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Original research

Long-term impact of ivacaftor on mortality rate and health outcomes in people with cystic fibrosis

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ABSTRACT

Background Ivacaftor (IVA) has been shown to improve lung function and other clinical outcomes in people with cystic fibrosis (CF). A decade of real-world IVA availability has enabled the examination of long-term outcomes with this treatment. This retrospective, longitudinal cohort study investigated the impact of IVA on mortality rate and health outcomes among people with CF in the US.

Methods Data from the US CF Foundation Patient Registry from January 2010 to December 2019 were analysed. The IVA-treated cohort included people with a CF transmembrane conductance regulator (*CFTR*) gating mutation (excluding *R117H*); age-matched comparator cohort included people with a *F508del* and a minimal function *CFTR* mutation who had no prior CFTR modulator treatment. Baseline characteristics were balanced between cohorts using standardised mortality ratio weighting generated from propensity scores. Outcomes of interest were overall survival, lung transplant, percent predicted forced expiratory volume in 1 s ($ppFEV_1$), body mass index (BMI), pulmonary exacerbations (PEx), outpatient visits and hospitalisations.

Findings Over a maximum follow-up of 7.9 years, the IVA-treated cohort (N=736) had lower rates of mortality (hazard ratio [HR] (95% CI): 0.22 (0.09 to 0.45)), lung transplant (HR: 0.11 (95% CI 0.02 to 0.28)), PEx (rate ratio: 0.49 (95% CI 0.42 to 0.55)) and all-cause hospitalisations (rate ratio: 0.50 (95% CI 0.43 to 0.56)) as well as better lung function (mean difference in $ppFEV_1$: 8.46 (95% CI 7.34 to 9.75)) and higher BMI/BMI *z*-scores (mean difference 1.20 (95% CI 0.92 to 1.71) kg/m^2 and 0.27 (95% CI 0.25 to 0.40), respectively) than the comparator cohort (N=733).

Interpretation Our analysis suggests that IVA provides sustained clinical benefits in people with CF over a follow-up period of approximately 8 years. These findings reinforce the existing real-world evidence that IVA can slow disease progression and decrease the healthcare burden of CF over the long term.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In long-term safety studies using registry data, people with cystic fibrosis (CF) who received ivacaftor (IVA), the first targeted therapy to address the underlying cause of CF, had better-preserved lung function and improved clinical outcomes versus an untreated cohort. However, the maximum follow-up time in these studies was 5 years from IVA initiation.

WHAT THIS STUDY ADDS

⇒ The current investigation builds on the existing literature by analysing multiple clinical and disease progression endpoints in a large real-world sample of people with CF over a longer follow-up period (maximum, 7.9 years). In addition, this study's design and methodology allowed for a more robust examination of the impact of IVA on clinical outcomes. This analysis of US CF Foundation Patient Registry data demonstrated that treatment with IVA was associated with lower rates of mortality and lung transplant, improved lung function and body mass index (BMI)/BMI *z*-scores, and reduced rates of pulmonary exacerbations and hospitalisations. These results suggest that IVA has sustained clinical benefits in people with CF and can slow disease progression and decrease the healthcare burden of CF over the long term.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As the life expectancy of people with CF continues to increase, the long-term impact of novel therapies on health outcomes is of interest to healthcare stakeholders. Because CF transmembrane conductance regulator (CFTR) modulators were a new class of therapies with the introduction of IVA, this longitudinal analysis using a CF patient registry provides novel evidence of the long-term durability of CFTR modulator benefits in real-world settings.

Linked

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INTRODUCTION

Cystic fibrosis (CF) is a life-limiting, autosomal recessive disease that affects >88 000 people globally.[1–5] CF is caused by mutations in the CF transmembrane regulator (*CFTR*) gene that result in impaired expression, trafficking or function of the CFTR protein.[1] This leads to multisystem disease that is characterised by progressive lung damage, pancreatic insufficiency and nutritional deficits that result in impaired growth.[1] Lung disease is the leading cause of death among people with CF, and most die prematurely.[1 2] The median predicted age of survival among people with CF in the US was 36.8 years in 2011, prior to the advent of CFTR modulators (CFTRm).[6 7]

Ivacaftor (IVA) was the first CFTRm designed to address the underlying protein defect by increasing

the open probability of CFTR channels,[8] thereby potentiating CFTR function. In 2012, the US Food and Drug Administration (FDA) approved IVA for the treatment of CF in people aged ≥6 years with ≥1 *G551D CFTR*-gating mutation based on phase 3 clinical trials showing that IVA improved lung function over up to 48 weeks.[7 9 10] Approval in the US was expanded in 2014 to include 8 additional *CFTR*-gating mutations,[11] and later to include people ≥1 month of age with ≥1 of 97 IVA-responsive mutations,[11] based on data from additional clinical trials and extrapolation of IVA clinical and safety data from older patients.[12]

Real-world studies have shown that IVA results in preserved lung function, improved nutritional status and decreases in pulmonary exacerbation (PEx), hospitalisations, death and organ transplant over periods of up to 5 years.[13–16] With a longer follow-up period of up to 7.9 years, this study builds on the existing literature, using robust analytical methods to assess the long-term effectiveness of IVA by comparing clinical outcomes, overall survival (OS), outpatient visits and hospitalisations between people with CF who have *CFTR*-gating mutations and received IVA (ie, IVA-treated cohort) and a comparator cohort of people who are heterozygous for *F508del* and a minimal function mutation and did not receive any CFTRm therapies.

METHODS

Data source and collection

Person-level data from the US Cystic Fibrosis Foundation Patient Registry (US CFFPR)[17] from January 2010 to December 2019 were used in this study. Data in the US CFFPR are collected using five electronic data-capture forms that include assessments of vital status, medications, genetic mutations, hospitalisations, PEx, respiratory microbiology, pulmonary function and organ transplants. This study relied on the use of deidentified, retrospective data from the US CFFPR.

