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Real-world impact of ivacaftor in people with cystic fibrosis and select ivacaftor-responsive mutations

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ABSTRACT

Background Ivacaftor approval was extended to people with cystic fibrosis (CF) with ≥1 of 28 additional ivacaftor-responsive mutations in the USA in 2017 based on preclinical in vitro data. This retrospective, observational study assessed real-world clinical response to ivacaftor in people with CF with ≥1 of these mutations, using data from the US Cystic Fibrosis Foundation Patient Registry.

Methods Participants aged ≥2 years with ≥1 of 28 eligible mutations initiating ivacaftor between May 2017 and December 2018 were included. Clinical outcomes data were evaluated for ≤1 year before and ≤2 years after ivacaftor initiation. Participants initiating ivacaftor between May and December 2017 (2017 cohort) were used for the primary analysis because up to 2 years of post-ivacaftor-initiation data were available. Analyses were descriptive; key outcomes included percent predicted forced expiratory volume in 1 s ($ppFEV_1$), body mass index (BMI) and BMI z-score, pulmonary exacerbations (PEx) and hospitalisations.

Results The study included 1004 eligible participants. In the 2017 cohort (n=613), mean absolute change in $ppFEV_1$ from pre-ivacaftor initiation was 1.9 (95% CI 1.4, 2.4) and 1.8 (95% CI 1.0, 2.7) percentage points in years 1 and 2 post-ivacaftor initiation, respectively; mean absolute change in BMI was 0.6 (95% CI 0.5, 0.7) and 1.0 (95% CI 0.8, 1.2) kg/m^2 in years 1 and 2, respectively; BMI z-score was unchanged. Annualised event rates of PEx and hospitalisations per patient-year were lower with ivacaftor (0.24 (95% CI 0.21, 0.26) and 0.28 (95% CI 0.25, 0.31), respectively) compared with pre-ivacaftor initiation (0.41 (95% CI 0.37, 0.46) and 0.45 (95% CI 0.41, 0.49), respectively).

Conclusions These real-world observational study findings support the effectiveness of ivacaftor in people with CF aged ≥2 years with selected *CFTR* mutations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The CFTR modulator ivacaftor is known to be safe and efficacious in people with cystic fibrosis (CF) as young as 1 month of age with *CFTR* gating mutations.

WHAT THIS STUDY ADDS

⇒ We assessed real-world clinical response to ivacaftor treatment among people with CF aged ≥2 years with one of 28 eligible ivacaftor-responsive mutations approved in the USA in 2017 based on preclinical in vitro data. Following initiation of ivacaftor, improvements were seen in lung function, body mass index and rates of pulmonary exacerbations and hospitalisations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results confirm the effectiveness of ivacaftor treatment in people with CF who have these selected *CFTR* mutations.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal, recessive, progressive and life-threatening genetic disease[1] caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene.[2] CF affects >80 000 people worldwide[3 4] with >31 000 people affected in the USA as of 2020.[5]

Ivacaftor is a first-in-class therapy that potentiates the activity of the CFTR protein by increasing the time that activated CFTR channels remain open. Following initial regulatory approval in 2012 for people with CF with ≥1 *G551D* mutation, the ivacaftor indication in the USA was expanded in 2014 to include people with CF aged ≥6 years with any of 10 *CFTR* gating mutations, including *R117H*.[6] The US indication was expanded again in May 2017 to include treatment of CF caused by any of the additional 28 ivacaftor-responsive *CFTR* mutations, 23 of which were based on in vitro data.[7] Over time, the ivacaftor label has been expanded to include people with CF aged ≥1 month with any of the above mutations.[8]

People with these 28 mutations, relative to those with the original 10 mutations except *R117H*, typically have a less rapidly progressive form of CF, characterised by a lower incidence of pancreatic insufficiency and more moderate lung-function decline.[9] While disease burden in this population may be comparatively lower early in the disease course, people carrying these mutations nevertheless experience considerable burden

in terms of bacterial infections, pulmonary exacerbations (PEx) and hospitalisations over time.[9]

The ivacaftor development programme used in vitro studies to identify additional mutations that are likely to respond clinically to the drug. In this context, real-world evidence in people with CF with these mutations and treated with ivacaftor will aid in understanding the impact of ivacaftor on clinical outcomes.

The objective of this study was to describe real-world clinical response to ivacaftor therapy in people with any of 28 selected ivacaftor-responsive *CFTR* mutations using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR).

