ABSTRACT

Background Ivacaftor approval was extended to people with cystic fibrosis (CF) and an R117H variant in 2014 in the USA. This observational, real-world, postapproval study evaluated long-term outcomes among people with CF and an R117H variant on ivacaftor using data from the US Cystic Fibrosis Foundation Patient Registry.

Methods Key outcomes were evaluated in ivacaftor-treated people with CF and an R117H variant for up to 36 months before and after treatment initiation using within-group comparisons. Analyses were descriptive in nature, focusing on evaluation of observed outcome patterns over time and were performed both overall and for age groups ≥2 to <6 years, ≥6 to <18 years and ≥18 years. Key outcomes included lung function, body mass index (BMI), pulmonary exacerbations (PEx) and hospitalisations.

Results The ivacaftor cohort included 369 people with CF and an R117H variant who initiated therapy between 1 January 2015 and 31 December 2016. During each of the 12-month intervals following treatment initiation, the mean observed percent predicted forced expiratory volume in 1 s (ppFEV1) and BMI values were higher and the mean annualised number of PEx and hospitalisation events were lower than pretreatment values. Mean change in ppFEV1 from pretreatment baseline was an increase of 1.5 (95% CI 0.8 to 2.3), 1.7 (95% CI 0.7 to 2.7) and 1.8 (95% CI 0.6 to 3.0) percentage points in the first, second and third years of treatment, respectively. Similar trends were observed in adult and paediatric subgroups.

Conclusions The results support the clinical effectiveness of ivacaftor in people with CF and an R117H variant, including adult and paediatric subgroups.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal, recessive, progressive and life-threatening genetic disease most common in the Caucasian population.1 CF affects >80 000 people worldwide with >50 000 of those in the USA.2 3

Ivacaftor is a first-in-class therapy that potentiates the activity of the CF transmembrane conductance regulator (CFTR) protein. In the USA, ivacaftor is indicated for the treatment of CF in patients ages ≥4 months who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.4 This includes the R117H variant, which is present in approximately 2% to 4% of people with CF.5 People with CF and an R117H variant have a delayed onset, but ultimately a similar progression, of lung disease compared with people with CF homozygous for F508del.5

In December 2014, the US Food and Drug Administration (FDA) approved extension of the ivacaftor indication for the treatment of people with CF ages ≥6 years with an R117H mutation.4 6 In March 2015, the FDA approved ivacaftor for people with CF ages ≥2 years with at least one of the 10 mutations, including R117H.

At request from the FDA, this study was designed to evaluate long-term outcomes among people with CF and an R117H variant receiving ivacaftor therapy under real-world conditions of use, including adult and paediatric participants. The study leveraged existing data collected via the US Cystic Fibrosis Foundation Patient Registry.
Fibrosis Foundation Patient Registry (CFFPR), the largest national CF registry in the world. Here, we present results from the final analysis of this study.

METHODS
Study design
This study was designed to evaluate key outcomes in people with CF and an R117H variant for up to 36 months before and 36 months after initiation of ivacaftor treatment using within-group comparisons. The study was conducted as a postmarketing requirement from the FDA under FDAAA Section 505(o)(3), with the requirement considered fulfilled by the FDA at the writing of this manuscript.

Data sources
This was an observational study using data from the US CFFPR, which tracks the treatments and health outcomes of people with CF across >120 Cystic Fibrosis Foundation-accredited care centres. Investigators, who are physicians at certified CF care centres, collect and are responsible for data entry for enrolled people with CF into the registry database. Online registry data-collection forms capture data pertinent to CF and the medical care of people with CF. All people with CF included in this study took part in standard encounter-based data collection (approximately four encounters per year), which involved assessments of key CF disease outcomes including, but not limited to, pulmonary function, hospitalisations, pulmonary exacerbations (PEx) and body mass index (BMI). Informed consent/assent is obtained as part of registry enrolment procedures. Analyses in this study are covered by existing consent for participation in the CFFPR. Notably, to protect patient privacy, Cystic Fibrosis Foundation policy is currently to require researchers to replace numbers representing one to four people in study results with ‘<5’, reflecting that the number is fewer than five. This practice was followed in the present manuscript.