Study population

This was a longitudinal study with two cohorts (online supplemental figures S1, S2). The IVA-treated cohort included people with ≥1 *CFTR*-gating mutation (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*) who initiated IVA treatment between 31 January 2012 and 31 December 2018 (to allow for ≥1 year of possible follow-up data). The comparator cohort included people with an *F508del* mutation on one allele and a minimal function mutation on the second allele (*F508del*/minimal function genotypes; Online supplemental table S1) who were ineligible for IVA and had no prior CFTRm therapy use. In both cohorts, all individuals had a clinical diagnosis of CF, were aged ≥6 years on the index date (as defined in the 'Study design' section) and had data available for ≥24 months prior to the index date. The exclusion criteria were evidence of lung transplant or use of CFTRm therapy prior to the index date, evidence of pregnancy in the calendar year prior to or same year as the index date (based on annual data) and the presence of *R117H* or residual function *CFTR* mutations, to reduce heterogeneity arising from differences in disease severity and progression.

Study design

For the IVA-treated cohort, the index date was the date of IVA treatment initiation (ie, encounter date prior to that on which IVA use was first recorded in the US CFFPR). People were considered to have remained on treatment until there was evidence of IVA discontinuation, as determined by two sequential encounters ≥90 days apart where IVA use was not recorded; the second such encounter was defined as the date of IVA discontinuation. For the comparator cohort, the index date was the closest visit date within six calendar months of a corresponding IVA-treated person's index date; a 6-month time period was chosen because most people in the comparator cohort were expected to have at least one visit during a 6-month period. Each IVA-treated person's age at index date was matched with selected comparators and baseline demographic and clinical characteristics were adjusted as described below. The baseline period was defined as the 2-year period prior to the index date.

The follow-up period was defined as the time from the index date to death or end of data availability. The following censoring rules were applied for the analysis of specific outcomes: for OS, people were censored only at the end of data availability (including loss to follow-up); for other clinical outcomes (body mass index (BMI), BMI *z*-score, per cent predicted forced expiratory volume in 1 s ($ppFEV_1$) and PEx), outpatient visits and hospitalisations, people were censored at the first occurrence of treatment with a CFTRm therapy other than IVA, IVA discontinuation (for the IVA-treated cohort), death, pregnancy or end of data availability (including loss to follow-up). For pulmonary-related outcomes ($ppFEV_1$ and PEx), people were additionally censored at the time of lung transplant as transplant significantly affects lung function in people with CF.[18]

Ensuring comparability between cohorts

Because IVA is prescribed based on *CFTR* mutations[11] that are associated with clinical phenotype and differ from those in the CFTRm-untreated comparator cohort, differences in baseline characteristics and disease severity may exist between the IVA-treated and CFTRm-untreated cohorts. To minimise these differences, we included only people with *CFTR*-gating mutations in the IVA-treated cohort and selected people with *F508del*/minimal function genotypes as the CFTRm-untreated comparator cohort because in studies using the US CFFPR, these genotypes have been shown to have a broadly similar clinical phenotype and disease progression.[19–21] To further enhance the comparability of clinical outcomes between the two cohorts, we applied exact matching (1:4) on age at index date and standardised mortality ratio (SMR) weighting, using a propensity score model. The propensity score was defined as the probability of receiving IVA conditional on observed baseline covariates selected based on clinical significance (sex, race, ethnicity, type of health insurance, employment status, median household income by zip code (categorical), education level, $ppFEV_1$ (categorical), change in $ppFEV_1$ (categorical), number of PEx, average BMI/BMI z-scores (categorical), prevalence of CF-related complications, prevalence of respiratory microorganisms, the number of hospitalisations and outpatient visits, and medication use). Two years of baseline data were used for the lung function variables ($ppFEV_1$ and PEx) to better account for disease trajectory. When covariates had missing data, categories for missing data were created and included in the propensity score model. This approach reweighted the characteristics of people in the comparator cohort so that they were similar to those in the IVA-treated cohort at baseline. SMR weighting yields an estimate of the average treatment effect in the IVA-treated group (ie, the average difference that would be found if all people in the IVA-treated group received treatment vs if none received treatment).[22] Standardised mean differences were calculated to evaluate the comparability of baseline characteristics, with a difference <10% indicating that covariates were

adequately balanced by SMR weighting. Unbalanced covariates after SMR weighting were included in the regression analysis to control for residual confounding. For most of the years under study, the comparator cohort was ineligible for any CFTRm therapies so their CFTRm-untreated status was unrelated to disease severity or outcome.

Study measures

The outcomes of interest during the follow-up period were OS, time to lung transplant, $ppFEV_1$, BMI, BMI *z*-score, PEx, outpatient visits and hospitalisations. OS and time to lung transplant were evaluated as the time from the index date to the date of death and lung transplant, respectively. Lung function over each 6-month period during the follow-up period was defined as the average of the best available $ppFEV_1$ measurements for two quarters; if $ppFEV_1$ measurements were not available in one-quarter, the highest $ppFEV_1$ measurement in each 6-month period was used. BMI was calculated as the average BMI over 6-month periods for people aged ≥20 years; for people aged ≥6 to 19 years, average BMI *z*-scores over 6-month periods were calculated. If $ppFEV_1$, BMI and BMI *z*-scores data were missing over a 6-month period during follow-up, the value of the last observation was carried forward (ie, the value from the previous 6-month period was used in place of the missing observation). PEx included episodes requiring home intravenous antibiotic use or hospitalisations for PEx, both of which were also assessed separately as suboutcomes. Outpatient visits included those made to the CF centres and reported to the US CFFPR. Hospitalisations were categorised as all-cause hospitalisations, pulmonary-related hospitalisations (ie, for PEx and other pulmonary complications) and gastrointestinal complication-related hospitalisations. The same approach was used to calculate $ppFEV_1$, BMI, BMI *z*-scores, PEx, outpatient visits and hospitalisations during the baseline period. Values for $ppFEV_1$ and PEx were reported for both years during the baseline period to account for different rates of disease progression; all other baseline covariates were assessed in the year prior to or on the index date.

