BRIEF REPORT

Long-Term Impact of Ivacaftor on Healthcare Resource Utilization Among People with Cystic Fibrosis in the United States

Teja Thorat · Lisa J. McGarry · Krutika Jariwala-Parikh ·

Brendan Limone · Machaon Bonafede · Keval Chandarana ·

Michael W. Konstan

ABSTRACT

Introduction: Ivacaftor was first approved in 2012 for the treatment of a select population of individuals with cystic fibrosis (CF), a rare, life-shortening genetic disease. Reductions in healthcare resource utilization (HCRU) associated with ivacaftor have been observed during limited follow-up and for selected outcomes in real-world studies. This study aimed to further describe the long-term impact of ivacaftor treatment on multiple measures of HCRU among people with CF (pwCF).

Methods: This retrospective study used US commercial and Medicaid claims data from 2011–2018. We included pwCF $\geq$ 6 years of age with $\geq$ 1 claim for ivacaftor and 12 months of continuous health plan enrollment before ivacaftor initiation ("pre-ivacaftor" period) who also had 36 months of continuous enrollment and persistent ivacaftor use (i.e., no gap $\geq$ 90 days between refills) following initiation ("post-ivacaftor" period). We compared comorbidities occurring pre-ivacaftor versus the last 12 months post-ivacaftor. HCRU outcomes included medication use, inpatient admissions, and outpatient office visits. We compared medication use pre-ivacaftor versus the last 12 months post-ivacaftor and inpatient admissions and outpatient office visits pre-ivacaftor versus the post-ivacaftor period annualized across 36 months.

Results: Seventy-nine pwCF met all criteria, including persistent ivacaftor use during the post-ivacaftor period. Ivacaftor treatment was associated with a significant reduction in pneumonia prevalence (10.1% vs. 26.6%; $p < 0.001$) and significantly fewer mean [SD] antibiotics claims (8.0 [7.3] vs. 12.3 [11.1]; $p < 0.001$) in the last 12 months post-ivacaftor versus pre-ivacaftor. In comparing the 36-month post-ivacaftor period to the pre-ivacaftor period, we also observed fewer mean [SD] annual inpatient admissions (0.2 [0.4] vs. 0.4 [0.7]), CF-related inpatient admissions (0.1 [0.2] vs. 0.2 [0.5]), and outpatient office visits (8.8 [4.9] vs. 9.9 [5.4]) (all, $p < 0.05$).

Conclusion: Long-term ivacaftor treatment reduced HCRU, consistent with trends observed in prior real-world studies. Our results support the sustained, long-term value of ivacaftor treatment in reducing CF burden.

T. Thorat (✉) · L. J. McGarry · K. Chandarana
Vertex Pharmaceuticals Incorporated, 50 Northern Ave, Boston, MA 02210, USA
e-mail: Teja_Thorat@vrtx.com

K. Jariwala-Parikh · B. Limone
IBM Watson Health, Boston, MA, USA

M. Bonafede
Veradigm Life Sciences, An Allscripts Healthcare LLC, Chicago, IL, USA

M. W. Konstan
Case Western Reserve University and Rainbow Babies and Children's Hospital, Cleveland, OH, USA

Key Summary Points

Why carry out this study?

Cystic fibrosis (CF) is a rare, life-shortening, inherited disease associated with high use of healthcare resources, such as hospital visits, physician office visits, and prescription medications, throughout a person's life. In clinical trials and real-world studies, ivacaftor treatment has been shown to result in reductions in use of certain healthcare resources.

Given the progressive nature of CF, it is important to understand the long-term impact of ivacaftor treatment on healthcare resource utilization in real-world settings and to continue to demonstrate its effectiveness to the CF community.

This study aimed to describe the long-term impact of ivacaftor treatment on use of healthcare resources among people with CF aged ≥ 6 years.

What was learned from the study?

Using US administrative claims data, we showed that people with CF treated with ivacaftor for 36 months (3 years) had fewer all-cause and CF-related hospital stays, fewer physician visits, and lower prevalence of pneumonia, decreased use of mucolytics and opioids, and fewer prescription claims for antibiotics compared with before ivacaftor treatment.

These results support and reinforce the sustained, long-term value of ivacaftor treatment in lowering the burden of CF.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14236934.

