as a biomarker of CFTR activity: proof of concept and ivacaftor clinical trial data. *J Cyst Fibros* 2014;13:139–147.
24. Wilschanski M, Dupuis A, Ellis L, Jarvi K, Zielenski J, Tullis E, *et al.* Mutations in the cystic fibrosis transmembrane regulator gene and in vivo transepithelial potentials. *Am J Respir Crit Care Med* 2006;174: 787–794.
25. Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, *et al.*; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003;142:624–630.
26. Le TN, Anabtawi A, Putman MS, Tangpricha V, Stalvey MS. Growth failure and treatment in cystic fibrosis. *J Cyst Fibros* 2019;18(Suppl. 2):S82–S87.
27. Walkowiak J, Sands D, Nowakowska A, Piotrowski R, Zybert K, Herzig KH, *et al.* Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations. *J Pediatr Gastroenterol Nutr* 2005;40: 199–201.
28. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, *et al.*; KIWI Study Group. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med* 2016;4:107–115.
29. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, *et al.*; TRAFFIC Study Group; TRANSPORT Study Group. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:220–231.
30. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. *Pediatr Pulmonol* 2021;56:1271–1273.