



## Original article

# VOCAL: An observational study of ivacaftor for people with cystic fibrosis and selected non-*G551D-CFTR* gating mutations<sup>☆</sup>



Nicholas J. Simmonds<sup>a,\*</sup>, C. Kors van der Ent<sup>b</sup>, Carla Colombo<sup>c</sup>, Nils Kinnman<sup>d,1</sup>,  
Cynthia DeSouza<sup>d,2</sup>, Teja Thorat<sup>d</sup>, Marci L. Chew<sup>d,3</sup>, Keval Chandarana<sup>d</sup>, Carlo Castellani<sup>e</sup>

<sup>a</sup> Adult Cystic Fibrosis Centre, Royal Brompton Hospital, London, UK, and National Heart and Lung Institute, Imperial College London, London, UK

<sup>b</sup> Department of Pediatric Respiratory Diseases, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>c</sup> Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

<sup>d</sup> Vertex Pharmaceuticals Incorporated, Boston, MA, USA

<sup>e</sup> Cystic Fibrosis Centre, IRCCS Istituto Giannina Gaslini, Genoa, Italy

## ARTICLE INFO

## Article history:

Received 8 February 2022

Revised 9 May 2022

Accepted 15 May 2022

Available online 23 May 2022

## Keywords:

Cystic fibrosis

Ivacaftor

*CFTR* gating mutation

Real-world experience

Lung function

Healthcare resource utilization

## ABSTRACT

**Background:** VOCAL was an observational study of the effect of long-term ivacaftor on real-world clinical outcomes and healthcare resource utilization (HCRU) in people with cystic fibrosis (pwCF) in Italy, the Netherlands, and the UK.

**Methods:** pwCF aged  $\geq 6$  years with non-*G551D-CFTR* gating mutations were eligible. Prospective data were collected up to 48 months after enrollment; retrospective data were collected to ensure that 12 months of pre-ivacaftor data were available. Endpoints included absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) and measures of nutritional status. Pulmonary exacerbation (PEX) rates, HCRU, and respiratory microbiology during ivacaftor treatment were compared with data from the 12-month period before initiation.

**Results:** Seventy-three eligible pwCF were enrolled and received ivacaftor; 65 (89.0%) completed the study (48 [65.8%] completed  $\geq 48$  months of ivacaftor). During the first 6 months of ivacaftor, ppFEV<sub>1</sub>, body mass index (BMI), and BMI-for-age z-score showed least-squares mean absolute improvements of 10.8 percentage points, 0.79 kg/m<sup>2</sup>, and 0.54, respectively; improvements were maintained through 48 months. Rates of PEX, antibiotic use due to PEX, and hospitalization decreased by  $>50\%$  during ivacaftor treatment compared with before ivacaftor. The number of respiratory cultures and sputum was lower post-ivacaftor, as was the percentage of pwCF with positive respiratory cultures for 3 of 9 pathogens evaluated (*Pseudomonas aeruginosa*, *Aspergillus fumigatus*, *Stenotrophomonas maltophilia*). Reported safety results were consistent with CF and ivacaftor's known safety profile.

**Conclusions:** These results demonstrate the positive long-term effectiveness of ivacaftor on clinical outcomes and HCRU in pwCF with non-*G551D-CFTR* gating mutations in real-world settings.

© 2022 The Authors. Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

**Abbreviations:** AE, adverse event; BMI, body mass index; CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulator; ECFS, European Cystic Fibrosis Society; HCRU, healthcare resource utilization; IEC, independent ethics committee; IRB, institutional review board; LS, least squares; MMRM, mixed model for repeated measures; PEX, pulmonary exacerbation; ppFEV<sub>1</sub>, percent predicted forced expiratory volume in 1 second; pwCF, people with cystic fibrosis.

<sup>☆</sup> **Data from this study were presented at the following meetings:** *First interim analysis:* 41st Annual European Cystic Fibrosis Conference; June 6–9, 2018; Belgrade, Serbia. *23rd Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR);* May 19–23, 2018; Baltimore, MD, USA. *Second interim analysis:* BTS (British Thoracic Society) Winter Meeting; December 4–6, 2019; London, UK. *Third interim analysis:* 34th Annual North American Cystic Fibrosis Conference (virtual); October 7–23, 2020. *Final analysis:* European Respiratory Society

## 1. Introduction

Cystic fibrosis (CF) is a progressive, life-shortening, genetic disease that affects more than 49,000 people in Europe and more than 80,000 people worldwide [1, 2]. It is caused by mutations in

Virtual International Congress; September 5–8, 2021. BTS (British Thoracic Society) Winter Meeting (virtual); November 24–26, 2021.

\* Corresponding author at: Adult Cystic Fibrosis Centre, Royal Brompton Hospital, Sydney Street, London, UK, SW3 6NP.

E-mail address: [n.simmonds@rbht.nhs.uk](mailto:n.simmonds@rbht.nhs.uk) (N.J. Simmonds).

<sup>1</sup> Current affiliation: Swedish Orphan Biovitrum AB, Stockholm, Sweden.

<sup>2</sup> Current affiliation: Independent consultant, Boston, MA, USA.

<sup>3</sup> Current affiliation: Biogen, Weston, MA, USA.