INTRODUCTION

Cystic fibrosis (CF) is a progressive, life-shortening genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, resulting in absent or dysfunctional CFTR protein channels at the cell surface [1, 2]. CF affects approximately 30,000 people in the United States and approximately 90,000 people globally [3, 4]. CF is a multiorgan disease that leads to significant morbidity and mortality and requires complex polypharmacy and engagement with health systems from diagnosis (often at or shortly after birth) until death [2, 3, 5, 6]. The progressive nature of the disease is evident in the observed annual decline of 1–3 percentage points in lung function among people with CF (pwCF), as well as their increasing healthcare burden over time [7–9]. Progressive loss of lung function is the leading cause of mortality [2, 10].

Ivacaftor is a small-molecule CFTR potentiator that increases CFTR channel opening probability, leading to increased chloride transport and thus addressing the underlying cause of the disease in pwCF with select mutations (e.g., gating mutations) [11]. Ivacaftor is approved in the USA, Europe, and other parts of the world for pwCF across a range of genotypes [12–14]. Indications vary among regions by age and *CFTR* mutations [12–14]. In clinical trials, ivacaftor use has demonstrated substantial reductions in pulmonary exacerbations (PEx), as well as improvement in lung function, reduction in annual rate of decline in lung function, and improvement in quality of life [15–17]. Since ivacaftor's approval in 2012, there has been growing interest in the long-term impact of ivacaftor on healthcare resource utilization (HCRU) in real-world settings.

Administrative claims data are an important real-world data source for HCRU and are widely used to identify a sample of people who meet select criteria in order to evaluate the impact of a treatment on resource use [18]. Prior real-world studies that used administrative claims data to assess the impact of ivacaftor on HCRU have reported reductions in medication use, hospitalizations, and office visits over a follow-up period of 12 months after ivacaftor initiation [19, 20]. To support and build on these findings, it is important to understand the long-term impact of ivacaftor treatment on HCRU given the progressive nature of the disease, as well as to continue demonstrating the effectiveness of ivacaftor to pwCF, physicians, and payers. Here, we evaluated the impact of long-term ivacaftor use on HCRU among pwCF ≥ 6 years of age using administrative claims data in the USA.

METHODS

This non-interventional, retrospective study used data from the IBM® MarketScan® Commercial Claims and Encounters Database and the Medicaid Multi-State Database (both, IBM Watson Health; Sacramento, CA) spanning the period from January 1, 2011, to December 31, 2018. We identified pwCF with ≥ 1 prescription claim for ivacaftor from January 1, 2012, through December 31, 2015. The date of the first prescription claim for ivacaftor was defined as the index date. PwCF were required to be ≥ 6 years of age on the index date. A 12-month period of continuous enrollment in medical and pharmacy benefits (i.e., a health plan) prior to the index date, defined as the pre-ivacaftor initiation period (pre-ivacaftor), was required for study inclusion. Individuals were required to have ≥ 1 medical claim with an International Classification of Diseases (ICD)–9 (277.0x) or ICD-10 (E84.x) diagnosis code for CF during the pre-ivacaftor period or on the index date. PwCF were also required to have ≥ 36 months of continuous enrollment in the health plan after the index date and persistent use of ivacaftor, defined as no gap of ≥ 90 days after the end of supply and the start of the next refill. The 36-month period following ivacaftor

initiation was defined as the post-ivacaftor initiation period (post-ivacaftor). The requirement for persistent ivacaftor use was important in order to evaluate the long-term impact of ivacaftor treatment with minimal or no treatment interruption.

Baseline characteristics, including age, sex, payer type, population density, insurance plan type, and year of ivacaftor initiation, were collected at the index date. Comorbidities were identified during the pre-ivacaftor period and during the last 12 months of the post-ivacaftor period (months 25–36) using ICD-9 or ICD-10 diagnosis codes in the primary or secondary position of inpatient and outpatient claims. Data on the following comorbidities were collected: anxiety, arthritis, asthma, bronchiectasis, chronic sinus disease, constipation, depression, diabetes, distal intestinal obstruction syndrome, gastroesophageal reflux disease (GERD), hemoptysis, insomnia, intestinal malabsorption, nasal polyps, osteopenia, osteoporosis, pancreatic insufficiency, pancreatitis, pneumonia, pulmonary infection, and pregnancy. HCRU outcomes included prescription medication use, all-cause and CF-related inpatient admissions, and outpatient office visits. Medication use was identified using National Drug Code and Healthcare Common Procedure Coding System codes. Data were collected on the use of the following medication classes: antibiotics (inhaled, oral, injectable, intravenous [IV], and other), bronchodilators, antidiabetic agents, antidepressants, antifungals, antihypertensives, anti-inflammatory agents, appetite stimulants, constipation treatments, digestive or pancreatic enzymes, immunosuppressants, mucolytics, opioids, ursodeoxycholic acid, and vitamins. CF-related admissions were defined by the ICD-9 or ICD-10 diagnosis code for CF in the primary diagnosis position on inpatient claims or in any position on outpatient claims.