METHODS

Study design and data sources

This study was designed to evaluate real-world clinical response to ivacaftor in people with CF with ≥1 of 28 selected ivacaftor-responsive *CFTR* mutations. Clinical outcomes data were evaluated up to 1 year before and 2 years after ivacaftor initiation, until the end of available data (31 December 2019), or loss to follow-up, or death or discontinuation of ivacaftor treatment, whichever occurred first.

The CFFPR is an established source for comprehensive data collection and analyses in a real-world setting from individuals diagnosed with CF in the USA. This observational study used data collected by the US CFFPR between 2016 and 2019. The CFFPR tracks the treatments and health outcomes of participants across >120 Cystic Fibrosis Foundation-accredited care centres[10] (see Online supplemental material methods for additional information on data collection and procedures at US CFFPR sites).

The source population for the study included male and female participants aged ≥2 years at ivacaftor initiation who had ≥1 year of data before initiating ivacaftor therapy in the US CFFPR. Two cohorts were assessed. The 2017 cohort comprised eligible participants who initiated ivacaftor between 17 May 2017 and 31 December 2017, and who had available data for up to 2 years after the start of ivacaftor treatment. The 2018 cohort comprised eligible participants who initiated ivacaftor between 1 January 2018 and 31 December 2018; participants in this cohort provided <2 years of data, due in part to censoring in the second 12-month period. Other reasons for <2 years of data in both cohorts include treatment discontinuation and loss to follow-up. Eligible participants must have had ≥1 of 28 eligible *CFTR* mutations (*E193K*, *F1052V*, *K1060T*, *R74W*, *A1067T*, *D110H*, *D1270N*, *D110E*, *E56K*, *F1074L*, *R1070Q*, *G1069R*, *S977F*, *P67L*, *D1152H*, *L206W*, *R347H*, *D579G*, *R352Q*, *R117C*, *A455E*, *S945L*, *R1070W*, *3849+10kbC->T*, *2789+5G->A*, *3272–26A->G*, *711+3A->G*, *E831X*). Individuals with a history of organ transplantation before ivacaftor initiation, those who were previously treated with other CFTR modulators, and those with any of the *G178R*, *S549N*, *S459R*, *G551D*, *G551S*, *G970R*, *G1244E*, *G1251N*, G1255P, *G1349D* or *R117H CFTR* mutations were excluded from the study. See Online supplemental material methods for additional eligibility criteria.

Online supplemental figure S1 illustrates the pre- and post-ivacaftor-initiation periods. The pre-ivacaftor-initiation period was defined as the 12-month period before, and not including, the ivacaftor initiation date. The post-ivacaftor-initiation period included the two 12-month periods following ivacaftor initiation (year 1 and year 2).

Study measures

Key outcomes included lung function, as measured by percent predicted forced expiratory volume in 1 s ($ppFEV_1$), body mass index (BMI) and BMI-for-age z-score, PEx, hospitalisations and *Pseudomonas aeruginosa* colonisation. At each CFFPR site, forced expiratory volume in 1 s values were recorded and $ppFEV_1$ was calculated using Global Lung Function Initiative standards.[11] BMI was calculated for adult participants. In participants aged 2–<20 years, BMI-for-age z-scores were calculated using Centers for Disease Control and Prevention growth charts to adjust for age and sex.[12] A PEx event was defined as a CF care episode for which PEx was the reason, as recorded in the CFFPR; a CF care episode was defined as intravenous antibiotic use at home or in hospital. Hospitalisations, which included hospitalisation for any reason, were categorised as PEx or non-PEx based on the reason recorded in the CFFPR. *P. aeruginosa* colonisation was defined by evidence of *P. aeruginosa* in bacterial culture.

Statistical analysis

All study analyses were descriptive in nature; no hypothesis tests were performed.

For continuous endpoints, the 2017 cohort was used for primary analyses because it provided up to 2 years of post-ivacaftor-initiation data and had a higher likelihood of longer median follow-up versus the 2018 cohort. For $ppFEV_1$, BMI and BMI z-score, summary statistics were presented for observed values in the pre-ivacaftor-initiation period and each post-ivacaftor-initiation period (year 1 and year 2); absolute changes from the pre-ivacaftor-initiation period through years 1 and 2 were provided. For $ppFEV_1$, pre-ivacaftor initiation was defined as the mean of all $ppFEV_1$ measurements during the pre-ivacaftor-initiation period and the value for each analysis year was defined as the mean of all $ppFEV_1$ measurements in years 1 or 2. For BMI and BMI z-score, the value for each year was the last measurement collected during that year; patients with <3 months duration of ivacaftor exposure in the second 12-month period (year 2) were not included in year 2 analyses. Participants aged <6 years were excluded from analyses of change in $ppFEV_1$ because this clinical outcome cannot be reliably measured in this age group. The full analysis set (FAS) consisted of the pooled 2017 and 2018 cohorts and was used for sensitivity analyses.