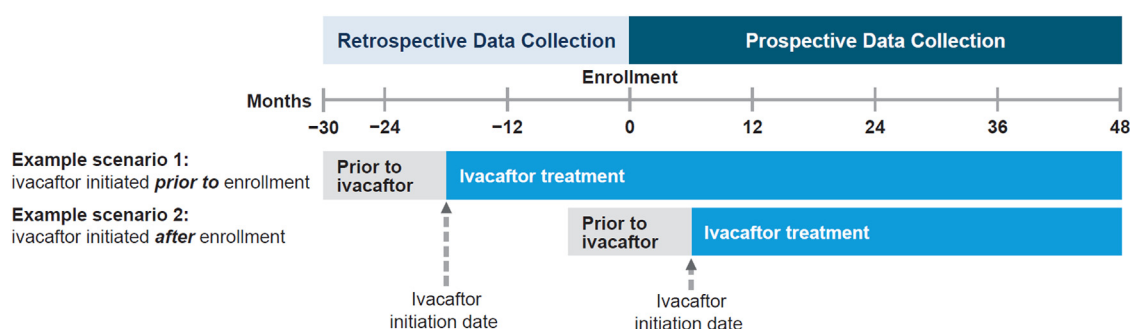


Fig. 1. Study design.

the *CFTR* gene, which encodes the CF transmembrane conductance regulator (CFTR), an anion channel in epithelial cells [2]. Ivacaftor is a CFTR potentiator that treats the underlying cause of CF by increasing the open channel probability of CFTR, which in turn enhances chloride transport [3]. Ivacaftor has been shown to be safe and efficacious in clinical trials of participants  $\geq 4$  months of age with CF and *CFTR* gating or non-gating mutations [4–10]. Ivacaftor is approved in Europe to treat people with CF (pwCF)  $\geq 4$  months of age with indicated *CFTR* mutations [11].

Several studies have demonstrated the long-term real-world effectiveness of ivacaftor [12–21]. An analysis of US and UK CF registry data showed better-preserved respiratory function, improved nutritional status, reduced pulmonary exacerbation (PEX) and hospitalization rates, trends toward lower prevalence of *Pseudomonas aeruginosa* infections, and favorable trends in prevalence of CF-related diabetes in pwCF who received ivacaftor compared with untreated pwCF over 4 to 5 years [12]; reduced risk of death and lung transplant were noted as well [13]. A study of 36 months of ivacaftor treatment in pwCF with *G551D-CFTR* in the CF Registry of Ireland showed improvements in lung function and body mass index (BMI) and reduced antibiotic use [14]. Observational studies of ivacaftor in pwCF with *G551D-CFTR* or non-*G551D-CFTR* gating mutations in France also showed improvements in lung function, nutritional status, and PEX rates and reductions in the proportion of pwCF with select respiratory pathogens [15, 16].

Here, we report results from VOCAL, an observational study with up to 48 months of prospectively collected data, describing the long-term impact of ivacaftor on real-world clinical outcomes and healthcare resource utilization (HCRU) in pwCF with non-*G551D-CFTR* gating mutations in Italy, the Netherlands, and the UK. This work expands on results from prior real-world studies by providing additional long-term ivacaftor data from pwCF with non-*G551D-CFTR* gating mutations across  $\geq 4$  years of follow-up and in additional countries.

## 2. Materials and methods

### 2.1. Observational study design and participants

VOCAL (VX14-770-116; NCT02445053) was a Phase 4, European, multicenter, observational study of pwCF  $\geq 6$  years of age with  $\geq 1$  non-*G551D-CFTR* gating mutation (*G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*). Full eligibility criteria and additional study methods are reported in the **Supplementary Methods**. During the conduct of this study, pwCF were treated by investigators (eg, their treating/responsible physician) per their medical judgment and standard of care in accordance with the approved summary of product characteristics. pwCF initiated ivacaftor before, at, or after enrollment (Fig. 1). Prospective data were collected for up to 48 months after enrollment. Retrospective data were collected to ensure that 12 months of data prior to ivacaftor initia-

tion were available. pwCF could have initiated ivacaftor up to 18 months before enrollment, meaning up to 30 months of retrospective data could have been collected. Retrospective and prospective data were gathered from paper or electronic medical records, abstracted by local site staff, and transferred directly at the site onto secure web-based electronic case report forms.

The study objectives were to describe the effectiveness of ivacaftor treatment on outcomes in a real-world setting in pwCF who have 1 of 8 non-*G551D-CFTR* gating mutations and to evaluate the effect of ivacaftor on HCRU in the studied population. Clinical outcome endpoints were percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) based on the Global Lung Function Initiative reference equations, BMI, BMI-for-age z-score, weight, weight-for-age z-score, number and duration of PEX (defined as any change in clinical course defined by the clinician as an exacerbation, and included treatment with oral, IV or inhaled antibiotics), prevalence of comorbidities, incidence and cause of deaths, incidence of organ transplant by type, percentage of all cultures obtained in a given time period that were positive, and percentage of pwCF with at least 1 positive respiratory culture positive for *P. aeruginosa*, other bacteria, or fungi. Wherever possible, baseline values were obtained from the first recorded date of ivacaftor initiation in the record; otherwise, they were obtained from the most recent encounter prior to ivacaftor initiation. HCRU endpoints included number of all-cause hospitalizations (defined as an overnight stay in the hospital) and days of hospitalization, number of courses and days of intravenous antibiotic treatment (including IV antibiotics administered at home), number of courses of acute oral or inhaled antibiotic treatment, number of outpatient visits (including physician/office visits, hospital visits without an overnight stay, and emergency room visits), and use of concomitant chronic CF medications (including chronic inhaled antibiotics).

Clinical outcomes were collected retrospectively at enrollment and then prospectively every  $3 \pm 1.5$  months, a schedule selected to minimize missing data by coinciding with standard clinical visits recommended by the European Cystic Fibrosis Society. BMI and weight were assessed in pwCF  $\geq 20$  years of age at ivacaftor initiation; BMI-for-age and weight-for-age z-scores were assessed in pwCF  $< 20$  years of age at ivacaftor initiation. PEX were defined as any change in clinical course defined by the clinician as an exacerbation. Hospitalization was defined as an admission including an overnight stay. Respiratory samples were obtained according to standard practice at sites and at every clinic visit per recommendations from the European Cystic Fibrosis Society (ECFS) [22]. Data monitoring and auditing procedures were followed to ensure the quality of data collected.