Comorbidities and HCRU outcomes were summarized using descriptive statistics; continuous variables were summarized by mean (SD), and categorical variables, by frequency (%). Comorbidities were calculated as number and proportion of pwCF with comorbidities during the pre-ivacaftor period and during the last

12 months of the post-ivacaftor period. Prescription medication use was also reported as the number and proportion of pwCF with medication use and as the mean (SD) number of medication claims during the pre-ivacaftor period and the last 12 months of the post-ivacaftor period. All-cause and CF-related inpatient admissions and outpatient office visits were reported as the mean (SD) annual number of events during the pre-ivacaftor period and across the post-ivacaftor period (annualized). In addition, the numbers and proportions of pwCF with an all-cause inpatient and CF-related admission and outpatient office visit during the pre-ivacaftor period and the last 12 months of the post-ivacaftor period were reported. For comorbidities and HCRU outcomes, the absolute difference between the pre-ivacaftor period and the last 12 months of the post-ivacaftor period or the entire post-ivacaftor period was reported. Probability values for continuous variables were based on paired t tests, and categorical variables were based on asymptotic McNemar tests. Values of $p < 0.05$ were considered nominally significant; no multiplicity adjustment was conducted.

Compliance with Ethics Guidelines

This study did not involve primary data collection from human participants and relied on de-identified retrospective data from administrative claims; thus, institutional review board approval to conduct this study was not necessary. This study was conducted in accordance with Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6, GCP, Consolidated Guidance (April 1996). The ICH GCP guideline is consistent with the World Medical Assembly Declaration of Helsinki.

RESULTS

Of the total eligible pwCF with continuous health plan enrollment for 48 months during the pre- and post-ivacaftor periods ($n = 121$), 79 pwCF were persistent in ivacaftor use during the entire 36-month post-ivacaftor period and were

included in the analysis (Fig. 1). Most pwCF in this analysis were < 18 years of age ($n = 50$ [63.3%]), with the largest age group being those 6 to < 12 years of age ($n = 31$ [39.2%]). The majority of pwCF (64.6%) had commercial insurance. More than half of pwCF ($n = 44$ [55.7%]) initiated ivacaftor use in 2012, and the remaining 35 (44.3%) initiated ivacaftor between 2013 and 2015 (Table 1). The prevalence of comorbidities in the pre-ivacaftor period is reported in Table 1.

In comparing the last 12 months of the post-ivacaftor period to the pre-ivacaftor period, no notable changes were observed in the prevalence of most frequently identified CF-related comorbidities occurring in $\geq 5\%$ of pwCF, such as asthma, bronchiectasis, chronic sinus disease, diabetes, distal intestinal obstruction syndrome, GERD, intestinal malabsorption, nasal polyps, pancreatic insufficiency, and pulmonary infections (data not shown). However, a significant reduction in the prevalence of pneumonia was noted for individuals treated with ivacaftor, with a decrease in prevalence between the last 12 months of the post-ivacaftor period and the pre-ivacaftor period (10.1% vs. 26.6%; absolute difference, −16.5 percentage points; $p < 0.001$).