Statistical methods

All analyses were performed by using SAS Enterprise Guide V.7.1 (SAS Institute). Baseline characteristics were summarised with frequencies and percentages for categorical variables and with means and SDs for continuous variables. We performed SMR-weighted time-to-event analyses for OS and lung transplant using Kaplan-Meier estimation of survival functions and Cox proportional hazard model estimation of adjusted HRs. SMR-weighted cumulative risk differences were estimated as the difference in mortality risk between cohorts at specific time points, as calculated from the Kaplan-Meier analysis. The mean differences in $ppFEV_1$, BMI and BMI *z*-scores between cohorts were estimated using an SMR-weighted generalised estimating equation approach, with a normal distribution and autoregressive covariance structure; time was included in the model to adjust for differences in follow-up time between individuals. Mean differences in $ppFEV_1$ between cohorts at 12, 24, 36, 48 and 60 months postindex were estimated using SMR-weighted generalised estimating equations with an interaction term between IVA treatment and time in months. Analyses stratified by age group at index date (ie, 6 to <12, 12 to <18 and ≥18 years) were conducted to assess mean differences in $ppFEV_1$ at 12-month increments. The age groups were selected to isolate the 12 to <18 year range due to its high rate of lung function decline but were not stratified further to maximise sample size and power. PEx, outpatient visit and hospitalisation rates (per person-year) were calculated by dividing PEx, outpatient visit or hospitalisation frequency by person-time accrued. SMR-weighted generalised linear models with negative binomial distribution were used to calculate adjusted rate ratios for PEx, outpatient visits and hospitalisations. For all SMR-weighted analyses, 95% CIs were calculated using a nonparametric bootstrap procedure with 999 replications, where SMR weights were re-estimated within each replication.

Role of the funding source

The funder (Vertex Pharmaceuticals Incorporated; no award/grant number) was involved in study design and data interpretation, and reviewed and provided feedback during the writing of this manuscript. All authors had appropriate access to study data, based on their role, for purposes of fully appraising results, and all authors had final responsibility for the decision to submit for publication.

RESULTS

Most (90.4%; 1394/1542) people aged ≥6 years with *CFTR*-gating mutations (and without *R117H* and RF mutations) in the US CFFPR initiated IVA after 31 January 2012 to 31 December 2018. The IVA-treated and comparator cohorts included 736 and 2944 people with CF, respectively. SMR weighting reweighted the people in the comparator cohort (N=2944) to be similar to those in the IVA-treated cohort (N=736) at baseline resulting in a sample size of 733 people with CF in the comparator cohort. SMR weighting balanced the distribution of baseline characteristics between cohorts (online supplemental table S2). In both cohorts, approximately 48% of people were female and >90% were white. The mean (SD) best-available quarterly $ppFEV_1$ during the first and second years of the baseline period were 80.6 (24.6) and 80.2 (25.3) percentage points, respectively, in the IVA-treated cohort versus 79.7 (12.3) and 79.3 (12.7) percentage points, respectively, in the comparator cohort. Both cohorts had similar, modest declines in lung function between the first and second years of the baseline period, with mean (SD) changes in $ppFEV_1$ of −0.9 (8.7) and −1.1 (4.5) percentage points per year for the IVA-treated and comparator cohorts, respectively. The mean (SD) number of PEx during the first and second years of the baseline period were 0.6 (1.1) and 0.6 (1.2), respectively, in the IVA-treated cohort and 0.7 (0.6) and 0.6 (0.6), respectively, in the comparator cohort. The mean (SD) BMI in people ≥20 years of age was 22.9 (3.7) kg/m^2 in the IVA-treated cohort and 22.7 (1.6) kg/m^2 in the comparator cohort. Select SMR-weighted baseline characteristics of the study population are shown in table 1.

Over a maximum follow-up period of 7.9 years (mean follow-up: ≈6 years), the IVA-treated cohort had a significantly lower mortality rate (78% lower) than the comparator cohort (HR (95% CI): 0.22 (0.09 to 0.45); figure 1). When mortality risk in the two cohorts was compared at 12-month increments over a 5-year follow-up period, the SMR-weighted cumulative risk of mortality was lower in the IVA-treated cohort than in the comparator cohort at all time points, with a risk difference (95% CI) of −1.27% (−2.04% to −0.47%) at 12 months and −3.54% (95% CI −5.15% to −1.89%) at 60 months postindex (online supplemental figure S3). The IVA-treated cohort also had a significantly lower rate of lung transplant than the comparator cohort (89% lower; HR (95% CI): 0.11 (0.02 to 0.28); figure 2).

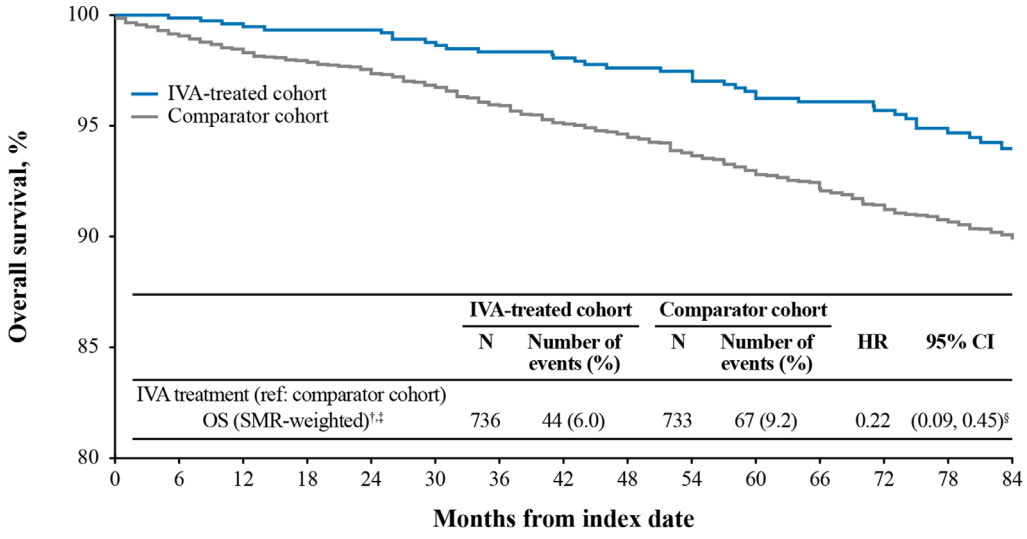
IVA was associated with a marked improvement in lung function (figure 3). Over a mean (range) SMR-weighted follow-up