Study population
The source population for this study comprised people with CF and an R117H variant who were included in the US CFFPR, had a record of ivacaftor treatment initiation from 1 January 2015 (following FDA approval) to 31 December 2016 and were ages ≥2 years at time of therapy initiation.

Study measures
Key outcomes of interest included lung function, PEx, hospitalisations, BMI and BMI-for-age z-score. Spirometry for lung function measurements was performed according to the standard procedure at each US CFFPR site and forced expiratory volume in 1 s (FEV₁) values were evaluated as recorded in the registry. PEx events were defined by evidence of a CF care episode with the reason for PEx as recorded in the registry. Hospitalisations were defined as participants hospitalised for any reason (PEx, pulmonary complication, gastrointestinal complication, transplant related, sinus infection, non-transplant surgery or other reasons). BMI was calculated for adult participants (ages ≥18 years), whereas for paediatric participants (ages ≥2 and <18 years) BMI-for-age z-scores, height-for-age z-scores and weight-for-age z-scores were calculated using Centers for Disease Control and Prevention growth charts.

Statistical analysis
All study analyses were primarily descriptive in nature and focused on evaluation of observed patterns over time (described qualitatively as trends). For the analyses of lung function, percent predicted FEV₁ (ppFEV₁) was calculated using Global Lung Function Initiative (GLI) standards. Evaluations of lung function included tabulations of summary statistics (mean, SE or 95% CI) for ppFEV₁ for each analysis year, as well as for changes from pretreatment baseline year (defined as average of all available measures within 12 months prior to ivacaftor initiation). If participants had more than one encounter visit in the interval, all participant data within the interval were averaged. Analyses of lung function were performed for participants who were ages ≥6 years, since lung function cannot be reliably measured in children ages <6 years. For the analyses of PEx and hospitalisations, the number of participants with at least one event and the mean number of events were calculated for each analysis year in the pretreatment and post-treatment periods. Statistical comparisons of the number of PEx and hospitalisations between the analysis year in the period immediately preceding ivacaftor therapy initiation and each analysis year after ivacaftor therapy initiation were performed using Wilcoxon signed-rank test for paired data. Evaluation of BMI and BMI-for-age z-scores included tabulations of summary statistics (eg, mean, SE) for each analysis year.

RESULTS
Demographics and clinical characteristics
The study cohort included 369 people with CF with an R117H variant and treated with ivacaftor, of whom 64 were ages ≥2 to <6 years, 108 were ages ≥6 to <18 years and 197 were ages ≥18 years.

Baseline demographic and clinical characteristics of the cohort are shown in table 1, overall and by age subgroup. Mean ppFEV₁ at treatment initiation was lower in the adult cohort compared with the cohort ages ≥6 to <18 years (table 1), consistent with CF disease progression. Mean (SD) duration of ivacaftor exposure was 25.3 (13.6) months (online supplemental table S1). Of
369 participants in the cohort, 263 remained in the cohort by the start of year 2 and 236 remained by the start of year 3 of follow-up (online supplemental figure S1). Overall, 20.3% of participants discontinued ivacaftor treatment prior to the end of the 3-year study period, 3.8% were censored as they were administered other modulator therapy, 11.9% were lost to follow-up and fewer than five participants died (online supplemental table S1).

**Lung function**

Among people with CF with available lung function data, mean observed ppFEV₁ values were consistently higher than pretreatment values during each of the 12-month intervals following ivacaftor therapy initiation; this trend was observed in the overall population as well as in the paediatric and adult subgroups (figure 1). The mean absolute change in ppFEV₁ from pretreatment baseline in people with CF with available lung function data in the respective intervals was an increase of 1.5 (95% CI 0.8 to 2.3) percentage points in the first 12 months of ivacaftor treatment, 1.7 (95% CI 0.7 to 2.7) in the second 12 months and 1.8 (95% CI 0.6 to 3.0) in the third 12 months in the overall cohort, with improvements also observed in the adult and paediatric subgroups (table S1). The results were consistent in the sensitivity analyses restricted to 173 patients with non-missing baseline and post-treatment initiation data in each of the time intervals (online supplemental figure S2).