For HCRU outcomes, the proportion of pwCF receiving prescription medication decreased numerically for most drug classes after initiation of ivacaftor treatment (Fig. 2). No statistically significant changes were noted for most classes of prescription medication; however, significant reductions in the proportion of pwCF receiving inhaled and IV antibiotics, mucolytics, and opioids were observed (Fig. 2, Table 2). During the last 12 months of the post-ivacaftor period versus the pre-ivacaftor period, the proportion of pwCF receiving mucolytics decreased 11.4 percentage points (75.9% vs. 87.3%; $p = 0.003$) and receiving opioids decreased 12.7 percentage points (8.9% vs. 21.5%; $p = 0.012$). We also observed a numeric decrease in the proportion of pwCF receiving antibiotics and a significant reduction of 35% in the mean number of claims for antibiotics per person in the last 12 months of the post-ivacaftor period compared with the pre-ivacaftor period ($p < 0.001$) (Table 2). Reductions were also observed in the mean number of antibiotics
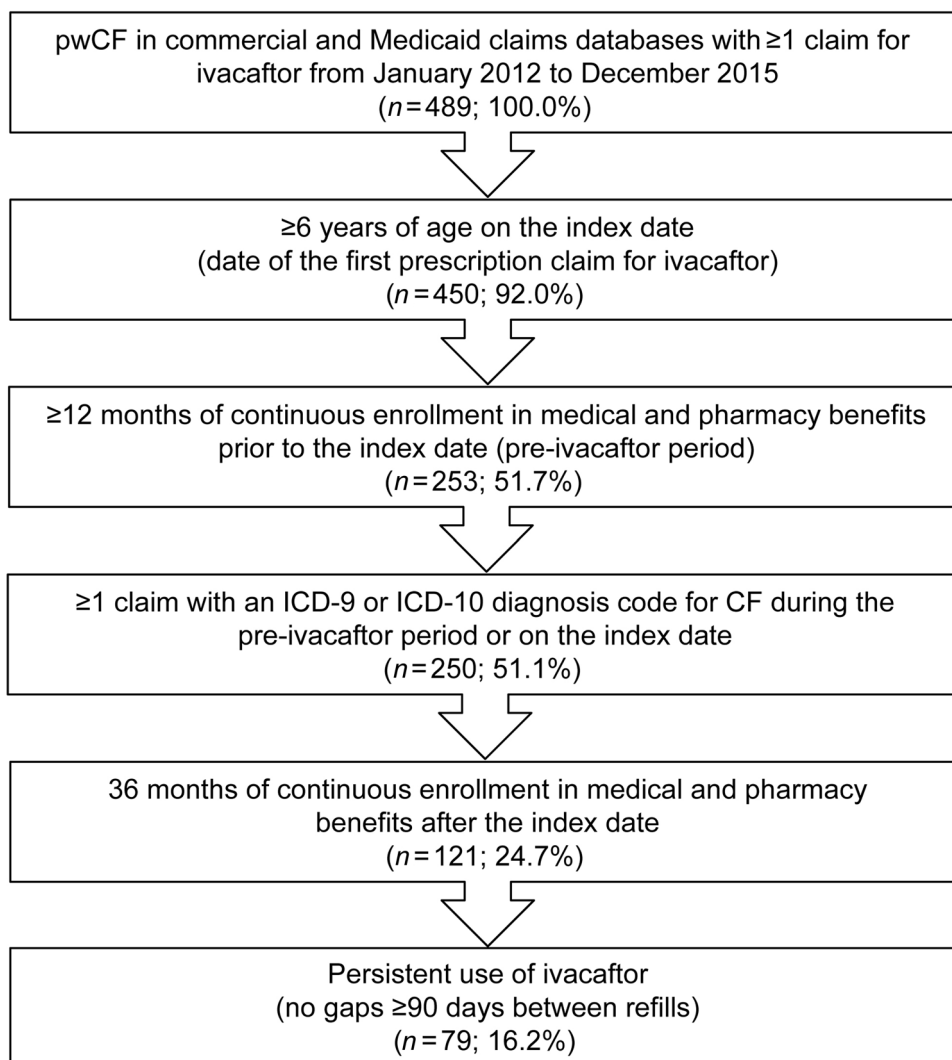
Fig. 1 Sample attrition. *CF* cystic fibrosis, *ICD* International Classification of Diseases, *pwCF* people with cystic fibrosis

claims per person by the route of administration during the last 12 months of the post-ivacaftor period compared with the pre-ivacaftor period (inhaled [26% reduction; $p = 0.012$], oral [26% reduction; $p = 0.003$], injectable [70% reduction; $p = 0.043$], and IV [77% reduction; $p = 0.028$]) (Table 2).