### 2.2. Statistical analysis

The full analysis set was defined as all pwCF who enrolled in the study and started ivacaftor treatment before, at, or after en-

rollment and met all eligibility criteria. Continuous variables were summarized using the number of pwCF (n), mean, SD, SE, median, minimum value, and maximum value. Categorical variables were summarized using counts and percentages. Demographics, ppFEV<sub>1</sub>, and nutritional status were summarized at baseline, which was defined as the last available value at or prior to the ivacaftor initiation date. Analyses of lung function and nutritional status summarized the average changes from baseline within each 6-month interval after ivacaftor initiation. Analyses of clinical events and HCRU evaluated rates in the 12 months prior to ivacaftor compared with the 12 months post ivacaftor initiation. Clinical events and HCRU in the overall post-ivacaftor initiation period were summarized to provide an annualized rate.

A mixed model for repeated measures (MMRM) was used to assess changes in ppFEV<sub>1</sub> and nutritional status from baseline within each 6-month interval through 48 months of treatment with ivacaftor, based on all available data from baseline through 48 months of treatment with ivacaftor. Least-squares (LS) means with 95% CIs were obtained from the MMRM model.

A negative binomial regression model was used to assess cumulative PEx and HCRU outcomes in the 12 months prior to ivacaftor initiation, 12 months post ivacaftor initiation, and from ivacaftor initiation to end of study (overall post-ivacaftor period).

The percentage of pwCF with  $\geq 1$  positive respiratory culture, percentage of positive respiratory cultures, percentage of pwCF with comorbidities, and percentage of pwCF using chronic CF medications (including chronic antibiotics) were compared in 4 sequential 12-month intervals after ivacaftor initiation (up to 48 months after ivacaftor initiation) versus 12 months prior to ivacaftor initiation. CIs were nominal and did not control for multiplicity. All analyses were performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA). There was no imputation for missing data with the exception of start and stop dates for treatment and clinical events that only specified the month, which were imputed as the first day of the month and the last day of the month, respectively.

### 2.3. Ethics

The study was conducted in accordance with current guidelines for Good Pharmacoepidemiology Practices and local applicable laws and regulations. An institutional review board (IRB) or independent ethics committee (IEC) reviewed all appropriate study documentation. The study was only conducted at sites where IRB/IEC approval had been obtained. The protocol, sample informed consent form, and other documents were provided to the IRB/IEC by the investigator or Vertex Pharmaceuticals Incorporated, as allowable by local applicable laws and regulations. Written informed consent was obtained from the person with CF or their legal representative or guardian (if applicable), and assent was obtained from the person with CF (if applicable) before study participation. Written informed consent was obtained from caregivers, as required by local laws and regulations.

## 3. Results

### 3.1. Population

VOCAL was conducted from April 13, 2015, through October 16, 2020. Seventy-five pwCF were enrolled across 15 sites in Italy, the Netherlands, and the UK; Table 1 summarizes the dispositions of the pwCF. Two pwCF did not meet eligibility criteria; the full analysis set included 73 pwCF. The mean (SD) age at ivacaftor initiation was 26.9 (13.5) years, and the majority of pwCF ( $n = 50$  [68.5%]) were  $\geq 18$  years of age (Table 2). Mean (SD) baseline ppFEV<sub>1</sub> was 64.8 (23.6) percentage points. Mean ivacaftor exposure was 49.5

**Table 1**  
Disposition of pwCF.

	n (%)
All enrolled pwCF	75
Enrolled but did not meet eligibility criteria	2
Full analysis set <sup>a</sup>	73
Completed study <sup>b</sup>	65 (89.0)
Discontinued from study	8 (11.0)
Lost to follow-up	3 (4.1)
Death	1 (1.4)
Other <sup>c</sup>	4 (5.5)
Started ivacaftor treatment at or after enrollment	16 (21.9)
Started ivacaftor 0 to 3 months after enrollment	15 (20.5)
Started ivacaftor >3 to 6 months after enrollment	0
Started ivacaftor >6 to 9 months after enrollment	1 (1.4)
Started ivacaftor treatment before enrollment	57 (78.1)
Started ivacaftor >0 to 6 months before enrollment	22 (30.1)
Started ivacaftor >6 to 12 months before enrollment	17 (23.3)
Started ivacaftor >12 to 18 months before enrollment	18 (24.7)
Months of ivacaftor treatment completed <sup>b</sup>	
$\geq 12$ months	72 (98.6)
$\geq 24$ months	69 (94.5)
$\geq 36$ months	68 (93.2)
$\geq 48$ months	48 (65.8)

pwCF, people with cystic fibrosis.

<sup>a</sup> The full analysis set was defined as all enrolled pwCF who met the eligibility criteria and were either being treated with ivacaftor at or before the time of enrollment or began treatment with ivacaftor after the time of enrollment. Percentages are based on the full analysis set.

<sup>b</sup> Last completed assessment was up to 48 months (inclusive) of informed consent date.

<sup>c</sup> Four pwCF discontinued due to other reasons (change in hospital, enrollment in an interventional clinical study, or personal reasons). One person with CF discontinued treatment due to pregnancy but did not discontinue from the study; data collected after the discontinuation of ivacaftor were not included in the analyses.

