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.

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Abstract

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Background—Ivacaftor is a safe, effective treatment for cystic fibrosis (CF) in patients aged 6 years with a CFTR gating mutation. This open-label, multicenter, phase 3 study assessed ivacaftor in children aged 2–5 years.

Methods—Children aged 2–5 years with a *CFTR* gating mutation received ivacaftor (<14 kg: 50 mg every 12 hours; 14 kg: 75 mg every 12 hours) for 4 days (Part A; n=9) or 24 weeks (Part B; n=34). Primary outcomes were pharmacokinetics (PK) and safety. Other markers of disease were also evaluated.

Findings—Ivacaftor PK was similar to that reported in adults. Common adverse events in Part B included cough (n=19; 55·9%) and vomiting (n=10; 29·4%). Five patients (15%) experienced liver function test (LFT) elevations >8× ULN (study drug interrupted, n=4; study discontinuation, n=1). At week 24, sweat chloride improved on average by −46·9 mmol (SD 26·2, p<0·0001), BMI *z*-score by 0·4 (SD 0·4, p<0·0001), fecal elastase by 99·8 (138·4) μg/g (p=0·0009) and immunoreactive trypsinogen by −20·7 ng/mL (SD 24·0, p=0.0002).

Interpretation—Ivacaftor appears safe and beneficial in young CF children with a gating mutation followed for 24 weeks. The safety profile was similar to that seen in older CF patients, although the frequency of LFT elevations suggests consideration of more frequent monitoring in younger children, particularly those with a history of elevated LFTs. Improvements in sweat chloride and nutritional parameters, with a suggestion of enhanced pancreatic function were observed.

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—www.clinicaltrials.gov **identifier:**

INTRODUCTION

The consequences of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, pancreatic insufficiency, poor nutritional status, and structural lung damage, begin early in infancy.[1–3] Computerized tomography scans in children with CF aged 1 month through 6 years[4] reveal structural lung disease that precedes detection by spirometry. Nutritional deficits are typically the earliest clinical manifestations of CF and are not completely reversed by pancreatic enzyme replacement therapy.[5,6] To improve the trajectory of long-term outcomes, early interventions should be implemented before structural lung disease is established. Few studies have explored chronic therapies for children <6 years, and there have been no studies of treatments targeting the basic defect in CFTR in this population.[7,8]

Ivacaftor, a CFTR potentiator, improves chloride transport through CFTR channels by increasing the channel gating activity of CFTR protein at the cell surface.[9,10] The most common gating mutation is *Gly551Asp-CFTR*, present in approximately 4% of individuals with CF.[11] Phase 3 studies showed ivacaftor to be well tolerated, safe, and effective in

patients aged 6 years with CF and the *Gly551Asp* or other *CFTR* gating mutations, as evidenced by sustained reduction in sweat chloride concentrations and substantial, durable improvements in lung function, respiratory symptoms, and weight gain.[12–14]

This study evaluated the safety, pharmacokinetics (PK) and pharmacodynamics (PD, based on sweat chloride concentrations) of ivacaftor in children with CF aged 2 to 5 years with a CFTR gating mutation on 1 allele and explored the efficacy of ivacaftor in this population.

METHODS

This open-label, single-arm, phase 3 study (clinicaltrials.gov-identifier NCT01705145) was conducted from January 8, 2013 to March 28, 2014 at 15 sites in the United States, United Kingdom, and Canada. An independent ethics committee or institutional review board for each site approved the study protocol. Written informed consent was obtained from each child's parent or legal guardian.

Patients

Children aged 2 to 5 years weighing 8 kg with a confirmed diagnosis of CF[15] and a *CFTR* gating mutation on 1 allele (*Gly551Asp, Gly178Arg, Ser549Asn, Ser549Arg, Gly551Ser, Gly970Arg, Gly1244Glu, Ser1251Asn, Ser1255Pro,* or *Gly1349Asp*) were eligible for enrollment. Exclusion criteria were current or recent (within 4 weeks) pulmonary exacerbation, anemia, liver disease, or renal dysfunction; infection with organisms associated with a more rapid decline in pulmonary function (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa, Mycobacterium abscessus*); or use of moderate or strong cytochrome P450–3A inhibitors or inducers within 2 weeks of ivacaftor dosing.

Study Design

This study comprised two phases (Figure 1). Part A (4 days) assessed PK and safety of ivacaftor and its metabolites. Patients who completed Part A were eligible to enroll in Part B, which assessed longer-term (24-week) safety of ivacaftor. Patients completing Part B could enroll in the treatment arm of an ongoing open-label extension study; those who discontinued early or did not wish to continue ivacaftor therapy could enroll in an observational arm.

Following screening, patients received weight-based ivacaftor every 12 hours: 50 mg if <14 kg, and 75 mg if 14 kg. Study medication was supplied as granules in a capsule, with instructions to break open the capsule and mix the contents in approximately 5 mL of applesauce (or other suitable food) at the time of a high-calorie, high-fat meal.

In Part A, patients received ivacaftor every 12 hours for 4 days. Analysis of PK data from Part A confirmed that these doses were appropriate to use in Part B, in which patients received ivacaftor every 12 hours for 24 weeks. Details regarding study site visits and blood sample collection for PK analysis are provided in the supplemental online appendix.

Outcome Measures

The primary outcomes were PK and safety of ivacaftor. Safety evaluations included adverse events (AEs), clinical laboratory parameters, vital signs, 12-lead electrocardiogram (ECG), coagulation studies, and physical and ophthalmologic examinations. Adverse events were monitored throughout the study, including the screening period and up to 4 weeks ± 7 days after last dose in Part B. Ophthalmologic examinations were performed at screening before each study part, at 12 weeks after last ivacaftor dose in Part A, and at weeks 12 and 24 in Part B.

PK parameters included area under the plasma drug concentration-vs-time curve (AUC) and minimum plasma drug concentration (C_{min}). Secondary outcome measures in Part B included absolute change from baseline in sweat chloride concentration (as a measure of PD) and weight, body mass index (BMI), and height z-scores. Exploratory post-hoc analyses evaluated changes in percent predicted FEV_1 in children   3 years of age,[16] fecal elastase-1, and immunoreactive trypsinogen (IRT).

Additional details regarding study procedures, including palatability assessment and outcome measures, are provided in the supplemental online appendix.

Statistical Analysis

Plasma concentrations of ivacaftor from Parts A and B were evaluated using nonlinear mixed-effects modeling software, version 7 (ICON Development Solutions; Hanover, MD). The PK samples were analyzed using a previously developed population PK model for ivacaftor to describe ivacaftor disposition in patients aged 2 to 5 years.