For categorical endpoints, analyses were performed on the FAS to enhance sample size for event-based variables. Annualised rates of PEx and hospitalisations (with 95% CIs) were calculated for the pre-ivacaftor-initiation period and over the full post-ivacaftor-initiation period. The proportion of participants with *P. aeruginosa* infection in the pre- and post-ivacaftor-initiation periods was calculated as the number of participants with *P. aeruginosa*-positive culture (n)/the number of participants with *P. aeruginosa* culture available during the time period (N1).

Subgroup analyses were performed using the 2017 cohort to assess potential differences in clinical characteristics by age (<18 years, ≥18 years) at the time of ivacaftor initiation.

Additionally, an ad hoc analysis was performed on the subset of participants carrying ≥1 of the following five splicing mutations: *3849+10kbC→T*, *2789+5G→A*, *3272–26A→G*, *711+3A→G* and *E831X*.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study.

RESULTS

Demographics and clinical characteristics

The FAS included 1004 participants with ≥1 of 28 selected *CFTR* mutations and treated with ivacaftor (n=613, 2017 cohort; n=391, 2018 cohort).

Demographic and clinical characteristics of the study population at ivacaftor initiation are presented in table 1. In the FAS, mean (SD) age at ivacaftor initiation was 26.7 (19.7) years, half were male (50.2%), and mean (SD) BMI and $ppFEV_1$ were 22.5 (6.1) kg/m^2 and 77.3 (25.6) percentage points, respectively. Mean (SD) duration of ivacaftor exposure in the FAS was 16.5 (7.3) months (table 1). It is worth noting that a greater proportion of participants in the 2017 cohort (11.8%) versus the 2018 cohort (5.6%) had $ppFEV_1$<40% pre-ivacaftor initiation, indicating higher disease severity in the 2017 cohort.

Of 1004 participants in the FAS, 30.6% discontinued follow-up in year 1. Reasons for discontinuation were death (0.7%), loss to follow-up (3.9%) and ivacaftor discontinuation (95.4%), with 65.9% of the latter transitioning to another CFTR modulator (figure 1). In year 2, 17.3% of participants in the FAS discontinued, due to death (1.1%), loss to follow-up (2.3%) and ivacaftor discontinuation (96.6%), with 79.8% of the latter transitioning to another CFTR modulator (figure 1). Overall, 327 (32.6%) participants discontinued the study to transition to another CFTR modulator.

Online supplemental table S1 summarises the frequency of the 23 non-splicing and five splicing mutations. In the FAS, the two most common mutations were splicing mutations (*3849+10kbC→T* [22.5%] and *2789+5G→A* [18.4%]).

Lung function

In the 2017 cohort of the FAS, mean absolute change in $ppFEV_1$ from pre-ivacaftor initiation was an increase of 1.9 (95% CI 1.4, 2.4) percentage points in year 1 and 1.8 (95% CI 1.0, 2.7) in year 2 (table 2). Results of the subgroup analysis by age were similar to the overall 2017 cohort; there was a numerical increase in mean $ppFEV_1$ in both age categories, although smaller in the <18 years subgroup in year 2. In addition, the increase in $ppFEV_1$ in the sensitivity analysis of the FAS was similar to that in the 2017 cohort (table 2).

BMI and BMI z-score

In the 2017 cohort, mean absolute change in BMI from pre-ivacaftor initiation was an increase of 0.6 (95% CI 0.5, 0.7) kg/m^2 in year 1 and 1.0 (95% CI 0.8, 1.2) kg/m^2 in year 2 (table 3). BMI z-score remained stable with ivacaftor in the 2017 cohort (mean absolute change from pre-ivacaftor initiation was an increase of 0.1 (95% CI 0.1, 0.2) in year 1 and 0.1 (95% CI 0.1, 0.2) in year 2) (table 3).

In the subgroup analysis, BMI increased in years 1 and 2 in both age groups (table 3). The increases in BMI and BMI z-score in the sensitivity analysis of the FAS were similar to those in the 2017 cohort (table 3).