**Table 2**  
Demographics and clinical characteristics at baseline<sup>a</sup>.

Characteristic	n = 73 <sup>b</sup>
Sex, n (%)	
Female	48 (65.8)
Male	25 (34.2)
Age at ivacaftor initiation, mean (SD), years	26.9 (13.5)
Age at ivacaftor initiation category, n (%)	
<12 years	10 (13.7)
$\geq 12$ to <18 years	13 (17.8)
$\geq 18$ years	50 (68.5)
Country, n (%)	
Italy	37 (50.7)
Netherlands	27 (37.0)
UK	9 (12.3)
CFTR non-G551D gating mutations, n (%)	
G178R	10 (13.7)
S549N	8 (11.0)
S549R	3 (4.1)
G551S	0
G1244E	20 (27.4)
S1251N	28 (38.4)
S1255P	0
G1349D	4 (5.5)
ppFEV <sub>1</sub> , <sup>c</sup> mean (SD), percentage points	64.8 (23.6); n = 72
ppFEV <sub>1</sub> severity, n (%)	
<70 percentage points	42 (57.5)
$\geq 70$ and $\leq 90$ percentage points	15 (20.5)
>90 percentage points	15 (20.5)
Missing	1 (1.4)
BMI <sup>d</sup> ( $\geq 20$ years of age), mean (SD), kg/m <sup>2</sup>	22.95 (3.81); n = 49
BMI-for-age z-score (<20 years of age), mean (SD)	-0.41 (0.89); n = 24

BMI, body mass index; ppFEV<sub>1</sub>, percent predicted forced expiratory volume in 1 second.

<sup>a</sup> Baseline was the last available assessment at or before ivacaftor initiation.

<sup>b</sup> Full analysis set.

<sup>c</sup> ppFEV<sub>1</sub> values were based on the Global Lung Function Initiative equations.

<sup>d</sup> BMI was calculated as weight divided by square of height.

(median, 51.0; range, 10–64) months. The majority of pwCF ( $n=57$  [78.1%]) initiated ivacaftor treatment before enrollment. Sixty-five pwCF (89.0%) completed the study, with 48 (65.8%) completing  $\geq 48$  months of ivacaftor treatment.

### 3.2. Clinical outcomes

Treatment with ivacaftor led to an LS mean absolute increase in ppFEV<sub>1</sub> of 10.8 (SE, 1.3) percentage points from baseline during the first 6 months of treatment, which was maintained through 48 months (Fig. 2A). The LS mean absolute change in BMI ( $\geq 20$  years of age) was 0.79 (SE, 0.14) kg/m<sup>2</sup> from baseline during the first 6 months of treatment with ivacaftor, with an increasing trend through 36 months, after which BMI remained relatively stable through 48 months (Fig. 2B). The LS mean absolute change in BMI-for-age z-score ( $<20$  years of age) was 0.54 (SE, 0.11) from baseline during the first 6 months of treatment with ivacaftor and showed minor fluctuations through 48 months (Fig. 2C). The LS mean absolute changes in weight ( $\geq 20$  years of age) and weight-for-age z-score ( $<20$  years of age) were 2.2 (SE, 0.4) kg and 0.4 (SE, 0.1), respectively, from baseline during the first 6 months of ivacaftor treatment, with trends similar to those for BMI and BMI-for-age z-score, respectively, through 48 months (Figures S1A; Figure S1B). Estimated annualized rates and number of days of all PEx and PEx requiring hospitalization decreased by  $>50\%$  during the first 12 months after ivacaftor initiation compared with 12 months prior to ivacaftor; these changes were maintained throughout the post-ivacaftor period (Table 3; Table S1).

The most commonly reported comorbidities were pancreatic insufficiency, nasal polyps, and CF-related diabetes. There was little difference in the prevalence of comorbidities in the 12 months prior to ivacaftor initiation compared with the 12-month intervals after ivacaftor initiation. There were no organ transplants. One death was attributed to an illicit drug overdose and was not considered related to ivacaftor.

### 3.3. Respiratory microbiology

The number of pwCF with  $\geq 1$  respiratory microbiology specimen collected and the collection methods are reported in Table S2. Respiratory microbiology results are reported in Figures S2A and S2B and the **Supplementary Results**. The percentage of pwCF with  $\geq 1$  respiratory culture positive for  $\geq 1$  of the assessed pathogens was lower during the 12-month intervals of ivacaftor treatment relative to the 12 months prior to ivacaftor. The percentage of pwCF with  $\geq 1$  respiratory culture positive for *P. aeruginosa* was lower during the  $>12$ - to 24-month interval of ivacaftor treatment (41.5%) relative to the 12 months prior to ivacaftor (55.1%); this was maintained through 48 months of ivacaftor treatment. The percentage of pwCF with  $\geq 1$  respiratory culture positive for *Aspergillus fumigatus* or *Stenotrophomonas maltophilia* was lower during the  $>0$ - to 12-month interval of ivacaftor treatment (18.6% or 7.1%, respectively) relative to the 12 months prior to ivacaftor (30.4% or 11.6%, respectively); this was maintained through 48 months of ivacaftor treatment. Similar trends were observed in the percentage of positive cultures. The prevalence of the 6 other pathogens evaluated was either variable or remained low.

### 3.4. HCRU

Estimated annualized rates and number of days of all-cause hospitalizations and acute antibiotic use due to PEx decreased by  $>50\%$  during the first 12 months after ivacaftor initiation compared with 12 months prior to ivacaftor; these changes were maintained throughout the overall post-ivacaftor period (Table 3; Table S1). For hospitalizations not due to PEx, the most common cause was

perceived worsening of pulmonary status as measured by either ppFEV<sub>1</sub> (1 patient) or radiographic background worsening (2 patients). Other non-PEx hospitalizations were for a variety of causes consistent with those expected in CF (e.g. hemoptysis, embolization, distal intestinal obstruction, constipation, sinus surgery), as well as causes not related to CF (e.g. torn tendon, cord compression from cervical disc, urinary tract infection), with each diagnosis represented by no more than one patient. For acute antibiotic use due to PEx, similar trends were seen for the course rate of intravenous and oral or inhaled antibiotics and the number of days of any, intravenous, and oral or inhaled antibiotic use. The majority of outpatient visits were routine clinic visits (Table S3). There was no difference in the estimated annualized rate of outpatient visits during the first 12 months after ivacaftor initiation compared with 12 months prior to ivacaftor. However, the estimated annualized rate of sick clinic and emergency room visits was numerically lower during the first 12 months after ivacaftor initiation compared with 12 months prior to ivacaftor; this trend was maintained throughout the overall post-ivacaftor period. Use of chronic therapies was stable throughout the study (Table S4).