Table 1 Select baseline demographic and clinical characteristics

	Original sample			SMR-weighted sample*		
	IVA-treated cohort N=736	Comparator cohort N=2944	Std diff (%)†	IVA-treated cohort N=736	Comparator cohort N=733	Std diff (%)†
Demographic characteristics						
Female, n (%)	353 (48.0)	1369 (46.5)	2.9	353 (48.0)	348 (47.5)	0.9
Race, n (%)‡						
Black/African American	30 (4.1)	133 (4.5)	−2.2	30 (4.1)	28 (3.8)	1.2
White	691 (93.9)	2794 (94.9)	−4.4	691 (93.9)	693 (94.6)	−3.0
Other§	25 (3.4)	51 (1.7)	10.5#	25 (3.4)	23 (3.2)	1.1
Index year, n (%)						
2012	446 (60.6)	1790 (60.8)	−0.4	446 (60.6)	440 (60.0)	1.2
2013	121 (16.4)	473 (16.1)	1.0	121 (16.4)	122 (16.6)	−0.5
2014	98 (13.3)	401 (13.6)	−0.9	98 (13.3)	103 (14.1)	−2.2
2015	33 (4.5)	125 (4.2)	1.2	33 (4.5)	30 (4.2)	1.6
2016	11 (1.5)	47 (1.6)	−0.8	11 (1.5)	10 (1.4)	1.0
2017	14 (1.9)	57 (1.9)	−0.2	14 (1.9)	15 (2.0)	−0.8
2018	13 (1.8)	51 (1.7)	0.3	13 (1.8)	13 (1.8)	0.1
Clinical characteristics						
$ppFEV_1$ during first year of the baseline period¶						
People with available data, n	658	2593	14.0#	658	653	4.6
Mean±SD, percentage points	80.6±24.6	77.1±25.4		80.6±24.6	79.7±12.3	
$ppFEV_1$ during second year of baseline period¶						
People with available data, n	663	2660	15.6#	663	660	4.6
Mean±SD, percentage points	80.2±25.3	76.2±26.0		80.2±25.3	79.3±12.7	
Change in $ppFEV_1$¶,††						
People with available data, n	620	2451	10.7#	620	616	2.9
Mean±SD, percentage points	−0.9±8.7	−1.8±8.4		−0.9±8.7	−1.1±4.5	
95% CI, percentage points	−1.58,−0.22	−2.13,−1.47		−1.58,−0.22	−1.46,−0.74	
No. of PEx during first year of baseline period, mean±SD	0.6±1.1	0.7±1.2	−7.8	0.6±1.1	0.7±0.6	−0.5
No. of PEx during second year of baseline period, mean±SD	0.6±1.2	0.8±1.3	−12.2#	0.6±1.2	0.6±0.6	−0.7
BMI in people ≥20 years						
People with available data, n	282	1136	28.3#	282	280	6.4
Mean±SD, kg/m^2	22.9±3.7	21.9±3.4		22.9±3.7	22.7±1.6	
BMI *z*-score in people aged 6–19 years**						
People with available data, n	403	1635	15.9#	403	402	1.7
Mean±SD	0.1±1.0	−0.1±0.9		0.1±1.0	0.0±0.5	
No. of all-cause hospitalisations, mean±SD	0.7±1.2	0.8±1.3	−10.7#	0.7±1.2	0.7±0.6	−0.6

*Covariates included in the propensity score used to generate SMR weights were sex, race, ethnicity, type of health insurance, employment status, median household income by zip code (categorical), education level, average of best available $ppFEV_1$ in each quarter (categorical), change in $ppFEV_1$ (categorical), number of PEx, average BMI/BMI *z*-scores (categorical), prevalence of cystic fibrosis-related complications, prevalence of respiratory micro-organisms, number of hospitalisations and outpatient visits, and medication use.
†Standardised differences >10% in magnitude are denoted with "#".
‡People may belong to ≥1 category; therefore, the sum of percentages may exceed 100%.
§Other race included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander and other races that were not specified.
¶$ppFEV_1$ data were not available for people ≤6 years of age.
**BMI *z*-scores were calculated using BMI percentiles for patients aged 6–19 years at index.
††Change in $ppFEV_1$ was calculated as the average of the best available $ppFEV_1$ in each quarter of the second year in the baseline period minus the average of the best available $ppFEV_1$ in each quarter of the first year in the baseline period. A negative change indicates a decline in $ppFEV_1$, and a positive change indicates improvement during the baseline period.
BMI, body mass index; Std diff, standardised difference; IVA, ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, per cent predicted forced expiratory volume in 1 s; SD, standard deviation; SMR, standardised mortality ratio.

duration of 5.6 (0.1–7.9) years in the IVA-treated cohort and 6.0 (0.0–7.9) years in the comparator cohort, the mean $ppFEV_1$ was >8 points higher in the IVA-treated cohort than in the comparator cohort (mean difference in $ppFEV_1$ (95% CI): 8.46 (7.34 to 9.75); online supplemental table S3). Notably, the mean difference (95% CI) in $ppFEV_1$ between cohorts increased over time, from 7.98 (6.71 to 9.34) at 12 months to 10.95 (9.22 to 12.72) at 60 months postindex. Across age groups, the largest



	IVA-treated cohort		Comparator cohort			
	N	Number of events (%)	N	Number of events (%)	HR	95% CI
IVA treatment (ref: comparator cohort)						
OS (SMR-weighted)†,‡	736	44 (6.0)	733	67 (9.2)	0.22	(0.09, 0.45)§