Because the primary goal was confirmation of ivacaftor PK and safety, the study was not designed to detect statistically significant treatment effects. For Part B, a post-hoc analysis using a one-sample two-sided t test was performed to assess mean absolute change from baseline at week 24 for secondary and exploratory endpoints. In addition, for fecal elastase-1, a Fisher's exact test was performed to compare the proportion of patients with a value >200 µg/g between baseline and the on-treatment period.

Role of funding source

The sponsor designed the protocol in collaboration with the authors, analyzed data, participated in data interpretation, and provided editorial/writing assistance. All authors had full access to the study data and made the final decision to submit for publication.

RESULTS

Study Population

Part A.—Nine patients were enrolled (six male, three female); aged 2 years (n=3), 3 years (n=4), and 4 to 5 years (n=2). All had a *Gly551Asp-CFTR* mutation on   1 allele; the most common genotype was *Gly551Asp/Phe508del* (n=7). All patients received ivacaftor 50 mg every 12 h (n=4) or 75 mg every 12 h (n=5) for the 4-day treatment period and were included in the safety analysis. Eight of these patients were enrolled in Part B. The other

patient turned 6 years of age between study periods and switched to commercially available ivacaftor.

Part B.—Of 34 patients enrolled, 32 had *Gly551Asp* and two had *Ser549Asn* mutations. Ten received ivacaftor 50 mg every 12 h and 24 ivacaftor 75 mg every 12 h. Thirty-three patients (97%) completed the 24-week treatment period; one receiving ivacaftor 50 mg discontinued study drug treatment because of an AE (elevated liver transaminase). Demographic and baseline characteristics are summarized in Table 1.

Primary Outcomes:

Pharmacokinetics—Population PK results (Parts A and B) for ivacaftor indicated that exposures to ivacaftor (Figure 2) for both doses in patients aged 2 to 5 years were similar to each other and to that reported in adults in phase 3 studies. Body weight was the most important predictor of ivacaftor disposition, which was consistent with the previous population PK model for ivacaftor (data not shown). Age and sex did not contribute to variability in ivacaftor PK in a meaningful manner after accounting for body weight.

Safety and Tolerability

Part A.: Eight patients (88·9%) experienced AEs. The only AEs reported by 2 patients were pyrexia (n=4; 44·4%); vomiting, ecchymosis, and rhinorrhea (all n=2; 22·2%).

Part B.: In total, 33 patients (97·1%) experienced AEs (Table 2); the most common were respiratory or gastrointestinal in nature. Most AEs were mild or moderate in severity. In total, two patients (5·9%), both receiving ivacaftor 50 mg every 12 h, experienced severe AEs (transaminase increased and device-related sepsis); they were included in the serious AE (SAE) group (Table 2).

In total, 6 patients experienced 7 serious AEs (SAEs). Of patients receiving ivacaftor 50 mg every 12 hours, 4 SAEs occurred in 3 patients (30%): infective pulmonary exacerbation of CF, device-related sepsis, positive *Pseudomonas aeruginosa* culture, and increased transaminases. In the ivacaftor 75 mg every 12 hours group, 3 SAEs occurred in 3 patients (12·5%): infective pulmonary exacerbation of CF, vomiting, and convulsion. Increased transaminases was the only SAE considered related to ivacaftor and the only AE that resulted in study discontinuation.

Five patients (14·7%) experienced elevations in alanine transaminase (ALT) or aspartate transaminase (AST) >8× the upper limit of normal (ULN) (n=3, ivacaftor 50 mg; n=2, ivacaftor 75 mg). All had a history of elevated transaminases before enrollment and had elevated LFTs (>2× but <3x ULN) at baseline (screening exclusion criteria: 3× ULN). In four of these patients, ivacaftor treatment was interrupted, in accordance with the protocol. In all four patients, LFTs returned to baseline levels following interruption of ivacaftor. The remaining patient discontinued the study due to an SAE of severe transaminases after 18 days of treatment. No patients had notable bilirubin, alkaline phosphatase, or gamma-glutamyl transferase elevations or clinical symptoms related to the LFT elevations (Additional details in the supplemental online appendix).

Eight additional patients experienced AEs resulting in study drug interruption in Part B: In the 50 mg group, croup (n=1), and vomiting and device-related sepsis (n=1); in the 75 mg group, vomiting (n=2), gastroenteritis (n=1), retching (n=1), cough (n=1), and rash (n=1). These AEs were not deemed study-drug related by the site investigators.

No new cataracts or lens opacities or other clinically relevant findings for chemistry, hematology, or ECG were reported. The mean adherence to study treatment in Part B was 96·1%; 31 patients had an adherence of 80% or higher. No patients were discontinued because of non-adherence.

Secondary endpoints:

Pharmacodynamics (Sweat Chloride As a Measure of CFTR Function)—By week 2, a mean (SD) decrease of 44·0 (20·3) mmol/L in sweat chloride concentrations was observed (p<0·0001). This effect was sustained through week 24, with a mean (SD) absolute change from baseline of −46·9 (26·2) mmol/L (p<0·0001 vs baseline; Figure 3). Similar changes from baseline to week 24 in sweat chloride were observed in both groups (50 mg, −47·1 [24·3] mmol/L; p=0·002; 75 mg, −46·8 [27·6] mmol/L; p<0·0001).

Palatability—Palatability assessments indicated that the ivacaftor granules were acceptable when administered in soft food. Overall, all 9 patients in Part A and 32 (94·1%) in Part B fully consumed the first dose of study drug.

Nutritional measures—Improvements in weight and BMI z-scores were similar in both dose groups. Mean weight z-scores increased by week 2 and were sustained throughout the treatment period to week 24 (0·2 [0·3]; p<0·0001; Figure 4A). Similarly, BMI z-scores increased during the 24-week treatment period (0·4 [0·4]; p<0·0001; Figure 4B). Height z-scores were similar to baseline at week 24 (−0·01 [0·3]; p=0·84; Figure 4C).

Exploratory endpoints:

Pancreatic function—In total, 27 patients contributed samples for fecal elastase-1 measurements. At baseline, measurements were: <50 μg/g [n=25], 53 μg/g [n=1], and >500 μg/g [n=1]). Overall, fecal elastase-1 increased on average by 99·8 (138·4) μg/g after 24 weeks of treatment (p=0·0009); improvements were observed in both dose groups (50 mg: 127·9 μg/g [191·8]; 75 mg, 93·5 [128·3] μg/g; Figure 5). Overall, 26 (76·5%) patients at baseline and 24 (70·6%) patients at week 24 had fecal elastase-1 measurements <200 μg/g, and 1 (2·9%) patient at baseline and 7 (20·6%) patients at week 24 had fecal elastase-1 measurements   200 μg/g (Fisher's exact test, P=0·0504). Eleven (42·3%) patients had   1 on-treatment value >100 μg/g and 10 patients (38·5%) demonstrated no improvement.