### 3.5. Safety

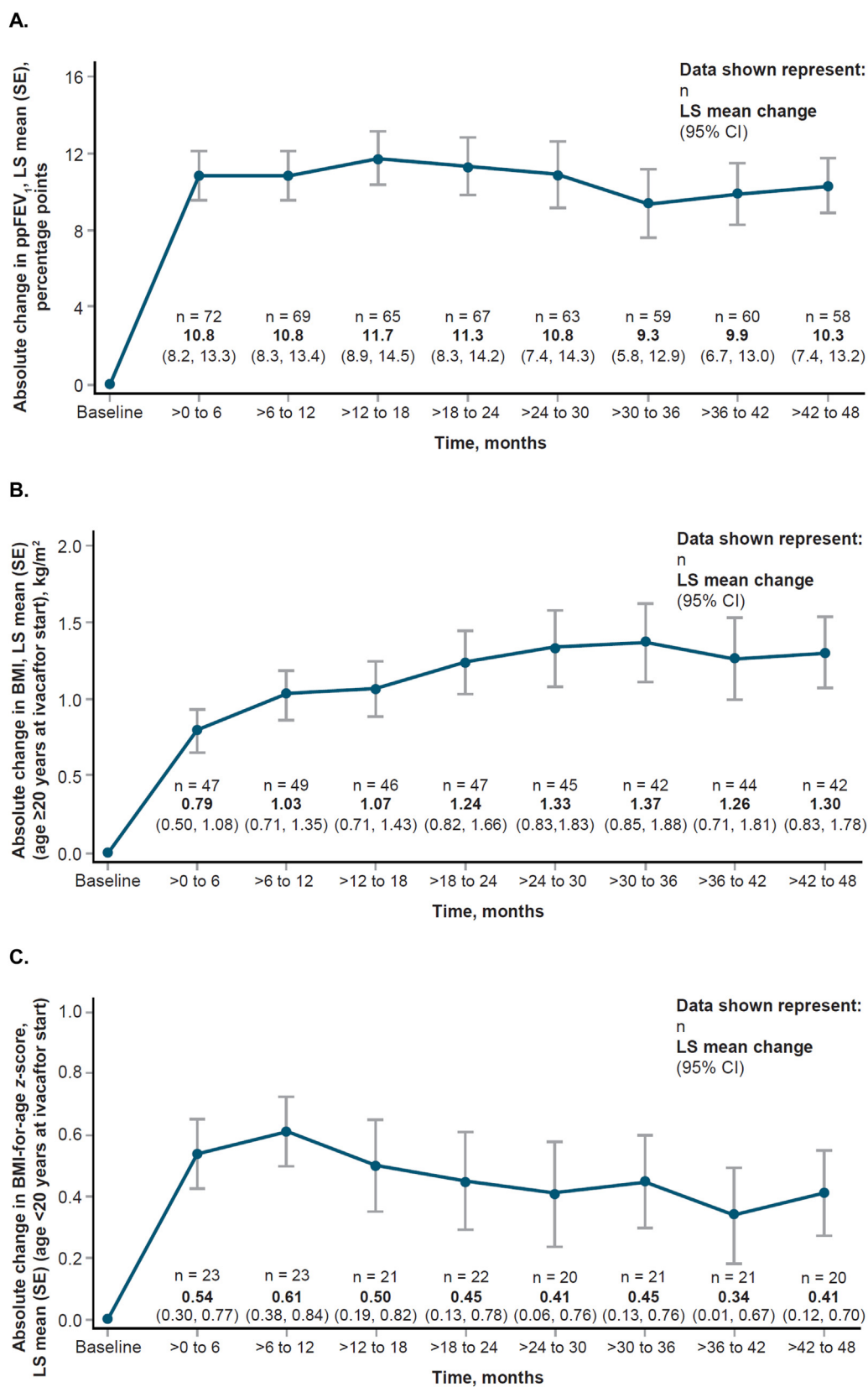
One hundred eighty adverse events (AEs) were reported; 154 (85.6%) were considered nonserious and 26 (14.4%) were considered serious. The majority of serious AEs occurred once, with the exception of infective PEx of CF (8 events) and tendon rupture (2 events, both reported in the same individual). One serious AE was considered related to ivacaftor; the initial tendon rupture was classified as possibly related, while the reinjury was classified as not related. The reported AEs were generally consistent with common manifestations of CF and the known safety profile of ivacaftor (**Supplementary Results**). Four pwCF were exposed to ivacaftor during pregnancy; 1 discontinued treatment (without discontinuing the study), 1 decreased the dose, and 2 continued treatment without changes.

## 4. Discussion

In this long-term observational study of pwCF  $\geq 6$  years of age with non-*G551D-CFTR* gating mutations in 3 European countries, treatment with ivacaftor was associated with improvements in ppFEV<sub>1</sub>, BMI, and BMI-for-age z-score in the first 6 months of treatment, decreases in PEx rates in the first year, and reductions in the prevalence of respiratory infections in the first 1 to 2 years in real-world settings. Ivacaftor treatment also led to reductions in HCRU, including rates of all-cause hospitalization and acute antibiotic use due to PEx. These improvements were generally maintained for up to 48 months. Safety results were consistent with common clinical manifestations of CF and the known safety profile of ivacaftor.