IVA-treated cohort															
Number with event	<5	<5	<5	5	5	9	12	14	17	18	26	27	29	34	37
Number at risk	736	734	729	724	714	704	691	682	669	658	619	597	524	462	397
Comparator cohort															
Number with event	<5	6	13	16	20	26	32	37	40	45	51	54	60	63	65
Number at risk	733	725	714	707	692	678	661	651	639	622	595	563	489	429	368

Figure 1 SMR-weighted Kaplan-Meier analysis and HRs for overall survival. Covariates included in the propensity score used to generate SMR weights were sex, race, ethnicity, type of health insurance, employment status, median household income by zip code (categorical), education level, average of best available ppFEV$_1$ in each quarter (categorical), change in ppFEV$_1$ (categorical), number of PEx, average BMI/BMI *z*-scores (categorical), prevalence of CF-related complications, prevalence of respiratory micro-organisms, number of hospitalisations and outpatient visits, and medication use. †People without the event were censored at their end of data availability, which was imputed as 31 December of the last year that the individual had annual data available. The mean SMR-weighted follow-up duration was 6.5 years in the IVA-treated cohort and 6.3 years in the comparator cohort. ‡Visual inspection of Schoenfeld residuals was performed to assess the proportional hazards assumption for IVA treatment. As the proportional hazards assumption was violated, a treatment-by-time interaction term was included in the model to account for time-dependent effects. §95% CI does not include the null. BMI, body mass index; CI: confidence interval; HR: hazard ratio; IVA, ivacaftor; PEx, pulmonary exacerbation; ppFEV$_1$, per cent predicted forced expiratory volume in 1 s; OS, overall survival; ref: reference; SMR, standardised mortality ratio.

mean difference (95% CI) in ppFEV$_1$ spanning all time points was observed in people aged 12 to <18 years, from 10.19 (7.29 to 12.74) at 12 months to 15.26 (11.48 to 18.69) at 60 months.

Over a mean (range) SMR-weighted follow-up duration of 5.3 (0.1–7.9) years for the IVA-treated cohort and 5.8 (0.0–7.9) years for the comparator cohort, people aged ≥20 years in the IVA-treated cohort had a significantly higher mean BMI than those in the comparator cohort (24.30 vs 22.92 kg/m^2), with a mean difference (95% CI) of 1.20 (0.92 to 1.71) kg/m^2 (online supplemental table S3). Similarly, for people aged 6–19 years, the IVA-treated cohort had a significantly higher mean BMI *z*-score than the comparator cohort (mean difference (95% CI): 0.27 (0.25 to 0.40)) over a mean follow-up duration of ≥6.0 years.

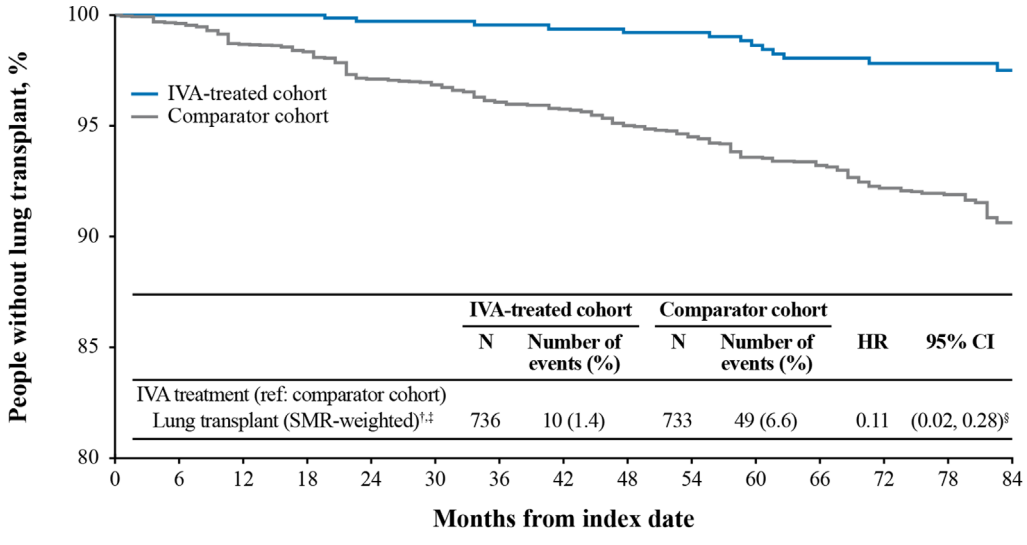
The rate of PEx was 51% lower in the IVA-treated than in the comparator cohort (rate ratio (95% CI): 0.49 (0.42 to 0.55); figure 4). People in the IVA-treated cohort had significantly lower rates of all-cause hospitalisations (rate ratio (95% CI): 0.50 (0.43 to 0.56)) and outpatient clinic visits (rate ratio (95% CI): 0.85 (0.81 to 0.88)) than those in the comparator cohort.

DISCUSSION

As advances in care continue to extend life expectancy in CF, it is becoming increasingly important to understand the long-term impact of novel therapies, including CFTRm, on clinical outcomes and survival. IVA, the first CFTRm therapy approved to treat the underlying cause of CF in the US,[7] reached its 10-year approval anniversary in 2022. At the time of its approval, expectations were high that IVA could alter the clinical course of CF in eligible patients, leading to increased survival, improved quality of life and reduced treatment burden.[23] With a maximum of 7.9 years of data on treatment outcomes with IVA, this study represents the longest follow-up of people receiving CFTRm to date. These long-term data provide evidence of the durable benefits of IVA, including decreased mortality and lung transplant, improvements in pulmonary outcomes and nutritional status, and reductions in hospitalisations and outpatient visits.