**PEx and hospitalisations**

In the overall cohort, annual percentages of people with CF who had at least one PEx event and the mean annualised number of PEx events were both numerically lower in every 12-month interval after ivacaftor treatment initiation compared with the 12-month interval before treatment initiation (figure 2). Similarly, the annual percentage of people with CF with at least one hospitalisation and the mean annualised number of hospitalisations were numerically lower in each of the 12-month intervals after ivacaftor treatment initiation than in the 12 months before (figure 2). Reductions from pretreatment baseline in both the mean number of PEx events and the mean number of hospitalisations were statistically significant in every 12-month interval after ivacaftor treatment initiation (table 3). For both PEx and hospitalisations, similar favourable trends were observed over time across the age subgroups (online supplemental figure S3, S4). The results were consistent in the sensitivity analyses restricted to 230 patients with non-missing baseline and post-treatment initiation data in each of the time intervals (online supplemental figure S2).

**Growth and nutritional parameters**

In each of the three 12-month intervals following ivacaftor treatment initiation, mean BMI-for-age z-scores among people with CF ages ≥6 to <18 years were numerically greater than the mean z-score at pretreatment baseline and remained within the normal range (values of approximately 0.4 to 0.6) (online supplemental figure S5). Similar patterns were observed in weight-for-age and height-for-age z-scores (online supplemental figure S6). Among adults, mean BMI increased in the first 12-month interval after ivacaftor treatment initiation and remained above pretreatment baseline throughout the study (online supplemental figure S5). The mean (SD)

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**Table 1** Demographic and clinical characteristics at ivacaftor initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ages ≥2 to &lt; 6 years (n=64)</th>
<th>Ages ≥6 to &lt; 18 years (n=108)</th>
<th>Ages ≥18 years (n=197)</th>
<th>All ages (n=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>43 (67.2)</td>
<td>54 (50.0)</td>
<td>85 (43.1)</td>
<td>182 (49.3)</td>
</tr>
<tr>
<td>Mean (SD) age at ivacaftor initiation, years</td>
<td>3.9 (1.1)</td>
<td>11.1 (3.4)</td>
<td>42.9 (14.1)</td>
<td>26.8 (20.3)</td>
</tr>
<tr>
<td>Mean (SD) age at CF diagnosis, years</td>
<td>0.4 (0.9)</td>
<td>2.8 (4.0)</td>
<td>25.2 (19.4)</td>
<td>14.4 (18.5)</td>
</tr>
<tr>
<td>White non-Hispanic, n (%)</td>
<td>62 (96.9)</td>
<td>105 (97.2)</td>
<td>192 (97.5)</td>
<td>359 (97.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>n</td>
<td>–</td>
<td>183</td>
<td>–</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>–</td>
<td>–</td>
<td>26.4 (5.8)</td>
<td>–</td>
</tr>
<tr>
<td>BMI-for-age z-score*</td>
<td>n</td>
<td>63</td>
<td>103</td>
<td>–</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.47 (1.04)</td>
<td>0.48 (1.00)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ppFEV₁, n</td>
<td>–</td>
<td>96</td>
<td>179</td>
<td>275</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>–</td>
<td>98.7 (12.9)</td>
<td>70.6 (24.7)</td>
<td>80.5 (25.2)</td>
</tr>
</tbody>
</table>

*z-scores only calculated for participants ages ≥2 to <6 years and ≥6 to <18 years. BMI z-scores were calculated using Centers for Disease Control and Prevention growth charts.

BMI, body mass index; CF, cystic fibrosis; n, sample size; ppFEV₁, percent predicted forced expiratory volume in 1 s.
absolute change from pretreatment baseline in BMI in adult people with CF and BMI-for-age z-score in paediatric subgroups are presented in online supplemental table S2. The mean (SD) absolute change from pretreatment baseline in weight-for-age z-score and height-for-age z-score in paediatric subgroups are presented in online supplemental table S3.