Improvements in lung function and BMI are like those previously reported in the KONNECTION trial of participants  $\geq 6$  years of age with non-*G551D-CFTR* gating mutations [6]. In KONNECTION, ivacaftor treatment led to within-group mean increases in ppFEV<sub>1</sub> of 13.5 percentage points through week 24, in BMI of 1.3 kg/m<sup>2</sup> at week 24, and in BMI-for-age z-score of 0.24 at week 8 [6]. Increased ppFEV<sub>1</sub> observed in this study is also generally consistent with results from randomized ivacaftor trials in pwCF with the *G551D-CFTR* mutation [4, 5] and real-world studies of pwCF with *G551D-CFTR* or non-*G551D-CFTR* mutations [12, 16–18]. These improvements are important because ppFEV<sub>1</sub> declines over time in pwCF, which is associated with mortality [23, 24], and nutritional status is associated with lung function and survival [25, 26]. Moreover, we observed that clinical effectiveness was maintained over several years; this is clinically meaningful because lung damage in





**Fig. 2.** Absolute change from baseline in (A) ppFEV<sub>1</sub>, (B) BMI, and (C) BMI-for-Age z- Score. BMI, body mass index; LS, least squares; ppFEV<sub>1</sub>, percent predicted forced expiratory volume in 1 second.

**Table 3**

Number of PEx, All-cause hospitalizations, and courses of acute antibiotic medications due to PEx prior to and post ivacaftor initiation.

	Prior to Ivacaftor –12 to 0 Months (N = 73)	Post Ivacaftor >0 to 12 Months (N = 73)	Post Ivacaftor Overall <sup>a</sup> (N = 73)
PEX <sup>b</sup>			
PEX			
Events, n	64	18	114
pwCF with events, n (%)	37 (50.7)	14 (19.2)	33 (45.2)
Estimated annualized event rate per person with CF (95% CI)	0.8 (0.6, 1.2)	0.2 (0.1, 0.4)	0.3 (0.2, 0.4)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.3 (0.2, 0.5)	-
PEX requiring hospitalization			
Events, n	30	6	40
pwCF with events, n (%)	19 (26.0)	6 (8.2)	13 (17.8)
Estimated annualized event rate per person with CF (95% CI)	0.3 (0.2, 0.5)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.2 (0.1, 0.4)	-
Hospitalizations (all causes) <sup>b</sup>			
Events, n	38	13	57
pwCF with events, n (%)	23 (31.5)	10 (13.7)	22 (30.1)
Estimated annualized event rate per person with CF (95% CI)	0.4 (0.3, 0.7)	0.1 (0.1, 0.3)	0.1 (0.1, 0.2)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.3 (0.2, 0.7)	-
Acute antibiotic medications due to PEX <sup>b,c</sup>			
All antibiotics			
Courses, n	113	26	170
pwCF taking antibiotics, n (%)	36 (49.3)	14 (19.2)	33 (45.2)
Estimated annualized medication course rate per person with CF (95% CI)	1.4 (0.9, 2.1)	0.3 (0.2, 0.6)	0.4 (0.3, 0.6)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.2 (0.1, 0.4)	-
Intravenous antibiotics			
Courses, n	65	14	87
pwCF taking antibiotics, n (%)	20 (27.4)	7 (9.6)	15 (20.5)
Estimated annualized medication course rate per person with CF (95% CI)	0.6 (0.3, 1.0)	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.2 (0.1, 0.4)	-
Oral or inhaled antibiotics			
Courses, n	48	12	83
pwCF using antibiotics, n (%)	26 (35.6)	9 (12.3)	27 (37.0)
Estimated annualized medication course rate per person with CF (95% CI)	0.7 (0.4, 1.1)	0.2 (0.1, 0.3)	0.2 (0.2, 0.3)
Estimated rate ratio vs prior to ivacaftor (95% CI)	-	0.3 (0.1, 0.6)	-

CF, cystic fibrosis; PEx, pulmonary exacerbation; pwCF, people with cystic fibrosis.

<sup>a</sup> Post-ivacaftor overall interval was from ivacaftor initiation through the end of the study.<sup>b</sup> pwCF could be counted in >1 interval for the same event (for PEx), >1 interval for the same type of event (for all-cause hospitalization), and >1 interval for the same type of acute antibiotic used (for acute antibiotic use due to PEx).<sup>c</sup> The number of antibiotic courses exceeds the number of exacerbations because pwCF are often treated with combinations of 2 or more antibiotics for a single PEx.

pwCF without CFTR modulator treatment is usually progressive to the point of respiratory failure, transplant, or even death [2, 23].

In this study, pwCF had reductions in PEx rates that were consistent with clinical trial data [4]. Reductions in rates of PEx and rates of PEx requiring hospitalization were also generally consistent with data from real-world studies [13, 16, 17]. PEx are associated with lung function decline and an increased risk of lung transplant or death [27, 28]. In this study, the majority of pwCF had positive respiratory cultures prior to ivacaftor initiation; *P. aeruginosa* was the most frequently identified pathogen. Following ivacaftor initiation, reductions were seen in the percentage of cultures positive for *P. aeruginosa*, *A. fumigatus*, or *S. maltophilia*. The prevalence of the 6 other pathogens evaluated was either variable or remained low. This is consistent with other real-world studies, which reported reductions in the proportion of pwCF with cultures positive for *P. aeruginosa* or *Aspergillus* spp with ivacaftor treatment [13, 15–19].

In this study, pwCF also experienced reductions in HCRU, including all-cause hospitalization and antibiotic use due to PEx. Similar reductions in HCRU have been observed in other real-world studies of ivacaftor [13, 14, 16, 21, 29]. Overall, these findings further suggest that ivacaftor treatment results in long-term HCRU reductions. These reductions will likely have a positive impact on

both pwCF and healthcare systems; disease burden, treatment burden, time spent managing CF, and healthcare costs may decrease. Decreased antibiotic use may also reduce the risk of development of antibiotic resistance in pwCF. In this study, the annualized rate of outpatient visits and the proportion of pwCF receiving chronic medications were stable, while the rate of sick clinic and emergency room visits numerically declined with ivacaftor treatment. These findings suggest the feasibility of reducing the treatment burden of pwCF, including the burden of standard medications, after initiation of CFTR modulator treatment, which is being assessed in an ongoing study [30].