Over a maximum follow-up period of 7.9 years, the mortality rate was 78% lower in the IVA-treated cohort than in the comparator cohort. People receiving IVA also had a significantly lower rate of lung transplant for up to 7 years after IVA initiation. These reductions in the rates of mortality and lung transplant are in line with findings from earlier analyses of US CFFPR data,[13 14 16] including a recent cross-sectional analysis in 2019 that reported that IVA reduced the risks of death and organ transplant by ≈60% and ≈70%, respectively.[16]

Long-term use of IVA was associated with improved pulmonary outcomes, with sustained improvements in ppFEV$_1$ and decreased rate of PEx in the IVA-treated versus comparator cohorts. In people with CF receiving IVA, a higher mean ppFEV$_1$ relative to that in the comparator cohort was observed over the total follow-up period, with increasing mean differences in ppFEV$_1$ over time. Taken together with data from clinical trials that demonstrated improvements in ppFEV$_1$ as early as 15 days



	IVA-treated cohort N	IVA-treated cohort Number of events (%)	Comparator cohort N	Comparator cohort Number of events (%)	HR	95% CI
IVA treatment (ref: comparator cohort)						
Lung transplant (SMR-weighted)†,‡	736	10 (1.4)	733	49 (6.6)	0.11	(0.02, 0.28)§

IVA-treated cohort															
Number with event	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	7	10	10	10	10
Number at risk	736	730	696	673	646	623	604	588	566	541	503	474	399	346	288
Comparator cohort															
Number with event	<5	<5	8	10	15	16	21	23	27	28	35	36	42	44	49
Number at risk	733	722	706	696	677	665	644	632	618	601	566	533	452	396	323

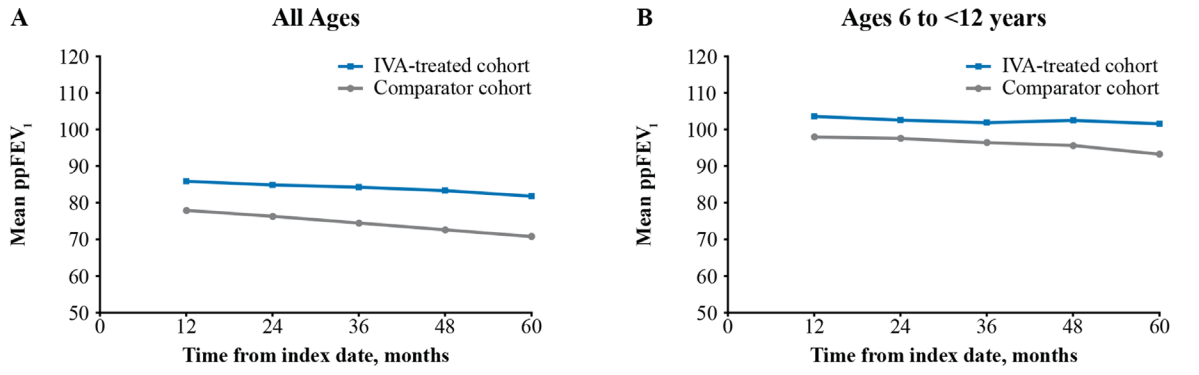
Figure 2 SMR-weighted Kaplan-Meier analysis and HRs for lung transplant. Covariates included in the propensity score used to generate SMR weights were sex, race, ethnicity, type of health insurance, employment status, median household income by zip code (categorical), education level, average of best available $ppFEV_1$ in each quarter (categorical), change in $ppFEV_1$ (categorical), number of PEx, average BMI/BMI *z*-scores (categorical), prevalence of CF-related complications, prevalence of respiratory microorganisms, number of hospitalisations and outpatient visits, and medication use. †People without the event were censored at the first occurrence of treatment with a CFTRm therapy other than IVA, death, pregnancy or end of data availability. As only annual pregnancy and lung transplant data were available, the date of pregnancy and lung transplant were imputed as 1 January. The end of data availability was imputed as 31 December of the last year that the individual had annual data available. People in the IVA-treated cohort were also censored at time of IVA discontinuation. Patients in the comparator cohort were also censored at the time of first occurrence of treatment with IVA. The mean SMR-weighted follow-up duration was 5.6 years for the IVA-treated cohort and 6.0 years for the comparator cohort. ‡Visual inspection of Schoenfeld residuals was performed to assess the proportional hazards assumption for IVA treatment. As the proportional hazards assumption was violated, a treatment-by-time interaction term was included in the model to account for time-dependent effects. §95% CI does not include the null. BMI, body mass index; CI: confidence interval; CF, cystic fibrosis; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; HR: hazard ratio; IVA, ivacaftor; PEx, pulmonary exacerbation; $ppFEV_1$, per cent predicted forced expiratory volume in 1 s; ref: reference; SMR, standardised mortality ratio.

after IVA initiation[9 10] and prior analyses of real-world data showing that improvements in $ppFEV_1$ were sustained over 3–5 years of IVA treatment,[13 14] these data suggest that IVA leads to better lung function that is sustained with long-term use (up to 7.9 years). Additionally, although higher mean $ppFEV_1$ values were observed between the IVA-treated versus comparator cohorts across all age groups evaluated in this study, the largest improvement in $ppFEV_1$ was observed in people aged 12 to <18 years at IVA initiation, highlighting the importance of treatment during adolescence, a period characterised by rapid lung function decline.[24 25]

In people who received IVA, the rate of PEx was less than half of that in the comparator cohort. While no differences in the number of PEx were observed between the IVA and placebo groups in the pivotal clinical trial evaluating people with CF aged 6–11 years (3 vs 4 PEx events, respectively),[10] IVA reduced the risk of PEx by 55% at 48 weeks in a clinical trial evaluating those aged ≥12 years,[9] consistent with the reduction in PEx observed in this study. Similarly, in real-world studies, reductions in the occurrence of PEx have been demonstrated over 1–5 years of IVA treatment.[13 14] Altogether these findings support that IVA leads to reductions in the rate of PEx that are maintained for up to 7.9 years. Because PEx is associated with increased risk of mortality, lung transplant and lung function decline,[26–29] the sustained reductions in PEx with long-term IVA treatment may contribute to the reductions in mortality and lung transplant and the improvements in lung function observed concurrently in this study.