In addition, during the post-ivacaftor period, significant reductions were observed in inpatient admissions, CF-related inpatient admissions, and outpatient office visits (Table 3). The mean (SD) number of inpatient admissions and CF-related admissions per person was reduced by about half during the post-ivacaftor period compared with the pre-ivacaftor period (0.2

[0.4] vs. 0.4 [0.7]; $p = 0.047$; 0.1 [0.2] vs. 0.2 [0.5]; $p = 0.024$, respectively). Also, we observed fewer outpatient office visits per person (8.8 [4.9] vs. 9.9 [5.4]; $p = 0.022$) during the post-ivacaftor period compared with the pre-ivacaftor period. Furthermore, there was a 30% reduction in the proportion of pwCF with an inpatient admission and 36% reduction in the proportion of pwCF with a CF-related admission during the last 12 months of the post-ivacaftor period compared with the pre-ivacaftor period (17.7% vs. 25.3% and 8.9% vs. 13.9%, respectively). Only a slight reduction was observed in the proportion of pwCF with outpatient office visits during the last 12 months of the post-

Table 1 Demographics and comorbidities of pwCF

	pwCF (n = 79)
Age, mean (SD), years	19.5 (15.6)
Age categories, n (%)	
6 to < 12 years	31 (39.2)
12 to < 18 years	19 (24.1)
18 to < 25 years	9 (11.4)
≥ 25 years	20 (25.3)
Male, n (%)	38 (48.1)
Payer, n (%)	
Commercial	51 (64.6)
Medicaid	28 (35.4)
Population density, n (%)	
Urban	57 (72.2)
Rural	20 (25.3)
Unknown	2 (2.5)
Insurance plan type, n (%)	
Comprehensive/indemnity	12 (15.2)
EPO/PPO	33 (41.8)
POS/POS with capitation	4 (5.1)
HMO	25 (31.6)
CDHP/HDHP	4 (5.1)
Unknown	1 (1.3)
Index year, n (%)	
2012	44 (55.7)
2013	14 (17.7)
2014	8 (10.1)
2015	13 (16.5)
Comorbidities in ≥ 5% of pwCF during pre-ivacaftor period, n (%)	
Distal intestinal obstruction syndrome	23 (29.1)
Asthma	27 (34.2)
Chronic sinus disease	17 (21.5)
Pancreatic insufficiency[a]	60 (75.9)

Table 1 continued

	pwCF (n = 79)
Pneumonia	21 (26.6)
Pulmonary infection	15 (19.0)
Bronchiectasis	13 (16.5)
GERD	10 (12.7)
Constipation	6 (7.6)
Depression	6 (7.6)
Diabetes	6 (7.6)
Hemoptysis	6 (7.6)
Anxiety	5 (6.3)
Intestinal malabsorption	4 (5.1)
Nasal polyps	4 (5.1)

Demographics were measured on the index date. Comorbidities were measured in the 12-month pre-ivacaftor period

CDHP consumer-driven health plan, *EPO* exclusive provider organization, *GERD* gastroesophageal reflux disease, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *ICD* International Classification of Diseases, *POS* point of service, *PPO* preferred provider organization, *pwCF* people with cystic fibrosis

[a] Calculated using ICD-9/10 diagnosis code for pancreatic insufficiency or the prescription medication use of digestive and pancreatic enzymes

ivacaftor period versus the pre-ivacaftor period (100% vs. 98.7%).