Safety results in this study were generally consistent with common clinical manifestations of CF and the known safety profile of ivacaftor. No pwCF discontinued ivacaftor due to AEs, even after a long follow-up period. pwCF initiated treatment with ivacaftor prior to, at, or after study enrollment; thus, data collected during both pre-ivacaftor and ivacaftor treatment periods were a mix of retrospective and prospective data collected under routine clinical care conditions. Limitations of the study design include the inability to stipulate that baseline measurements had to be at a specific time due to the real-world nature of data collection, and the definition of PEx as changes in the clinical course as determined by a clinician, limiting comparisons between this observa-

tional study and other clinical trials that used differing definitions. The number of microbial specimens collected during the study decreased over time, with fewer spontaneous sputum samples and more throat swabs, possibly contributing to the reduction in positive cultures that were observed. CIs for multiple endpoints were based on nominal confidence levels (i.e., without control for multiplicity) consistent with other real-world evidence studies. The lack of a comparator cohort prohibited controlling for changes in outcomes over time due to natural disease progression and changes in non-CFTR modulator-related standards of clinical care; therefore, it is possible that the comparisons of outcomes before and after ivacaftor initiation underestimated ivacaftor's treatment benefit. Despite this limitation, improvements were observed over the long follow-up period. The analysis was based on aggregated real-world data collected from 3 countries with varying clinical practices; however, study sites all followed the ECFS best practice guidelines [22].

This real-world long-term study was conducted in a heterogeneous population of pwCF with a broad range of baseline disease severity. The current findings are consistent with those of previously completed ivacaftor clinical trials [4–6]. Moreover, the current results demonstrated sustained effectiveness for several clinical outcomes across the duration of this study.

## 5. Conclusions

Results of this 48-month, European, observational study demonstrated the effectiveness in clinical outcomes and safety of ivacaftor in pwCF  $\geq 6$  years of age with select non-G551D-CFTR gating mutations in real-world settings. Treatment with ivacaftor resulted in improvements in mean ppFEV<sub>1</sub>, body mass index (BMI), and BMI-for-age z-score. Rates of PEx, antibiotic use due to PEx, and hospitalization decreased by >50% during ivacaftor treatment compared with before ivacaftor. Additionally, ivacaftor use was associated with reductions in HCRU rates. Improvements were generally maintained for up to 48 months. Safety results were consistent with CF and the known safety profile of ivacaftor. These results support the long-term effectiveness and use of ivacaftor for the treatment of pwCF with indicated CFTR mutations.

## Funding

This study was supported by Vertex Pharmaceuticals Incorporated. The sponsor was involved in the study design, analysis, and interpretation of the data, with collaboration from the authors. The sponsor helped develop the report with input, review, and approval from the authors.

## Data sharing statement

Vertex Pharmaceuticals Incorporated 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 Pharmaceuticals Incorporated 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.

## Declaration of Competing Interest

All authors received nonfinancial support (assistance with manuscript preparation) from ArticulateScience, LLC, which received funding from Vertex Pharmaceuticals Incorporated. Additional disclosures are as follows: **CCa** reports consulting fees from

Vertex, Chiesi, and Mylan in the past 36 months. **CCo** reports steering committee fees from Vertex during the conduct of the present study and participation in advisory boards for Vertex and Mylan in the past 36 months. **CD**, **MLC**, and **NK** are former employees of Vertex and may own stock in Vertex. **KC** and **TT** are employees of Vertex and may own stock or stock options in Vertex. **CKvdE** has nothing further to disclose. **MLC** owns stock or stock options in Pfizer Inc, in the past 36 months. **NJS** reports steering committee fees from Vertex since the initial planning of the work; honoraria for lectures from Vertex, Chiesi, and Zambon in the past 36 months; honoraria for lectures and speakers bureau from Gilead in the past 36 months; and participation on an advisory board for Vertex, Gilead, Chiesi, and Menarini in the past 36 months.

## Acknowledgments

The authors thank all the people with cystic fibrosis who took part in the study and their families, as well as the principal investigators and research coordinators at each site. The authors thank all the site investigators and clinical research associates who collected data at study sites. The authors acknowledge the study investigators who were not included as authors: Antonio Manca, Donatello Salvatore, Harm Tiddens, Giovanna Pizzamiglio, Joanna Whitehouse, Edward F. Nash, Renske van der Meer, Hester van der Vaart, Petrus Merkus, Josje Altenburg, Christof Majoor, Giulia Paiola, Elena Spinelli, Nicola Ferrara, and Simona Cristadoro. The authors acknowledge Marianna Passiu, Ilaria Meneghelli, and Arianna Bisogno for their contributions to the study. Editorial coordination and support were provided by Francesca Francois, PharmD, MPH, of Vertex Pharmaceuticals Incorporated; Francesca Francois may own stock or stock options in that company. Medical writing and editorial support were provided under the direction of the authors by Christopher Edwards, PhD, CMPP, an employee of ArticulateScience, LLC, which received funding from Vertex Pharmaceuticals Incorporated.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.05.007.

## References

- [1] Zolin A, Orenti A, van Rens J, Fox A, Krasnyk M, Cosgriff R, et al. European Cystic Fibrosis Society patient registry annual data report 2018. [Internet]. Karup, Denmark: European Cystic Fibrosis Society; 2020. [cited 2021 Nov 3]. Available from [https://www.ecfs.eu/sites/default/files/general-content-files/working-groups/ecfs-patient-registry/ECFSR\\_Report\\_2018\\_v1.4.pdf](https://www.ecfs.eu/sites/default/files/general-content-files/working-groups/ecfs-patient-registry/ECFSR_Report_2018_v1.4.pdf).
- [2] De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. *Lancet Respir Med* 2016;4:662–74. doi:10.1016/S2213-2600(16)00023-0.
- [3] Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson JP Jr, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. *J Cyst Fibros* 2012;11:237–45. doi:10.1016/j.jcf.2011.12.005.
- [4] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365:1663–72. doi:10.1056/NEJMoa1105185.
- [5] Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstone MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013;187:1219–25. doi:10.1164/rccm.201301-0153OC.
- [6] De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros* 2014;13:674–80. doi:10.1016/j.jcf.2014.09.005.
- [7] Davies JC, Cunningham S, Harris WT, Lapey A, Regelman WE, Sawicki GS, et al. 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;4:107–15. doi:10.1016/S2213-2600(15)00545-7.
- [8] Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. 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;6:545–53. doi:10.1016/S2213-2600(18)30202-9.