Overall, IRT (a marker of pancreatic stress) decreased from baseline by an average of 20·7 (24·0) ng/mL at week 24 (p=0·0002); similar improvements were noted in both ivacaftor doses (mean [SD] changes: 50 mg, −24·4 [21·7] ng/ml; 75 mg, −19·5 [25·1] ng/mL). Decreases in IRT were seen as early as week 2 (Figure 6). Patients with substantial improvements in fecal elastase-1 tended to be those with higher baseline IRT levels.

Lung function—Baseline spirometry measurements were submitted for 23 patients, of whom 21 had on-treatment measurements. Independent over-reading determined that only three participants (14·3%) had acceptable measurements at baseline and one time point on treatment, precluding any analysis of these data.

DISCUSSION

This report describes the first clinical study of a CFTR potentiator, ivacaftor, in children aged 2 to 5 years with CF and a *CFTR* gating mutation. Based on ivacaftor exposure similar to that observed in adults, ivacaftor 50 mg every 12 hours or 75 mg every 12 hours appear to be appropriate doses for children aged 2 to 5 years. The formulation was also determined to be palatable, with high treatment adherence (96% overall over 24 weeks). Over the 24-week open-label treatment period, improvements in sweat chloride and nutritional parameters, as well as a suggestion of improvement in markers of pancreatic function, were observed.

We selected an open-label, single-arm study design due to small group size, the *Gly551Asp-CFTR* mutation being present in only about 4% of CF patients worldwide.[11] As the primary objective was to assess safety, the number of children exposed to active drug could be maximized with this design. Additionally, PK evidence of appropriate dose, along with evidence of CFTR functional correction via the biomarker sweat chloride, was sufficient to allow extrapolation of presumed clinical efficacy from the older groups.

Both ivacaftor doses were generally well tolerated; most AEs were consistent with those expected for patients with CF and largely considered unrelated to study drug. However, the frequency of elevated LFTs exceeded that in studies of ivacaftor in older patients.[12,13] Five of 34 patients (15%) experienced significant (>8× ULN) increases in transaminases; four required dose interruption and one discontinued. All five had a history of elevated LFTs, with levels above the ULN, but within the protocol-accepted range. Although reduction in LFTs after interruption of ivacaftor suggests the drug played a role in these AEs, patients also had other potentially contributing factors (concomitant antibiotic use or intercurrent viral infection). Further, as all LFT elevations were asymptomatic, they were likely to have been undetected in standard clinical practice, in which monitoring is less frequent. The prevalence of transient LFT abnormalities in this age group is unknown and absence of a control group makes interpretation more difficult. Nonetheless, these data suggest that additional monitoring should be considered in children 2 to 5 years old receiving ivacaftor, particularly in the presence of any additional risk factors such as prior LFT elevation or whilst being treated with hepatotoxic drugs. An on-going long-term extension study, KLIMB, is collecting additional safety data.

The improvement observed in sweat chloride was similar in magnitude to that in studies in older age groups that showed associated improvements in pulmonary function and weight.[12,13,17] In our view, this confirms functional efficacy at the cellular level, but is no surrogate for clinical improvement. However, improvement in nutritional status and a suggestion of improvement in markers of exocrine pancreatic function indicate a possible clinical effect. Children entered this study with a mean weight z-score of −0·2, which significantly (p<0·0001) increased by a mean of 0·2 after 24 weeks. Previous trials of ivacaftor in older

populations similarly demonstrated a significant increase in weight. As previous studies have suggested the CF pancreas to be irreversibly damaged from early life,[2,3] restoration of pancreatic exocrine function has been considered an unlikely explanation for nutritional improvements observed with ivacaftor.[12–14] Studies based on intraluminal monitoring provide compelling evidence in support of improvement in intestinal pH related to restoration of CFTR-mediated bicarbonate secretion[18]; thus, improved absorption has been the leading hypothesis. Our study is the first to explore the effects of ivacaftor on pancreatic exocrine function. Fecal elastase-1, which was in the insufficient range in 26/27 (96·3%) patients at baseline, rose above the clinical cutoff for exocrine pancreatic insufficiency of 200 μg/g at least once in >25% of children, with more modest increases in others. There were also overall reductions in the serum pancreatic stress marker (IRT), which may support this observation; however, because this test is not widely used outside the neonatal screening period, results should be interpreted cautiously. These preliminary data suggest, for the first time, a window in early life wherein at least partial restoration of pancreatic exocrine function may be possible, and warrant further exploration of the effect of CFTR modulators on exocrine pancreatic function in infants with CF. The effect of ivacaftor on endocrine pancreatic function and risk of development of CF-related diabetes is not well understood and was not explored in this study.

Unfortunately, this study could not generate meaningful data on pulmonary function because only 3 patients produced research-quality measurements and we did not provide specific training or quality control in preschool lung function testing.[19] Although some have reported meaningful spirometry in this age group,[20,21] future studies in this group should consider lung clearance index (LCl) from multiple-breath washout tests as an alternative.[22] LCI, is a non–effort-dependent test with increased sensitivity to detect early disease than spirometry. [21,23–25]

In conclusion, this study confirmed a safe and tolerable dose of an acceptable formulation of ivacaftor in children 2 to 5 years old with a *CFTR* gating mutation, although liver function appears to require closer monitoring in this age range, particularly among those with a history of elevated LFTs. Ivacaftor administered for 6 months led to significant declines in sweat chloride concentrations, nutritional benefits, and a suggestion of improvement in markers of pancreatic exocrine function. The cohort is undergoing long-term follow-up in an extension study, during which durability of these effects and longer-term safety will be assessed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Research in context

Evidence before this study

Ivacaftor, a CFTR potentiator that corrects a gating defect, is the first CFTR modulator to show a clinical benefit in adults. As CFTR-directed therapy is expected to be most beneficial before secondary sequelae of CFTR dysfunction take hold (e.g., infection and inflammation), it is imperative to define the safety of ivacaftor in younger populations. A search of PubMed was conducted on May 1, 2015, using the terms "ivacaftor" or "Kalydeco" or "VX770" AND "G551D" or "gating" and "pediatric," with no restrictions on publication date or language.