PEx and hospitalisations

In the FAS, the PEx event rate per patient-year decreased from 0.41 (95% CI 0.37, 0.46) in the pre-ivacaftor-initiation period to 0.24 (95% CI 0.21, 0.26) in the post-ivacaftor-initiation period. Similarly, hospitalisation event rate per patient-year decreased from 0.45 (95% CI 0.41, 0.49) in the pre-ivacaftor-initiation period to 0.28 (95% CI 0.25, 0.31) in the post-ivacaftor-initiation period (figure 2).

The differences in rates of PEx and hospitalisations were more marked in participants aged ≥18 years than those <18 years. Between the pre-ivacaftor-initiation and post-ivacaftor-initiation periods, the PEx event rate was reduced by 0.25 in participants aged ≥18 years and by 0.06 in those <18 years. Similarly, the hospitalisations event rate reduced by 0.22 in participants aged ≥18 years and by 0.07 in those <18 years over the same period.

Bacterial colonisation

The prevalence of *P. aeruginosa* colonisation was 35.8% (n/N1=350/978) during the pre-ivacaftor-initiation period and was similar in the post-ivacaftor-initiation period at 37.4% (n/N1=370/988).

Ad hoc analysis in the subgroup of participants with a splicing mutation

The ad hoc analysis of a subset of participants with a splicing mutation comprised a total of 527 participants treated with ivacaftor (n=308, 2017 cohort; n=219, 2018 cohort).

Table 1 Demographic and clinical characteristics, and summary of ivacaftor exposure (FAS)

	2017 cohort (n=613)	2018 cohort (n=391)	Pooled 2017 and pooled 2018 cohorts (N=1004)
Male, n (%)	304 (49.6)	200 (51.2)	504 (50.2)
Mean (SD) age at ivacaftor initiation, years	28.2 (19.8)	24.4 (19.3)	26.7 (19.7)
Age category at ivacaftor initiation, n (%)			
2–<6 years	82 (13.4)	76 (19.4)	158 (15.7)
6–<12 years	98 (16.0)	71 (18.2)	169 (16.8)
12–<18 years	65 (10.6)	45 (11.5)	110 (11.0)
≥18 years	368 (60.0)	199 (50.9)	567 (56.5)
Race, n (%)			
White	577 (94.1)	369 (94.4)	946 (94.2)
Other (non-missing)	22 (3.6)	12 (3.1)	34 (3.4)
Unknown/missing	14 (2.3)	10 (2.6)	24 (2.4)
BMI pre-ivacaftor initiation, kg/m^2*			
n	609	387	996
Mean (SD)	22.7 (6.1)	22.2 (6.2)	22.5 (6.1)
BMI z-score pre-ivacaftor initiation*			
n	259	–	452
Mean (SD)	0.3 (1.0)	–	0.3 (1.0)
ppFEV$_1$ pre-ivacaftor initiation			
n	515	305	820
Mean (SD)	75.4 (26.1)	80.6 (24.4)	77.3 (25.6)
ppFEV$_1$ severity pre-ivacaftor initiation, n (%)			
<40	61 (11.8)	17 (5.6)	78 (9.5)
≥40–<70	153 (29.7)	84 (27.5)	237 (28.9)
≥70–<90	116 (22.5)	76 (24.9)	192 (23.4)
≥90	185 (35.9)	128 (42.0)	313 (38.2)
Mean (SD) ivacaftor exposure duration, months	17.0 (7.7)	15.6 (6.7)	16.5 (7.3)
Ivacaftor exposure duration, n (%)†			
<6 months	63 (10.3)	50 (12.8)	113 (11.3)
≥6–<12 months	140 (22.8)	54 (13.8)	194 (19.3)
≥12–<18 months	79 (12.9)	108 (27.6)	187 (18.6)
≥18–≤24 months	331 (54.0)	179 (45.8)	510 (50.8)

*Last BMI measurement before ivacaftor initiation.
†Precise ivacaftor initiation and discontinuation dates are not available in the US CFFPR; therefore, an algorithm was used to extrapolate duration of exposure based on timing of participant encounters and ivacaftor exposure data available.
BMI, body mass index; CFFPR, Cystic Fibrosis Foundation Patient Registry; FAS, full analysis set; ppFEV$_1$, percent predicted forced expiratory volume in 1 s.