DISCUSSION

This retrospective study of US commercial and Medicaid claims data showed that, over 36 months of ivacaftor treatment, substantial reductions in HCRU occurred, including a 50% reduction in annual all-cause and CF-related inpatient admissions, compared with 12 months prior to ivacaftor initiation. Ivacaftor treatment was also associated with a
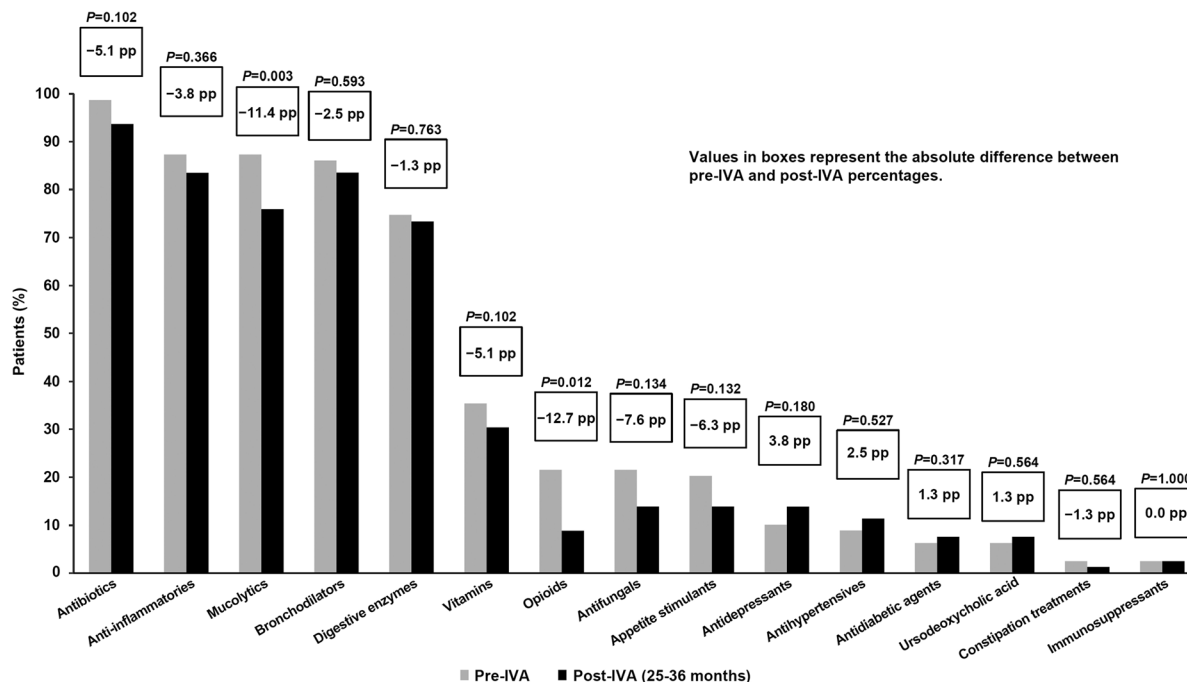
Fig. 2 Proportion of pwCF with ≥ 1 claim for prescription medications during the pre-IVA period and the last 12 months of the 36-month post-IVA period. *Diff* difference, *pp* percentage points, *pwCF* people with cystic fibrosis, *post-IVA* post-ivacaftor, *pre-IVA* pre-ivacaftor. Medication use was measured during the last 12 months of the post-IVA period. *p* values are based on asymptotic McNemar tests

significant reduction in outpatient office visits, a numeric reduction in use of several prescription medication classes, a significant reduction in the proportion of pwCF receiving either mucolytics or opioids, and a significant reduction in the number of antibiotics claims (inhaled, oral, injectable, and IV). We also observed a lower prevalence of pneumonia following 36 months of ivacaftor treatment than before ivacaftor initiation.

In a phase 3 clinical trial among participants ≥ 12 years of age with ≥ 1 *G551D* mutation, ivacaftor showed substantial improvements in lung function and body weight and a reduction in the risk of PEx events through 48 weeks, all of which were sustained for an additional 96 weeks in an open-label study, for a total study duration of approximately 33 months [21, 22]. The current study showed a reduction in the use of antibiotics (typically administered to treat PEx events [23]) following ivacaftor treatment for as long as 36 months, suggesting a reduction in the number of PEx events in a real-

world setting. Additionally, this study demonstrated the longer-term impact of ivacaftor on comorbidities, inpatient admissions, and outpatient office visits in routine clinical practice.

The impact of ivacaftor on HCRU has been reported in several real-world studies, usually over a follow-up period of 12 months [16, 19, 24–27]. A published study using the same data sources as the current study found that, among commercially insured pwCF in the USA, use of ivacaftor for 12 months was associated with a 55% reduction in the proportion of pwCF who had any inpatient admission, with a more pronounced reduction of 78% in the proportion of pwCF who had a CF-related inpatient admission [19]. Another study, which used data from the US Cystic Fibrosis Foundation Patient Registry to compare 12 months after ivacaftor initiation to 12 months before, reported a similar reduction of 65% in the rate of inpatient admissions [28]. Similarly, interim analyses of observational real-world studies across multiple centers in European countries

Table 2 Proportion of pwCF and mean number of filled prescriptions for antibiotics during the pre-IVA period and the last 12 months of the 36-month post-IVA period (n = 79)