Added value of this study

This study establishes the safety, dose, and therapeutic benefit of ivacaftor in young children (age 2 to 5 years) with CF. Ivacaftor at 50 mg (<14 kg) or 75 mg (14 kg) every 12 hours is well tolerated by CF toddlers, with improvements in sweat chloride and nutritional measures, and a suggestion of benefit to exocrine pancreatic function. Due to age limitations, impact on lung function was not assessed. Reported side effects are similar to those in the general CF population, although children with previous CF liver disease may experience transient elevation in transaminases.

Implications of all the available evidence

The findings of this study confirm the safety and potential therapeutic benefit of ivacaftor for CF children with a CFTR gating mutation. Based on the results of this study, ivacaftor should be considered (and has been approved by the FDA) for treatment of CF patients aged 2 years and older with a CFTR gating mutation (Gly551Asp, Gly1244Glu, Gly1349Asp, Gly178Arg, Gly551Ser, Ser1251Asn, Ser1255Pro, Ser549Asn, Ser549Arg).
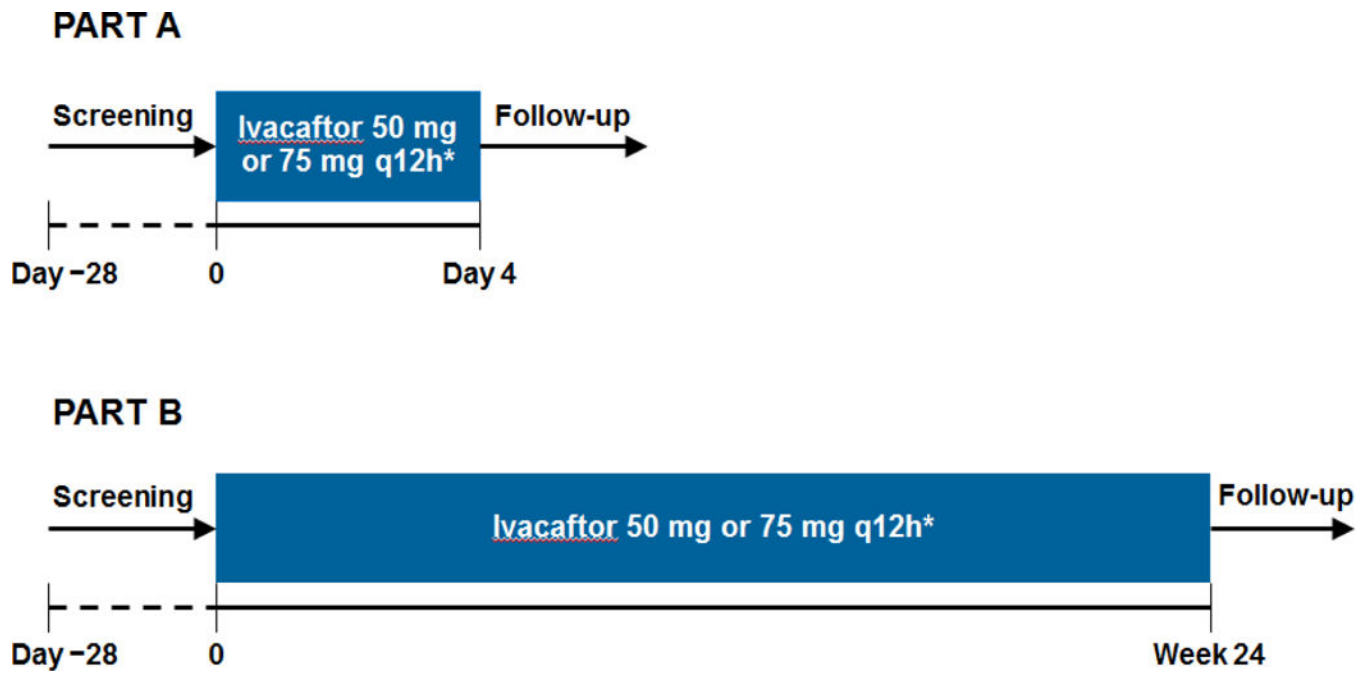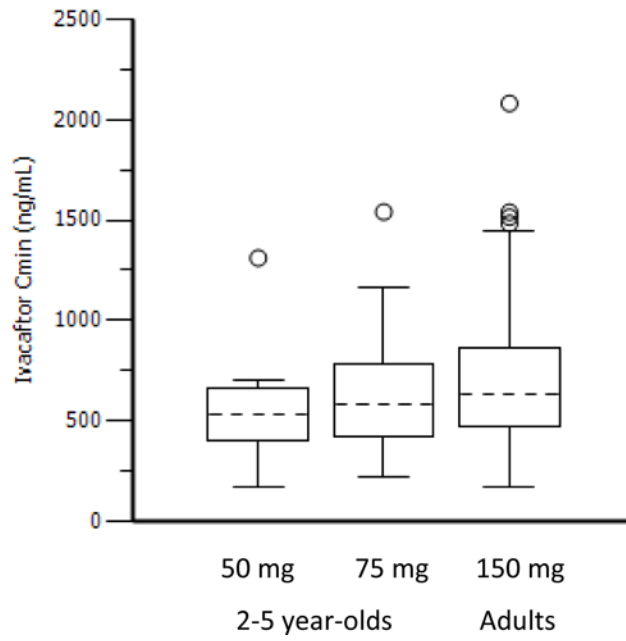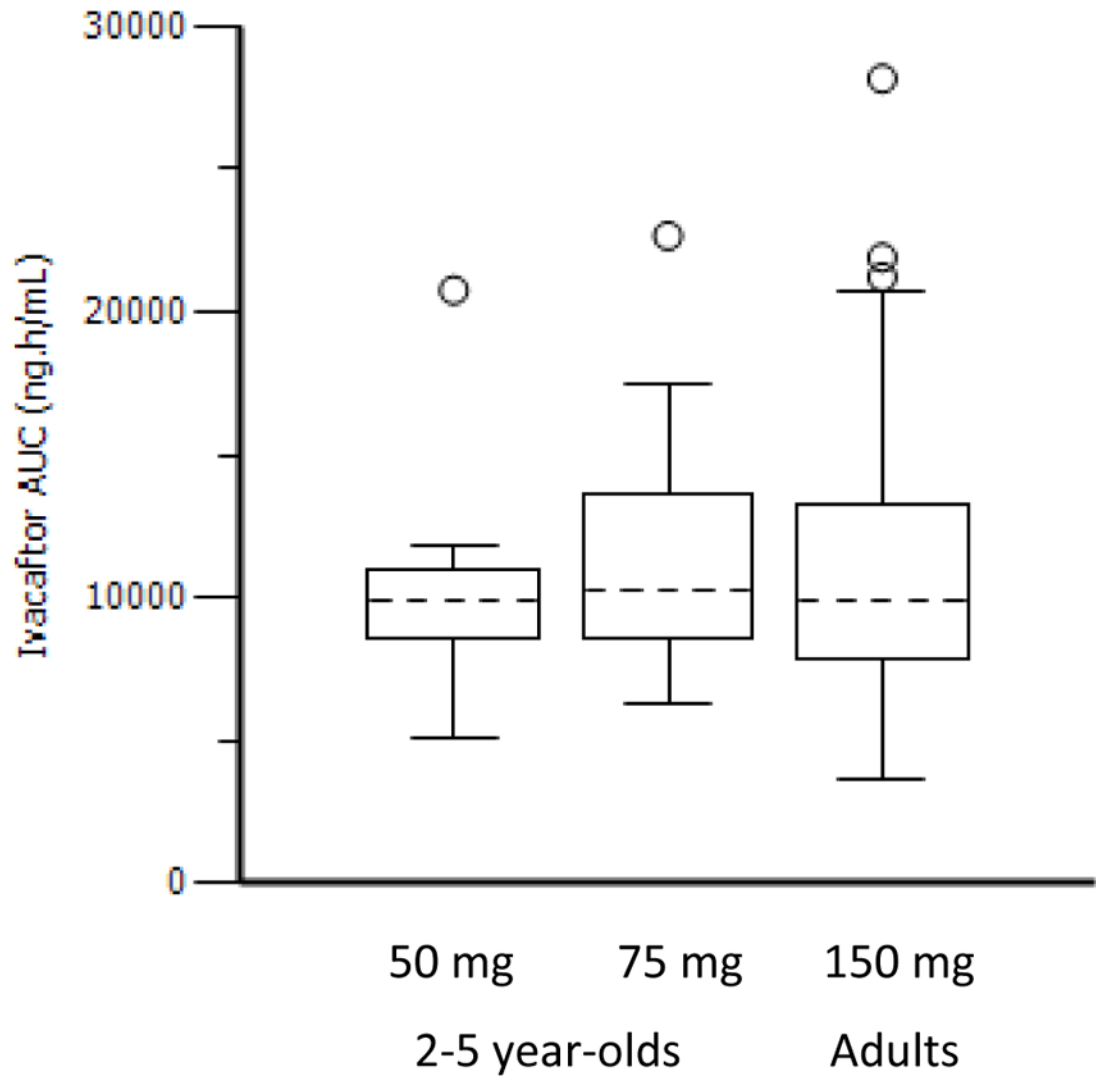
PART A