Demographic and clinical characteristics of the splicing mutation subset at ivacaftor initiation (online supplemental table S2) were comparable to those in the FAS of participants with ≥1 of 28 selected mutations (table 1): the proportions of participants with ppFEV$_1$<40% pre-ivacaftor initiation were 13.3% and 11.8% in the 2017 cohort, respectively, and 6.5% and 5.6% in the 2018 cohort, respectively.

In the 2017 cohort of the splicing mutation subset, mean absolute change in ppFEV$_1$ from the pre-ivacaftor-initiation period was an increase of 1.4 (95% CI 0.8, 2.1) percentage points in year 1 and 1.5 (95% CI 0.4, 2.6) in year 2 (online supplemental table S3), which was comparable to observations in participants with ≥1 of 28 selected mutations.

Mean absolute change in BMI from the pre-ivacaftor-initiation period was an increase of 0.6 (95% CI 0.4, 0.7) kg/m^2 in year 1 and 1.0 (95% CI 0.7, 1.3) kg/m^2 in year 2 (online supplemental table S4). Similar to participants with ≥1 of 28 selected mutations, BMI z-score remained stable with ivacaftor therapy in the splicing mutation subset (online supplemental table S4).

The PEx event rate per patient-year decreased from 0.50 (95% CI 0.44, 0.56) in the pre-ivacaftor-initiation period

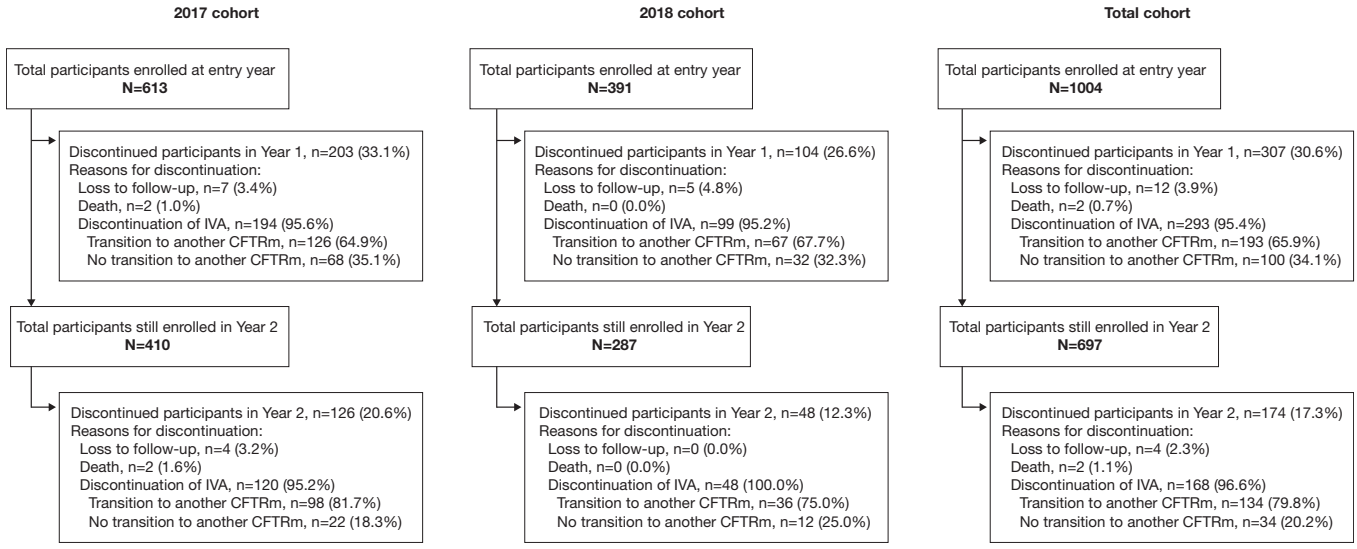

Figure 1 Participant disposition (full analysis set). CFTRm, cystic fibrosis transmembrane conductance regulator modulator; IVA, ivacaftor.

to 0.29 (95% CI 0.25, 0.34) in the post-ivacaftor-initiation period (online supplemental table S5). Similarly, the hospitalisation event rate reduced from the pre-ivacaftor-initiation period to the post-ivacaftor-initiation period, from 0.49 (95% CI 0.43, 0.55) to 0.32 (95% CI 0.28, 0.37) per patient-year, respectively (online supplemental table S5).

The prevalence of *P. aeruginosa* colonisation was higher in the splicing mutation subset versus participants with ≥1 of 28 selected mutations, at 43.3% (n/N1=223/515) during the pre-ivacaftor-initiation period and 45.0% (n/N1=233/518) in the post-ivacaftor-initiation period.