	Proportion of pwCF with filled prescriptions				Filled prescriptions			
	Pre-IVA, n (%)	Post-IVA, n (%)[a]	Absolute difference, (percentage points)	p value[b]	Pre-IVA, mean (SD)	Post-IVA, mean (SD)[a]	Absolute difference, (percentage points)	p value[b]
Antibiotics (all)	78 (98.7)	74 (93.7)	−5.1	0.102	12.3 (11.1)	8.0 (7.3)	−4.3	< 0.001
Inhaled	42 (53.2)	30 (38.0)	−15.2	0.007	2.2 (2.9)	1.5 (2.5)	−0.6	0.012
Oral	77 (97.5)	74 (93.7)	−3.8	0.257	7.2 (5.8)	5.3 (5.0)	−1.8	0.003
Injectable	15 (19.0)	8 (10.1)	−8.9	0.071	1.0 (3.0)	0.3 (1.2)	−0.6	0.043
Intravenous	19 (24.1)	9 (11.4)	−12.7	0.012	1.3 (4.8)	0.3 (1.0)	−1.1	0.028
Other	15 (19.0)	12 (15.2)	−3.8	0.513	0.4 (1.0)	0.3 (0.9)	−0.1	0.644

Post-IVA post-ivacaftor, *pre-IVA* pre-ivacaftor, *pwCF* people with cystic fibrosis

[a] Medication use was measured during the last 12 months of the post-IVA period

[b] p values are based on paired *t* tests for continuous variables and asymptotic McNemar tests for categorical variables

that compared the 12 months after ivacaftor initiation to the 12 months prior to initiation have reported reductions in the rate of all-cause inpatient admissions ranging from 60–62%, along with a 70–79% reduction in the rate of PEx requiring hospitalization [24–26]. Limited real-world studies have assessed the impact of ivacaftor on HCRU outcomes over a longer follow-up period. A study of 80 pwCF from the Irish CF registry reported a reduction of 38% in the use of oral and IV antibiotics; however, the study also reported a nonsignificant reduction of 18% in per-person inpatient admissions after 3 years of ivacaftor treatment compared with 1 year prior to ivacaftor initiation [29]. Additionally, the third interim analysis of a study assessing ivacaftor impact in pwCF in Europe reported decreases in all-cause inpatient admissions and acute antibiotic medications for up to 36 months of ivacaftor treatment compared with 12 months pre-ivacaftor initiation [27]. A post-authorization safety study using national CF patient registries in the USA and UK assessed the impact of ivacaftor over 5 years in the USA and 4 years in the UK. The study reported an approximately 40% lower risk of inpatient admissions along with improvement in clinical

outcomes in an ivacaftor-treated cohort versus a matched-comparator cohort during the follow-up years [16]. Notably, results from the current study using US administrative claims data over a follow-up of 36 months after ivacaftor initiation reported reductions in inpatient admissions and antibiotics use that were highly consistent with results from other real-world studies; taken together, these findings further confirm the durability of ivacaftor impact over a longer follow-up period.

Reduction in HCRU is not only an important surrogate for clinical outcomes and a measure of health system burden, but also a means to quantify disease burden. The reductions in HCRU that we observed following ivacaftor initiation are likely to have a positive impact on both time devoted to managing CF and CF treatment burden. Previous studies have documented an increase in HCRU over time in pwCF, given the progressive nature of the disease [7, 8, 30]; however, we observed the opposite with ivacaftor therapy, namely, a reduction in HCRU following ivacaftor treatment for 36 months. These findings highlight the sustained benefit of ivacaftor treatment in

Table 3 All-cause and CF-related inpatient admissions and outpatient office visits in pwCF during the pre-IVA period and the 36-month post-IVA period (n = 79)

	Events, mean (SD), n[a]		Absolute difference[b]	p value[c]
	Pre-IVA	Post-IVA		
All-cause inpatient admissions	0.4 (0.7)	0.2 (0.4)	0.1	0.047
CF-related inpatient admissions[d]	0.2 (0.5)	0.1 (0.2)	0.1	0.024
Outpatient office visits	9.9 (5.4)	8.8 (4.9)	1.1	0.022

CF cystic fibrosis, *ICD* International Classification of Diseases, *post-IVA* post-ivacaftor, *pre-IVA* pre-ivacaftor, *pwCF* people with cystic fibrosis

[a] The mean values for outcomes are reported as mean (SD) annual number of events during the 12-month pre-IVA period and as annualized values across the 36-month post-IVA period

[b] Due to rounding, the numbers presented may not add up precisely

[c] p values are based on paired t tests

[d] CF-related events were defined by a CF ICD-9 (277.0x) or ICD-10 (E84.x) in the primary diagnosis position on inpatient claims or any position on non-inpatient claims

terms of HCRU outcomes over multiple years of follow-up.