- [9] 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;203:585–93. doi:10.1164/rccm.202008-3177OC.
- [10] Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *Lancet Respir Med* 2015;3:524–33. doi:10.1016/s2213-2600(15)00201-5.
- [11] Vertex Pharmaceuticals (Ireland) Limited Kalydeco (ivacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Limited; 2021.
- [12] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. *J Cyst Fibros* 2020;19:68–79. doi:10.1016/j.jcf.2019.05.015.
- [13] Bessonova L, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018;73:731–40. doi:10.1136/thoraxjnl-2017-210394.
- [14] Kirwan L, Fletcher G, Harrington M, Jeleniewska P, Zhou S, Casserly B, et al. Longitudinal trends in real-world outcomes after initiation of ivacaftor. A cohort study from the Cystic Fibrosis Registry of Ireland. *Ann Am Thorac Soc* 2019;16:209–16. doi:10.1513/AnnalsATS.201802-149OC.
- [15] Hubert D, Dehillotte C, Munck A, David V, Baek J, Mely L, et al. Retrospective observational study of French patients with cystic fibrosis and a Gly551Asp-CFTR mutation after 1 and 2 years of treatment with ivacaftor in a real-world setting. *J Cyst Fibros* 2018;17:89–95. doi:10.1016/j.jcf.2017.07.001.
- [16] Hubert D, Marguet C, Benichou J, DeSouza C, Payen-Champenois C, Kinnman N, et al. Real-world long-term ivacaftor for cystic fibrosis in France: clinical effectiveness and healthcare resource utilization. *Pulm Ther* 2021;7:455–68. doi:10.1007/s41030-021-00158-5.
- [17] Guimbellot JS, Baines A, Paynter A, Heltshe SL, VanDalfsen J, Jain M, et al. Long term clinical effectiveness of ivacaftor in people with the G551D CFTR mutation. *J Cyst Fibros* 2021;20:213–19. doi:10.1016/j.jcf.2020.11.008.
- [18] Kawala CR, Ma X, Sykes J, Stanojevic S, Coriati A, Stephenson AL. Real-world use of ivacaftor in Canada: a retrospective analysis using the Canadian Cystic Fibrosis Registry. *J Cyst Fibros*. [Internet]. [cited 2021 Nov 3];S1569-1993(21)00057-6. Epub 2021 Mar 30. Available from: <https://doi.org/10.1016/j.jcf.2021.03.008>.
- [19] Frost FJ, Nazareth DS, Charman SC, Winstanley C, Walshaw MJ. Ivacaftor is associated with reduced lung infection by key cystic fibrosis pathogens. A cohort study using national registry data. *Ann Am Thorac Soc* 2019;16:1375–82. doi:10.1513/AnnalsATS.201902-122OC.
- [20] Hassan M, Bonafede MM, Limone BL, Hodgkins PS, Suthoff ED, Sawicki GS. Reduction in pulmonary exacerbations (PEs) after initiation of ivacaftor: a retrospective cohort study among patients with cystic fibrosis (CF) treated in real-world settings. Abstract presented at: 39th European Cystic Fibrosis Conference (ECFS); 2016 Jun 8–11; Basel, Switzerland. [https://doi.org/10.1016/S1569-1993\(16\)30268-5](https://doi.org/10.1016/S1569-1993(16)30268-5). *J Cyst Fibros* 2016;15:S58 [abstract 28].
- [21] Suthoff ED, Bonafede M, Limone B, O'Callaghan L, Sawicki GS, Wagener JS. Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis. *J Med Econ* 2016;19:845–51. doi:10.1080/13696998.2016.1178125.
- [22] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018;17:153–78. doi:10.1016/j.jcf.2018.02.006.
- [23] Harun SN, Wainwright C, Klein K, Hennig S. A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. *Paediatr Respir Rev* 2016;20:55–66. doi:10.1016/j.prpv.2016.03.002.
- [24] Breuer O, Caudri D, Stick S, Turkovic L. Predicting disease progression in cystic fibrosis. *Expert Rev Respir Med* 2018;12:905–17. doi:10.1080/17476348.2018.1519400.
- [25] Konstan MW, Butler SM, Wohl MEB, Stoddard M, Matousek R, Wagener JS, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003;142:624–30. doi:10.1067/mpd.2003.152.
- [26] Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr* 2013;162:530–5 e1. doi:10.1016/j.jpeds.2012.08.040.
- [27] de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax* 2011;66:680–5. doi:10.1136/thx.2011.161117.
- [28] Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012;40:61–6. doi:10.1183/09031936.00159111.
- [29] Thorat T, McGarry LJ, Jariwala-Pariikh K, Limone B, Bonafede M, Chandarana K, et al. Long-term impact of ivacaftor on healthcare resource utilization among people with cystic fibrosis in the United States. *Pulm Ther* 2021;7:281–93. doi:10.1007/s41030-021-00154-9.
- [30] Nichols D. Impact of discontinuing chronic therapies in people with cystic fibrosis on highly effective CFTR modulator therapy (SIMPLIFY). [last updated 2021 Oct 28; first posted 2020 May 7]. US National Library of Medicine; 2000. In: *ClinicalTrials.gov* [internet]. Bethesda (MD) Available from: <https://clinicaltrials.gov/ct2/show/NCT04378153> ClinicalTrials.gov Identifier: NCT04378153.