In addition to improving lung function and reducing the rates of mortality and lung transplant, long-term IVA led to improvements in nutritional status, with significantly higher mean BMI and BMI *z*-score in the IVA-treated cohort than in the comparator cohort. This is consistent with the shorter-term improvements in BMI and BMI *z*-score demonstrated in clinical trials[10 12] and in previous real-world studies with short-term and long-term follow-up data.[14 15] Because higher BMI has been linked to better lung function in CF,[30] the sustained improvements in BMI observed here provide further evidence for the overall long-term health benefits of IVA.

The improvements in lung function and nutritional status with long-term IVA were accompanied by a reduction in healthcare burden in this study. The rate of all-cause hospitalisations was reduced by half, and there were fewer outpatient clinic visits in the IVA-treated cohort than in the comparator cohort. This is consistent with previous real-world analyses, which reported decreases in the rate of hospitalisations as early as 6 months and up to 5 years after IVA initiation[14 31–33] and a decrease in outpatient clinic visits in the year after IVA initiation.[33] These findings



All Ages

N§					
IVA-treated cohort	669	690	694	697	699
Comparator cohort	661	681	685	689	690
Difference in ppFEV$_1$, percentage points**					
Mean	7.98	8.55	9.81	10.73	10.95
95% CI	(6.71, 9.34)††	(7.25, 10.01)††	(8.44, 11.38)††	(9.37, 12.26)††	(9.22, 12.72)††

Ages 6 to <12 years

N§					
IVA-treated cohort	166	178	178	179	180
Comparator cohort	163	175	175	176	176
Difference in ppFEV$_1$, percentage points**					
Mean	5.61	4.99	5.45	6.83	8.30
95% CI	(3.18, 7.88)††	(2.60, 7.16)††	(2.58, 8.17)††	(3.94, 9.52)††	(4.89, 11.10)††

Ages 12 to <18 years

N§					
IVA-treated cohort	159	161	163	164	164
Comparator cohort	154	157	159	160	160
Difference in ppFEV$_1$, percentage points**					
Mean	10.19	12.25	13.32	13.64	15.26
95% CI	(7.29, 12.74)††	(9.09, 15.02)††	(10.04, 16.34)††	(9.85, 17.18)††	(11.48, 18.69)††

Ages ≥18 years

N§					
IVA-treated cohort	344	351	353	354	355
Comparator cohort	336	341	343	344	345
Difference in ppFEV$_1$, percentage points**					
Mean	8.10	9.19	10.12	11.83	13.01
95% CI	(6.25, 10.23)††	(7.28, 11.24)††	(8.00, 12.36)††	(9.85, 14.11)††	(10.84, 15.60)††

Figure 3 SMR-weighted mean ppFEV$_1$ over time. **,†, ‡ For data missing over a 6-month period in the follow-up period, the value of the last observation was carried forward (ie, the individual's value from the previous 6-month period was used in place of the missing observations). †People were censored at the first occurrence of treatment with a CFTRm therapy other than IVA, death, pregnancy, lung transplant or end of data availability. As only annual pregnancy and lung transplant data were available, the date of pregnancy and lung transplant were imputed as 1 January. The end of data availability was imputed as 31 December of the last year that the individual had annual data available. People in the IVA-treated cohort were also censored at time of IVA discontinuation. People in the comparator cohort were also censored at time of first occurrence of treatment with IVA. ‡Covariates included in the propensity score used to generate SMR weights were sex, race, ethnicity, type of health insurance, employment status, median household income by zip code (categorical), education level, average of best available ppFEV$_1$ in each quarter (categorical), change in ppFEV$_1$ (categorical), number of PEx, average BMI/BMI *z*-scores (categorical), prevalence of CF-related complications, prevalence of respiratory micro-organisms, number of hospitalisations and outpatient visits, and medication use. Due to extreme propensity scores, trimming weights at the first and the 99th percentile was used to reduce the contribution of individuals with large weights, as they were unlikely to be representative of the overall study cohorts. §Matched groups with all individuals having ≥1 ppFEV$_1$ measurement between the index date and the end of 12, 24, 36, 48 or 60 months were included in the analysis for the corresponding time period. Matched groups were dropped if they included ≥1 individual with no outcome measurements available during the observation period. **The mean ppFEV$_1$ and mean differences were estimated using generalising estimating equation models with normal distribution and autoregressive covariance structure while adjusting for follow-up time. Interaction terms between IVA and time variables were also included in the model. SMR weights for the IVA-treated and comparator cohorts were incorporated in calculating the intercept and slope estimates in the model. This resulted in a small difference in the unadjusted and SMR-weighted mean ppFEV$_1$ values for the IVA cohort. ††95% CI does not include the null. BMI, body mass index; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; IVA, ivacaftor; PEx, pulmonary exacerbation; ppFEV$_1$, per cent predicted forced expiratory volume in 1 s; SMR, standardised mortality ratio.