Our study has a number of limitations. The 72-month period from 2012 (when ivacaftor was approved) to 2018, which was our window for identifying pwCF who had 48 months of continuous health plan enrollment, was relatively short. Thus, all pwCF who initiated ivacaftor from 2016 to 2018 were excluded by default due to lack of follow-up. Therefore, our study sample included only the subset of pwCF who initiated ivacaftor between 2012 and 2015 and were persistent for 36 months, resulting in a small number of pwCF included in the final analysis. We identified the demographic characteristics of populations at different stages of patient attrition from Fig. 1 to compare pwCF with persistent ivacaftor use in the final sample (n = 79) with the following nested sample populations prior to implementation of exclusion criteria: (1) pwCF ≥ 6 years of age on the index date (n = 450), (2) pwCF ≥ 6 years of age with ≥ 12 months of continuous enrollment in a health plan prior to the index date (n = 253), and (3) pwCF ≥ 6 years of age with ≥ 12 months of continuous enrollment in a health plan prior to the index date and at ≥ 36 months of continuous enrollment in a health plan post-index date (n = 121). The demographic characteristics such as sex, payer type (commercial vs. Medicaid), and population density (urban vs.

rural) in the final sample were qualitatively similar to the abovementioned sample populations during patient attrition. The inclusion criterion of persistent ivacaftor use during 36 months of continuous enrollment in a health plan post-index date required for the final sample was associated with relatively younger pwCF, with a mean (SD) age of 19.5 (15.6) years compared with 22.3 (13.2) years and 22.0 (13.9) years for pwCF ≥ 6 years of age on the index date and pwCF ≥ 6 years of age with ≥ 12 months of continuous enrollment in a health plan prior to the index date, respectively. Across the identified sample populations during patient attrition, pwCF initiating ivacaftor in 2012 constituted the largest proportion of the sample population. Future research to evaluate the long-term impact of ivacaftor with larger sample sizes should be considered. Furthermore, this analysis has inherent limitations due to its reliance on claims data, which are designed for claims processing and reimbursement, not for research purposes; thus, this analysis lacks information on clinical and laboratory test results, including genotyping and measures of lung function. Due to the lack of clinical and genotype information in the claims data, it is not possible to identify a matched, untreated comparator arm in order to control for change in outcomes over time due to natural disease progression. Hence, we used a study

design that compared outcomes before and after the initiation of ivacaftor treatment. As a result, our comparison of the outcomes of pwCF who received ivacaftor over a long period versus their treatment burden before ivacaftor initiation may have underestimated the benefits of ivacaftor treatment. Future studies are warranted to evaluate the long-term impact of ivacaftor using untreated contemporaneous controls to effectively account for natural disease progression. Our analysis excluded pwCF who died prior to 36 months of continuous enrollment in a health plan post-index date. This could have possibly resulted in selection of an ivacaftor-treated cohort with less severe disease characteristics; however, the study design of pre-/post-ivacaftor treatment allows each person with CF to serve as their own control, thus accounting for disease severity, and should not have biased the results. In this study, data for commercial- and Medicaid-insured populations were pooled and presented together to maximize sample size; however, it has been shown that Medicaid-insured individuals tend to be sicker and have poor health outcomes; thus, the results reported here may not be fully representative of either population [31, 32]. Subgroup analyses by age were not reported due to the small sample size and unequal payer mix in the study population. The methodology did not include a multiplicity adjustment, and the p values should therefore be considered nominal.

This study focused on pwCF $\geq$ 6 years of age; future studies should focus on evaluating the long-term impact of ivacaftor in younger age groups in order to demonstrate ivacaftor's ability to modify disease progression and prevent irreversible organ damage [33, 34].

CONCLUSION

This analysis builds on a growing body of literature estimating the impact of ivacaftor in reducing HCRU among pwCF by evaluating ivacaftor use over a longer time period and multiple endpoints. Our results support and reinforce the sustained long-term value of treating pwCF with ivacaftor, as observed through impact on HCRU. These findings are consistent with those of previous clinical and real-world studies of ivacaftor conducted over short- and long-term follow-up periods from a range of data sources.

ACKNOWLEDGEMENTS

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