Screening → Ivacaftor 50 mg or 75 mg q12h* → **Follow-up**

Day −28 — 0 — Day 4

PART B

Screening → Ivacaftor 50 mg or 75 mg q12h* → **Follow-up**

Day −28 — 0 — Week 24

Figure 1.
Study design.
*Weight-based dosing: 50 mg every 12 h for patients with body weight <14 kg; 75 mg every 12 h for patients   14 kg.

A.

B.

Figure 2.
Ivacaftor C_{min} distribution (A) and ivacaftor AUC distribution (B) in children aged 2–5 years compared with adults from previous Phase 3 studies.

Dashed black lines in the center of the boxes are medians, boxes are the interquartile range (IQR), whiskers are 1·5•IQR, and open circles are outliers.

AUC, area under the plasma drug concentration-vs-time curve; C_{min}, minimum plasma drug concentration.
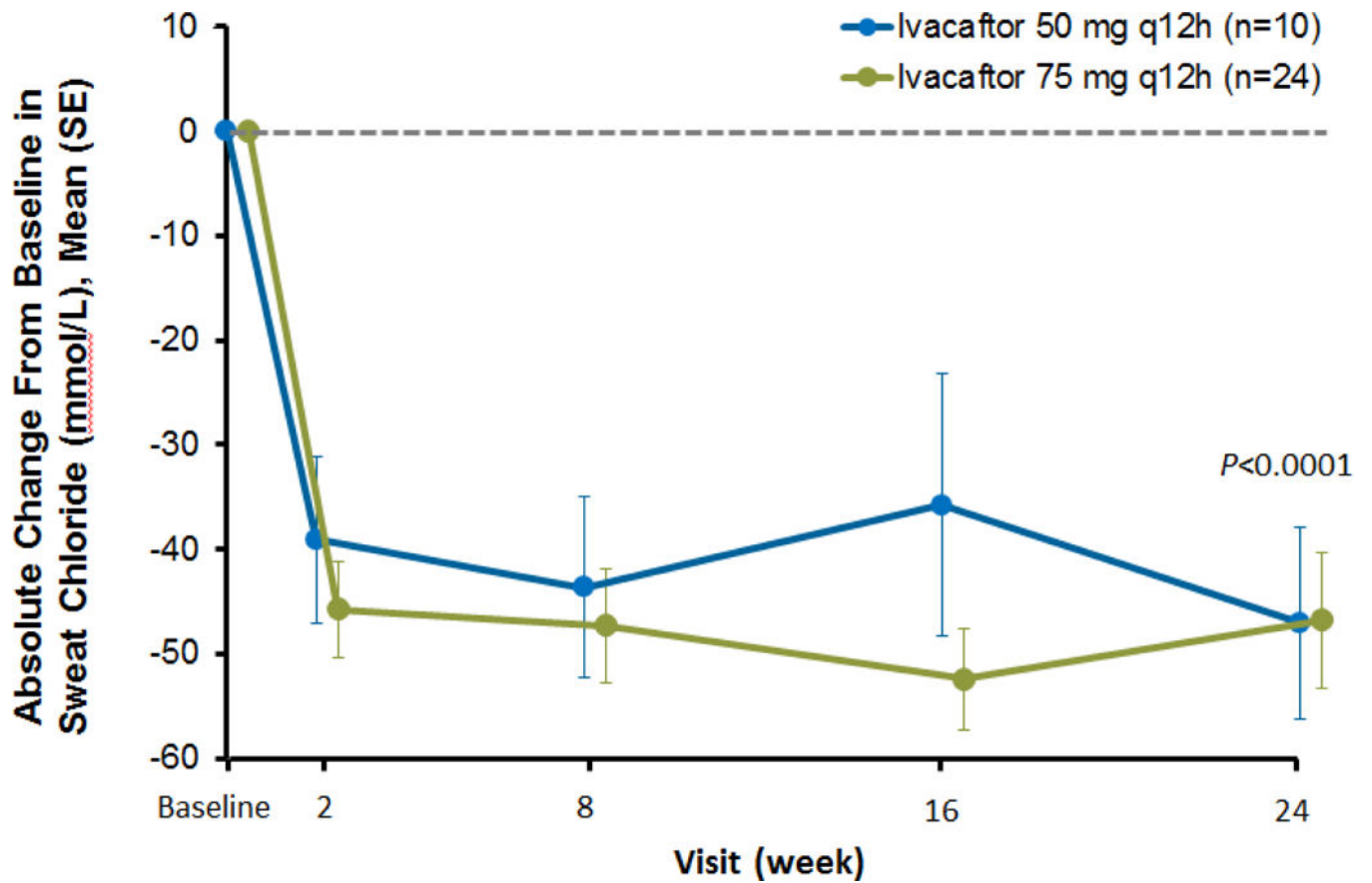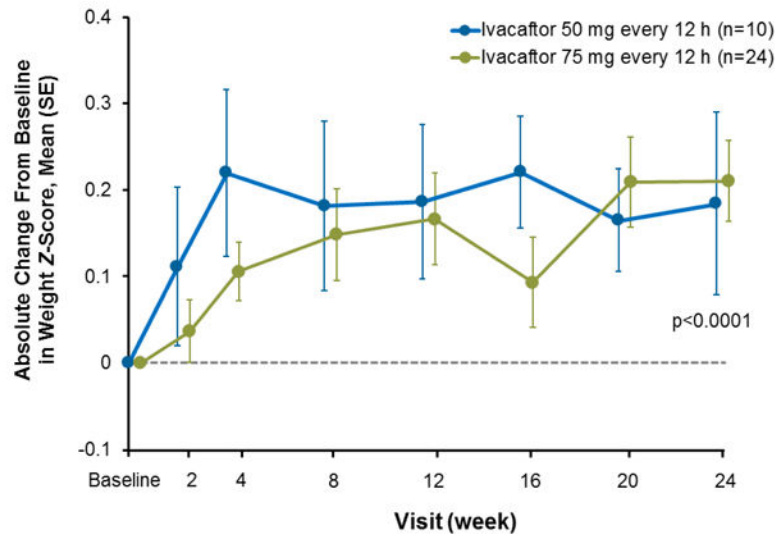
Figure 3.
Absolute change from baseline in sweat chloride concentrations during the 24-week ivacaftor treatment period, presented as means and SD for each dose group at each time point