DISCUSSION

The results of this real-world observational study using data from the US CFFPR support the effectiveness of ivacaftor to treat people with CF aged ≥2 years with selected *CFTR* mutations that were included in the US label based on preclinical in vitro data. The study evaluated clinical data from 1004 participants with a mean ivacaftor exposure of 16.5 months. Compared with before initiation of ivacaftor therapy, participants treated with ivacaftor for up to 2 years demonstrated an increase in lung function as measured by $ppFEV_1$, increased BMI and maintenance of BMI z-score, while rates of both PEx and hospitalisations decreased in the post-ivacaftor-initiation versus pre-ivacaftor-initiation period. The proportion of participants with *P. aeruginosa* colonisation, however, did not differ between the pre-ivacaftor-initiation and post-ivacaftor-initiation periods, a finding that contrasts with previous real-world studies showing reduced prevalence of *P. aeruginosa* colonisation with ivacaftor treatment in people with CF with *G551D* and non-*G551D* gating mutations from registries in the USA, UK and France.[13–15] This may be related to a longer post-ivacaftor-initiation period (mean: 16.5 months) compared with the 12-month pre-ivacaftor-initiation period. Furthermore, the post-ivacaftor-initiation period included pre-existing cases of

Table 2 Absolute change in $ppFEV_1$ from pre-ivacaftor initiation in each 12-month interval

Absolute change in ppFEV1 from pre-ivacaftor initiation	2017 cohort (n=613)	Subgroup analysis		Sensitivity analysis (FAS) (N=1004)
		2017 cohort, <18 years (n=245)	2017 cohort, ≥18 years (n=368)	
Year 1				
n	512	153	359	813
Mean (SD)	1.9 (5.7)	2.0 (6.1)	1.9 (5.5)	2.0 (6.0)
95% CI	1.4, 2.4	1.0, 2.9	1.3, 2.4	1.6, 2.4
Year 2				
n	266	99	167	434
Mean (SD)	1.8 (6.9)	0.7 (7.5)	2.5 (6.5)	1.8 (7.1)
95% CI	1.0, 2.7	−0.8, 2.2	1.5, 3.5	1.1, 2.5

FAS, full analysis set; $ppFEV_1$, percent predicted forced expiratory volume in 1 s.

Table 3 Absolute change in BMI and BMI z-score from pre-ivacaftor initiation in each 12-month interval*

	2017 cohort (n=613)	Subgroup analysis		Sensitivity analysis (FAS) (N=1004)
		2017 cohort, <18 years (n=245)	2017 cohort, ≥18 years (n=368)	
Absolute change in BMI from pre-ivacaftor initiation, kg/m^2				
Year 1				
n	604	243	361	989
Mean (SD)	0.6 (1.5)	0.7 (1.3)	0.5 (1.6)	0.6 (1.8)
95% CI	0.5, 0.7	0.6, 0.9	0.4, 0.7	0.5, 0.7
Year 2				
n	341	174	167	559
Mean (SD)	1.0 (1.9)	1.2 (1.8)	0.8 (2.1)	1.0 (2.0)
95% CI	0.8, 1.2	0.9, 1.4	0.5, 1.2	0.8, 1.1
Absolute change in BMI z-score from pre-ivacaftor initiation				
Year 1				
n	251	237	14	442
Mean (SD)	0.1 (0.5)	0.1 (0.5)	0.1 (0.4)	0.1 (0.6)
95% CI	0.1, 0.2	0.1, 0.2	−0.1, 0.4	0.1, 0.2
Year 2				
n	172	169	≤5	300
Mean (SD)	0.1 (0.6)	0.1 (0.6)	N/A	0.2 (0.6)
95% CI	0.1, 0.2	0.1, 0.2	N/A	0.1, 0.2

*BMI was calculated in participants aged ≥20 years; BMI z-score was calculated in participants aged 2–<20 years.
BMI, body mass index; FAS, full analysis set; N/A, not applicable.