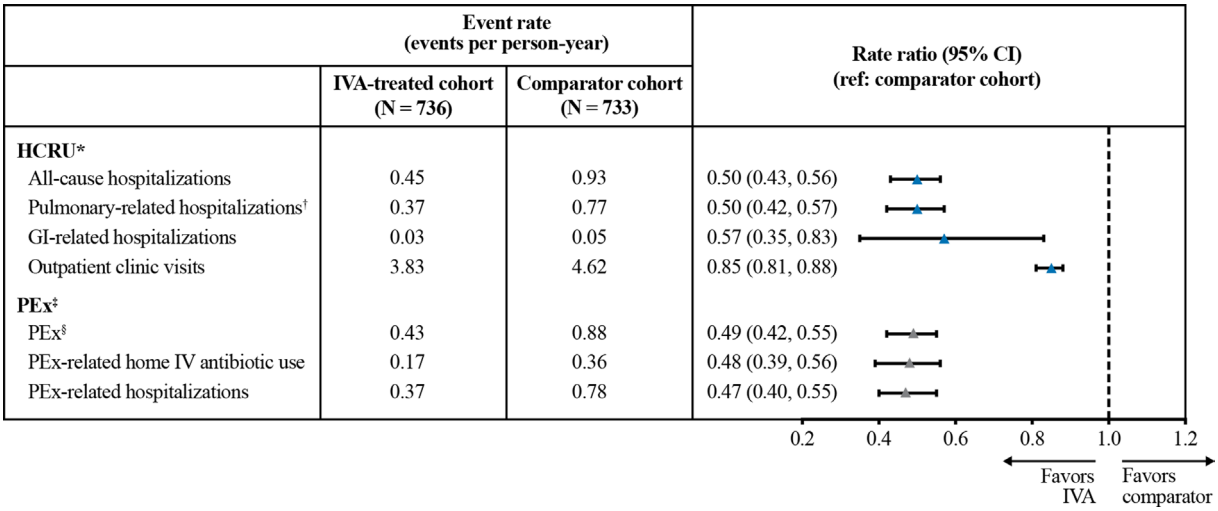


Figure 4 SMR-weighted IRRs for comparison of hospitalisations, outpatient visits and PEx. *The mean (min–max) SMR-weighted follow-up duration was 5.7 (0.1–7.9) years in the IVA-treated cohort and 6.2 (0.0–7.9) years in the comparator cohort. †Pulmonary-related hospitalisations included PEx-related hospitalisations and hospitalisations related to pulmonary complications. ‡The mean (min–max) SMR-weighted follow-up duration was 5.6 (0.1–7.9) years in the IVA-treated cohort and 6.0 (0.0–7.9) years in the comparator cohort. §PEx included episodes requiring home IV antibiotics or PEx-related hospitalisations. GI, gastrointestinal; HCRU: healthcare resource utilization; IV: intravenous; IVA, ivacaftor; PEx, pulmonary exacerbation; ref, reference; SMR, standardised mortality ratio.

suggest that IVA reduces disease burden in people with CF, as evidenced by a reduction in hospitalisations and outpatient visits, a benefit that was sustained with long-term treatment.

As the first drug to treat the underlying cause of CF, IVA represents a major change to the treatment landscape. Consistent with previous evidence[14 15 34] but over a longer follow-up, this study shows that IVA improves survival, preserves lung function, improves nutritional status, and reduces PEx and hospitalisations. More people with CF may be able to gain similar therapeutic benefits given the development and approval of elexacaftor/tezacaftor/IVA (ELX/TEZ/IVA)—a CFTRm therapy that combines IVA with the CFTR correctors TEZ and ELX—which expanded the eligibility for CFTRm to include ≈90% of people with CF in the US.[35] Although studies examining the long-term effectiveness of ELX/TEZ/IVA are ongoing, similarities in mechanism of action and shorter-term efficacy observed between IVA and ELX/TEZ/IVA in their indicated populations, suggest that similar long-term outcomes may be predicted with ELX/TEZ/IVA.

The US CFFPR includes data from an estimated 81% to 84% of people with CF in the US;[17] as such, this study offers a comprehensive view of the clinical profile and health outcomes of people with CF in the US. Importantly, we selected a comparator population that was phenotypically similar to the IVA-treated cohort and used robust methodology to enhance comparability between the cohorts, including SMR weighting based on propensity scores, which allowed for estimating the average treatment effect in the IVA-treated cohort and maximised sample size and power. However, this study had limitations that warrant consideration. First, since this was an observational study, it was only possible to control for measured covariates; this may have resulted in residual confounding despite the use of exact matching by age at index date and SMR weighting to minimise differences between groups in measured prognostic factors. A lack of standardised assessments and regular clinic visits for some people in the US CFFPR are also limitations of the data. Second, the results of this study may not be generalisable to all people with a *CFTR*-gating mutation in the CFFPR as people with a *CFTR*-gating mutation who did not initiate IVA during the study period and were not included in this study may be different from people in the IVA-treated cohort. Third, while we aimed to select a comparator population that was phenotypically similar to the IVA-treated cohort in the CFFPR, mutation classes include phenotypic variation and other differences may exist between people with a *CFTR*-gating mutation and people with *F508del*/minimal function *CFTR* mutations. While these differences may have impacted the results, we minimised this by adjusting for demographic and clinical differences at baseline between cohorts using SMR weighting.

Additionally, our analysis may have been subject to some degree of bias from informative censoring, which could have occurred if the patients who discontinued IVA (and were censored from the study) were different from the patients who continued receiving IVA in terms of disease severity, clinical outcomes or mortality. Finally, because ELX/TEZ/IVA was initially approved by the US FDA for the treatment of CF in October 2019 and a large proportion of people in the IVA-treated and comparator cohorts were expected to initiate ELX/TEZ/IVA thereafter, we limited our analysis to data collected through the end of 2019 to mitigate the impact of ELX/TEZ/IVA eligibility on cohort attrition.

CONCLUSION

This real-world study using US CFFPR data over 7.9 years of follow-up shows that people receiving IVA have lower rates of mortality and lung transplant, improvements in lung function and nutritional status, and reductions in PEx, outpatient visits, and hospitalisations compared with phenotypically similar CFTRm-untreated people with CF. These findings add to the body of real-world evidence demonstrating that IVA results in sustained and durable benefits in people with CF, including slowing disease progression and decreasing the associated healthcare burden.

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Contributors CAM (guarantor), TT, MD, LJM, JH, JLR and MAB contributed to study conception, design or supervision. CN and YMG accessed and verified the underlying deidentified patient-level data included in the study report and reported in this manuscript, prepared the analytical data files and conducted statistical analyses. CAM accessed and verified the study report and all underlying group-level data reported in this manuscript. All authors contributed to interpretation of the study results and drafting and critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Patient consent for publication Not applicable.

Ethics approval This study uses deidentified, retrospective data from the US Cystic Fibrosis Foundation Patient Regsitry (CFFPR). The US CFFPR protocol review committee provided feedback and approved the protocol prior to study start. The Advarra institutional review board (IRB) granted an exemption for this study based on the scope of the research in July 2020. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data supporting the findings of this study are available from the US CFFPR at https://www.cff.org/researchers/patient-registry-data-requests. The US CFFPR collects and manages its own data and maintains processes for researchers to request summarised data. Restrictions may apply to the availability of these data, which were used under the licence agreement for this study.

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