A.
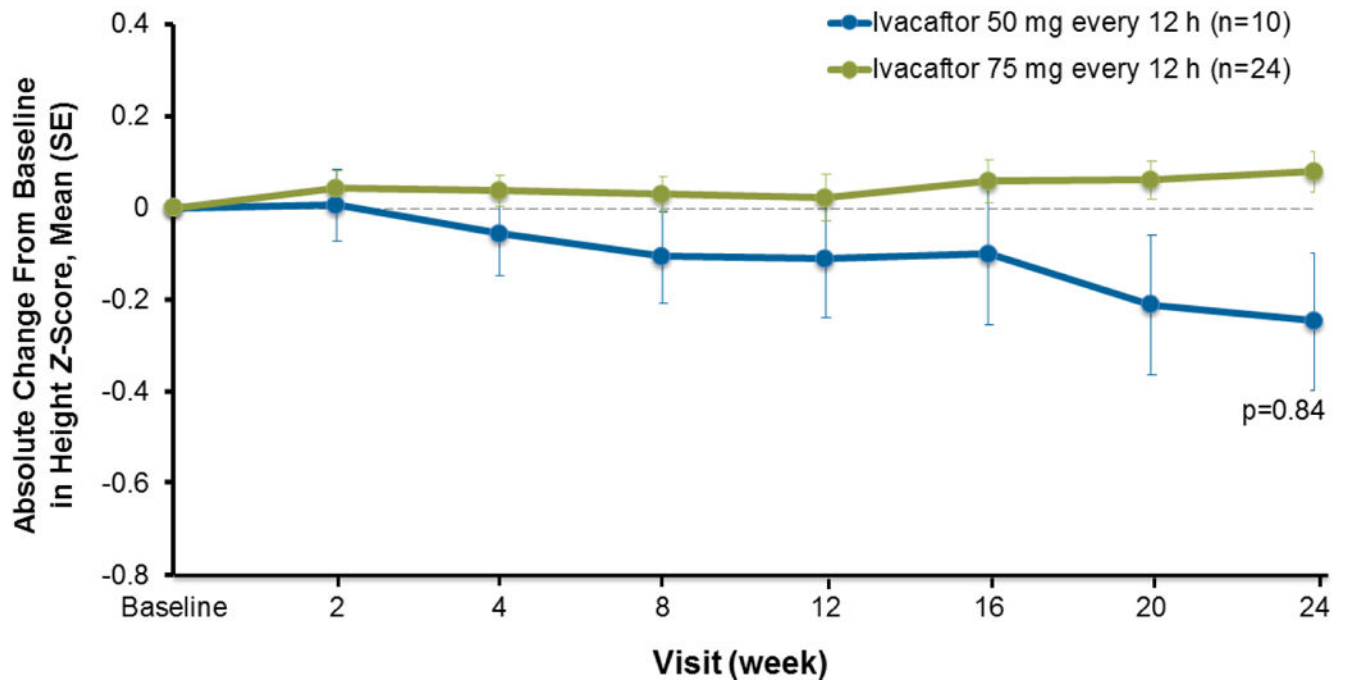

B.
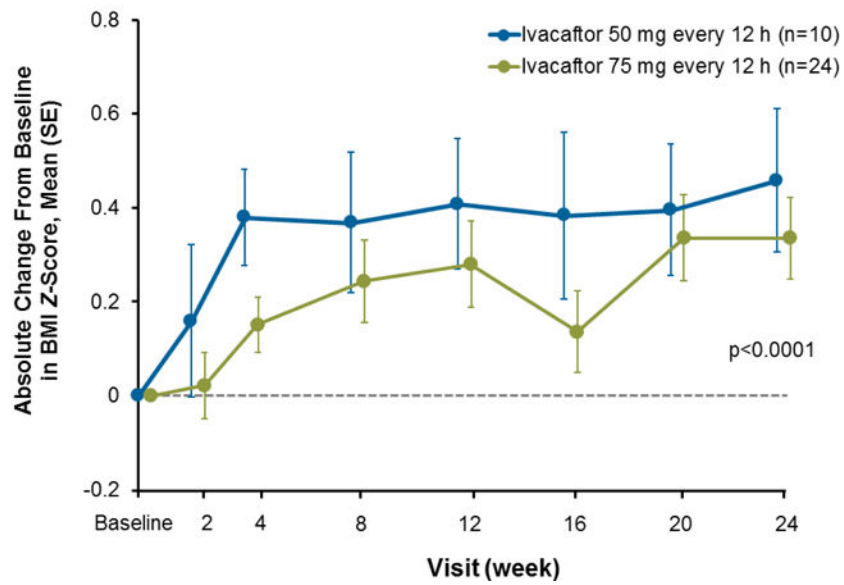
C.

Figure 4.
Absolute change from baseline in weight z-score (A), BMI z-score (B), and height z-score
(C) during the 24-week ivacaftor treatment period, presented as means and SD for each dose
group at each time point
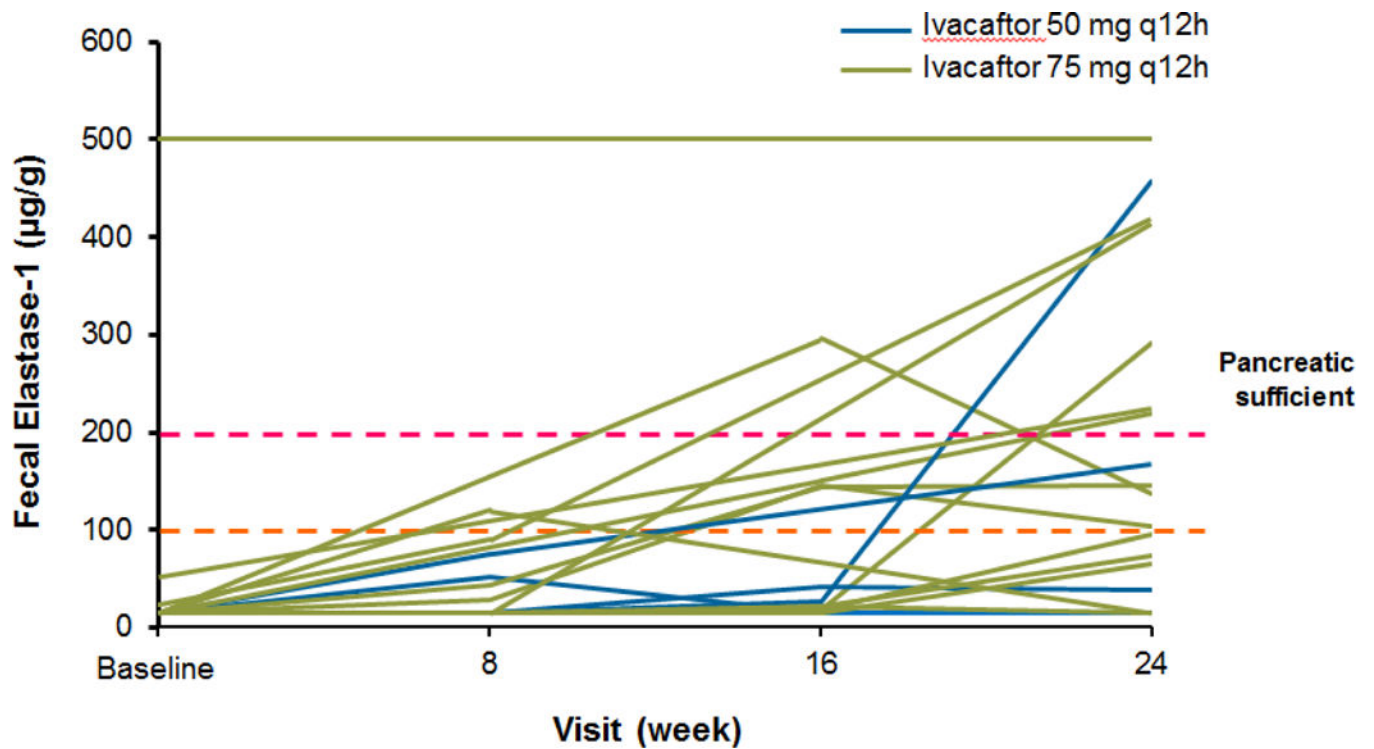
Figure 5.
Fecal elastase-1 for individual patients during 24-week ivacaftor treatment period among the 27 patients with fecal elastase data available. The one patient with baseline fecal elastase-1 >500 µg/g (upper limit of quantitation) had the *Gly551Asp/Arg117His* mutation and was not receiving pancreatic enzyme supplementation. A fecal elastase <200 mcg/g is associated with exocrine pancreatic insufficiency.[15]

Figure 6.
Immunoreactive trypsinogen concentrations for individual patients during the 24-week
ivacaftor treatment period.

Table 1.

Patient Demographics and Baseline Characteristics (Part B)