P. aeruginosa colonisation in addition to new cases arising in that time period.

In this study, consistent improvements were observed with ivacaftor across the outcomes of lung function, BMI, and rates of PEx and hospitalisations. Such improvements were observed in both age subgroups, with more marked improvements in PEx and hospitalisations in those aged ≥18 versus <18 years. The study findings are consistent with previous real-world observational data demonstrating the significant benefits of ivacaftor therapy

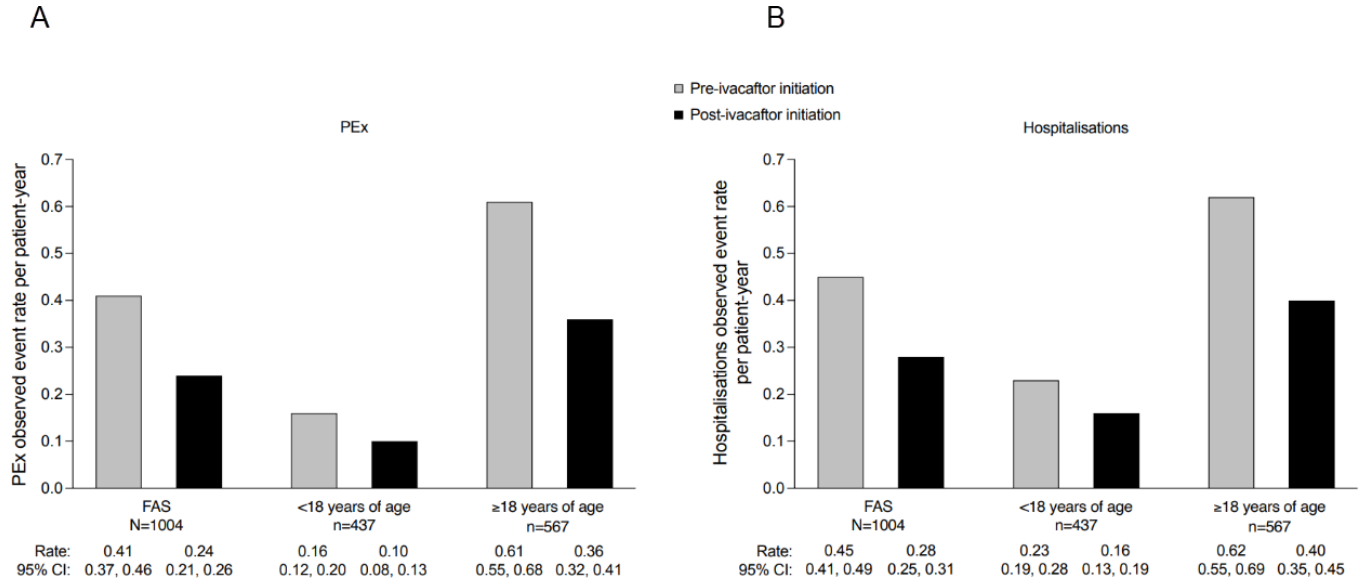

Figure 2 Rate of PEx (A) and hospitalisations (B) in the pre-ivacaftor-initiation and post-ivacaftor-initiation periods. FAS, full analysis set; PEx, pulmonary exacerbations.

across a range of ivacaftor-eligible participants in terms of improvements in lung function and reduced incidences of PEx and hospitalisations.[13–16]

While the observed improvements in clinical outcomes are consistent with the aforementioned studies, they are not as great in magnitude. Disease burden in the population under study is likely to be lower early in the disease course, and disease severity is lower, compared with those populations in which ivacaftor treatment has often been studied. This is evidenced by mean $ppFEV_1$ at baseline, which in the pooled cohort was 77.3, higher than that reported in people with CF with the *G551D* (69.0) and *F508del* (65.2) mutations, for example.[17] Improvements in lung function observed in this population are likely to be more moderate than in patients with more severe disease. Despite this, the ~42% reduction in rate of PEx and ~30% reduction in hospitalisations demonstrate the efficacy of ivacaftor in terms of clinically important outcomes, and its effectiveness in reducing patient and healthcare burden. Additionally, while a previous study using data from the US CFFPR demonstrated that people with CF who are not treated with CFTR modulators had an annual decline in $ppFEV_1$ of 1.92 percentage points,[18] increases in mean $ppFEV_1$ following ivacaftor initiation were observed in both year 1 and year 2 in the current study, further demonstrating the clinically meaningful impact of ivacaftor treatment on lung function.

Similar to the population in this study, people with CF with the *R117H* mutation generally demonstrate lower disease severity compared with those who carry other *CFTR* mutations.[19] The findings of the current study are similar to this other real-world investigation of ivacaftor in people with less severe CF, strengthening the evidence supporting the use of ivacaftor in this population.