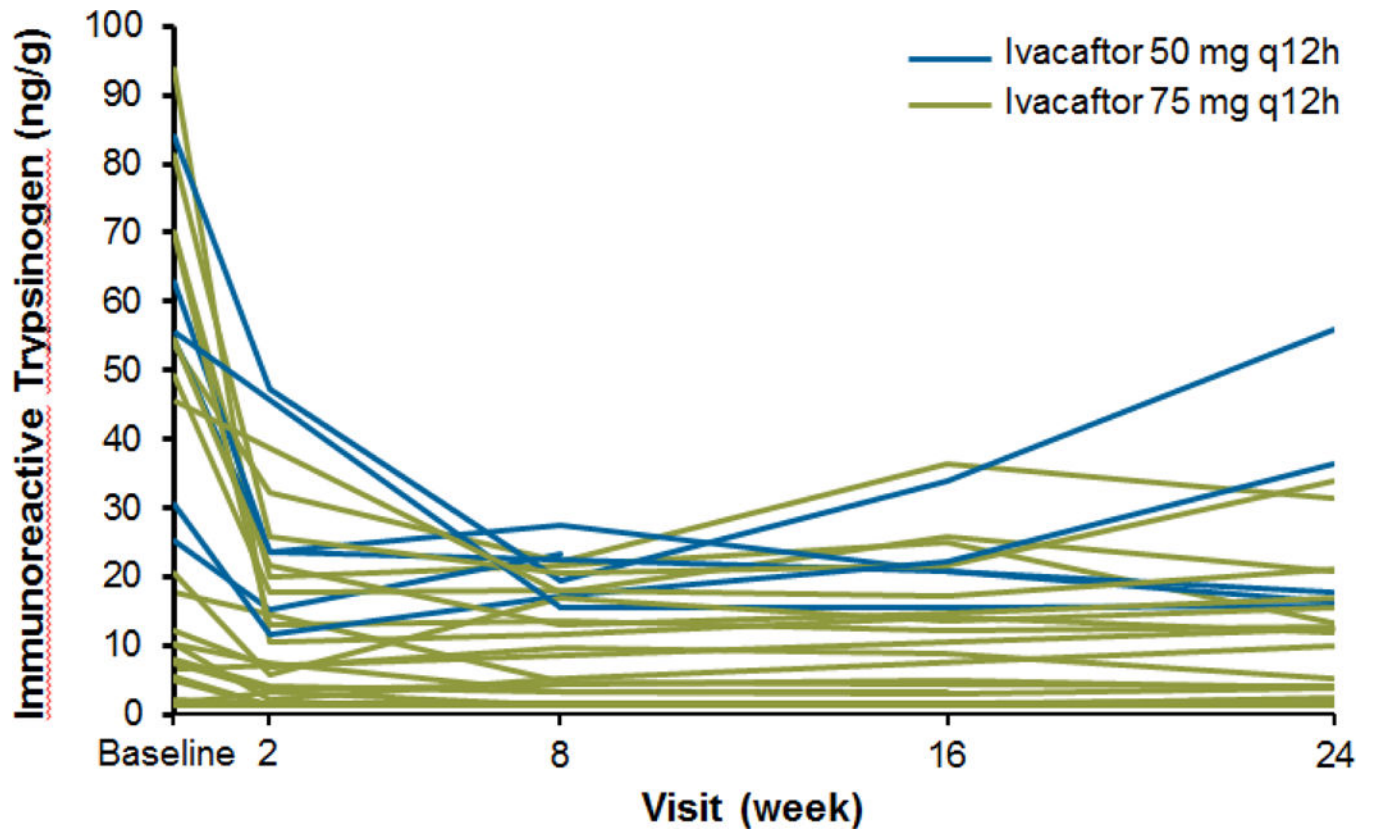| Characteristic	Overall (N=34)
Sex, n (%)	
Male	28 (82·4)
Female	6 (17·6)
Race, n (%)	
White	34 (100·0)
Ethnicity, n (%)	
Hispanic	1 (2·9)
Genotype, n (%)	
Gly551Asp/Phe508del	26 (76·5)
Gly551Asp/Lys447ArgfsX2	1 (2·9)
Gly551Asp/c.1585–1G>A	1 (2·9)
Gly551Asp/Leu1258PhefsX7	1 (2·9)
Gly551Asp/Leu88IlefsX22	1 (2·9)
Gly551Asp/Gly551Asp	1 (2·9)
Gly551Asp/Arg117His	1 (2·9)
Ser549Asn/Phe508del	1 (2·9)
Ser549Asn/Arg553X	1 (2·9)
Age category, years, n (%)	
2	9 (26·5)
3	11 (32·4)
4 to 5	14 (41·2)
Weight *z*-score, mean (SD)	−0·2 (0·8)
Height *z*-score, mean (SD)	−0·3 (0·8)
Fecal elastase-1 <200 μg/g, n (%) [*]	26 (96.3)
Immunoreactive trypsinogen (ng/mL), mean (SD)	33·6 (29·8)
Sweat chloride (mmol/L), mean (SD)	97·9 (14·0)

[*] Of patients with fecal elastase-1 data available (n=27); FE-1 <200 mcg/g is diagnostic if exocrine pancreatic insufficiency[15]; *Gly551Asp* was formerly *G551D*

Table 2.

Serious Adverse Events and Adverse Events Occurring in ≥3 Patients

Adverse Event, n (%)	Ivacaftor 50 mg Every 12 h (n=10)	Ivacaftor 75 mg Every 12 h (n=24)	Overall (N=34)
Serious Adverse Events (Part B)			
Infective pulmonary exacerbation of CF	1 (10·0)	1 (4·1)	2 (5·9)
Device related sepsis	1 (10·0)	0	1 (2·9)
Pseudomonas test positive	1 (10·0)	0	1 (2·9)
Transaminases (hepatic enzymes) increased	1 (10·0)	0	1 (2·9)
Vomiting	0	1 (10·0)	1 (2·9)
Convulsion	0	1 (10·0)	1 (2·9)
AEs Occurring in >3 Patients (Part B)			
1 AE	10 (100·0)	23 (95·8)	33 (97·1)
Cough	4 (40·0)	15 (62·5)	19 (55·9)
Vomiting	3 (30·0)	7 (29·2)	10 (29·4)
Nasal congestion	4 (40·0)	5 (20·8)	9 (26·5)
Upper respiratory tract infection	1 (10·0)	7 (29·2)	8 (23·5)
Rhinorrhea	2 (20·0)	5 (20·8)	7 (20·6)
Positive respiratory culture *	0	6 (25·0)	6 (17·6)
Pyrexia	4 (40·0)	2 (8·3)	6 (17·6)
Hepatic enzyme increased	3 (30·0)	2 (8·3)	5 (14·7)
Infective pulmonary exacerbation of CF	1 (10·0)	4 (16·7)	5 (14·7)
Constipation	0	4 (16·7)	4 (11·8)
Rash	2 (20·0)	2 (8·3)	4 (11·8)
Croup, infectious	2 (20·0)	1 (4·2)	3 (8·8)
Otitis media	2 (20·0)	1 (4·2)	3 (8·8)
Productive cough	0	3 (12·5)	3 (8·8)
Sinusitis	2 (20·0)	1 (4·2)	3 (8·8)

Adverse events were coded by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities v. 15·1 and were summarized descriptively.

*
Test was positive for *Haemophilus* in three patients, for methicillin-resistant *Staphylococcus aureus* in two patients, and for *Moraxella* in one patient. AE, adverse event; CF, cystic fibrosis. A serious adverse event (SAE) was defined as any adverse event that met any of the following criteria: (1) Fatal (death, regardless of cause occurring during participation in the study or occurred after participation in the study and was suspected of being a delayed toxicity due to administration of the study drug), (2) Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred, (3) Inpatient hospitalization or prolongation of hospitalization, with the exception of planned or elective hospitalization, (4) Persistent or significant disability/incapacity, (5) Congenital anomaly or birth defect, (6) Important medical event, that, based upon appropriate medical judgment, jeopardized the subject or required medical or surgical intervention to prevent 1 of the outcomes