Previous work has investigated the efficacy of ivacaftor in people with CF aged ≥6 years carrying *D1152H* (n=16) or the splicing mutation *3849+10kbC→T* (n=22).[20] The primary endpoint of absolute change in lung clearance index 2.5% from baseline through week 8 demonstrated improvement with ivacaftor versus placebo, with larger least squares mean improvement in those with the *D1152H* mutation (−93) versus *3849+10kbC→T* (−0.56). The sample size was small, however, and more robust data in populations with splicing mutations are needed. The two most common of the 28 ivacaftor-responsive mutations within the current study cohort were the splicing mutations *3849+10kbC→T* (22.5%) and *2789+5G→A* (18.4%) (online supplemental table S1). An ad hoc analysis of the cohort of participants carrying ≥1 of the five ivacaftor-responsive splicing mutations was conducted to evaluate whether there were any differences in the effectiveness of ivacaftor in that population. The impact of ivacaftor therapy on lung function, BMI, PEx and hospitalisations was similar in the splicing mutation subset compared with the overall cohort (participants with ≥1 of 28 selected mutations). One notable difference was that the prevalence of *P. aeruginosa* colonisation was higher in the splicing mutation subset, both pre- and post-ivacaftor initiation, versus the overall cohort.

This study adds to the growing real-world evidence of the long-term effectiveness of ivacaftor, particularly in a population with limited clinical trial data and considered to have less severe disease. A separate but similar analysis to the study described here is currently underway and is designed to evaluate the effectiveness of ivacaftor over 3 years of follow-up in people with CF aged ≥2 years with ≥1 of 23 non-splicing ivacaftor-responsive mutations.

Limitations

An important limitation of the US CFFPR data applicable to the PEx, hospitalisation and infection findings in this study is that precise dates of treatment initiation and event occurrences may not always be available. Consequently, there is potential for person-time data to be incorrectly classified as exposed or unexposed, creating a challenge in establishing the temporal relationship between exposure and outcome. Furthermore, mean change in $ppFEV_1$ from pre-ivacaftor through the post-ivacaftor-initiation period included $ppFEV_1$ values at the index date, which may not be long enough after treatment initiation; this may have lowered the observed mean $ppFEV_1$ in the post-ivacaftor-initiation period and potentially underestimated the treatment effect. It should also be noted that 15.7% of the study population was <6 years of age and were not able to contribute $ppFEV_1$ lung function data due to the difficulty of performing spirometry measurements in children of this age.

Biases may have arisen due to the different time frames between the pre- and post-ivacaftor-initiation periods, such as changes in the standard of care for CF and in data collection practices. As a result, comparisons between the pre- and post-ivacaftor periods should be treated with caution. Of note, 30.6% of participants in the FAS discontinued ivacaftor therapy during the first year of treatment and 17.3% discontinued during the second year, primarily because they transitioned to an alternative CFTR modulator due to its availability following US Food and Drug Administration approval within the analysis period. Such attrition is important to consider when interpreting the study findings over time but is not applicable to PEx and hospitalisations, for which person-time was assessed. If participants who discontinued early included non-responders then improvements in lung function may have been overestimated. However, the main reason for discontinuation was the availability of a new CFTR modulator; therefore, the bias is unlikely to have had a significant impact on the lung function results.

In observational studies such as this, missing data can introduce misclassification of exposure and/or outcomes. However, the CFFPR has robust systems in place to minimise missing data in the database, and a data audit suggested high accuracy and low missingness compared with medical records.[10] Finally, it should be noted that the variables assessed in this study were averaged over each

year for the entire study population, which was diverse in age and CF disease progression. However, subgroup and sensitivity analyses conducted as part of the study showed similar results to the overall cohorts, suggesting there was little impact on the results due to averaging.

Despite these limitations, we are confident the overall findings of this study are likely to be generalisable to other populations of people with CF with ivacaftor-responsive *CFTR* mutations, especially given the fact that the US CFFPR is one of the largest and most comprehensive national CF registries in the world. However, direct comparisons between the magnitude of change in outcome measures assessed in registry-based trials versus in controlled trials are challenging due to differences in data definitions and inclusion/exclusion criteria.

CONCLUSIONS

In conclusion, the findings from this real-world observational study, based on data from the US CFFPR, support the effectiveness of ivacaftor in terms of lung function, nutrition, and rates of PEx and hospitalisations in people with CF aged ≥2 years with ≥1 of 28 ivacaftor-responsive *CFTR* mutations.

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