**DISCUSSION**

The results of this real-world registry-based study are consistent with previous research demonstrating consistent improvements in lung function as well as reduced frequency of PEx and hospitalisations among people with CF treated with ivacaftor. Overall, the baseline demographic (sex) and clinical (ppFEV1, BMI z-scores) characteristics of the ivacaftor cohort were consistent with the known epidemiology of the CF population with *R117H* variants.

The present real-world registry-based study demonstrates the favourable effect of ivacaftor therapy on lung function among people with CF and an *R117H* variant, maintained over the course of up to 3 years of follow-up. The improvement in lung function is maintained, with no evidence of decline over 3 years of therapy, across both adult and paediatric subgroups. Of note, among paediatric participants with available data in this study, lung function values remained at about 100% predicted, supporting the benefits of early treatment initiation to reduce disease progression. In addition to the observed favourable trends in lung function, this study also demonstrates consistent reductions in the frequency of PEx and hospitalisations among people with CF and an *R117H* variant treated with ivacaftor.

**LIMITATIONS**

Unlike randomised clinical trials, registry-based studies relying on data collected under real-world conditions are subject to potential confounding and other limitations common to observational research in general.

Although this study could not include a concurrent untreated cohort of people with CF and *R117H* variant since the majority of the eligible population was treated with ivacaftor, evaluation of outcome trends in the 3 years before therapy initiation allowed for the contextualisation of patterns observed after therapy initiation. Analyses in this study were primarily descriptive in nature and were focused on the evaluation of observed outcome patterns over time (described qualitatively as trends).

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**Table 2** Absolute change in ppFEV₁, from pretreatment baseline

<table>
<thead>
<tr>
<th>Absolute change* in ppFEV₁, from pretreatment baseline</th>
<th>Ages ≥6 to &lt;18 years</th>
<th>Ages ≥18 years</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>12 months after treatment initiation</td>
<td>99</td>
<td>1.8 (0.3 to 3.3)</td>
<td>164</td>
</tr>
<tr>
<td>&gt;12 to 24 months after treatment initiation</td>
<td>89</td>
<td>0.4 (−1.5 to 2.2)</td>
<td>130</td>
</tr>
<tr>
<td>&gt;24 to 36 months after treatment initiation</td>
<td>84</td>
<td>0.9 (−0.9 to 2.7)</td>
<td>100</td>
</tr>
</tbody>
</table>

Baseline value was the average of all available measures within 12 months prior to ivacaftor initiation.

*Absolute change was calculated only among participants with non-missing baseline ppFEV₁, and ≥1 non-missing ppFEV₁, in the 12-month interval specified.

n, sample size; ppFEV₁, percent predicted forced expiratory volume in 1 s.
rather than statistical inference. In this real-world study, a substantial amount of attrition was observed during the 3-year follow-up period, which could have contributed to variability in the data and influenced the results over time. Specifically, while reasons for ivacaftor discontinuations were not known in this observational study (this information is not collected in the CFFPR database), it cannot be excluded that patients who discontinued therapy before the end of the 3-year study period could be sicker patients who did not experience improvement in symptoms while on treatment, which could bias the findings in favour of ivacaftor treatment.

Missing data may introduce misclassification of exposure and outcomes data in real-world observational studies. Although the US CFFPR has robust systems in place to minimise missing data in its database, missing data on specific parameters, such as lung function, may be reflecting the routine care patterns and patient adherence to the recommended clinic visit schedule in the real-world setting. Indeed, we found that 19.1% of adult patients included in our cohort (data not shown) had fewer than two clinic visits in the year prior to ivacaftor initiation versus four visits recommended by CF treatment guidelines. Another important limitation of the real-world CFFPR data is that precise treatment start dates may not be available.

The clinical outcome definitions used in the US CFFPR and the mechanisms and guidelines for data collection were different from those used in the interventional clinical study (VX11-770-110) in people with CF and an R117H variant. For example, ppFEV1 was calculated using GLI standards instead of Hankinson and Wang standards. However, the directional consistency of outcomes across age subgroups in this registry-based study supports the benefit of ivacaftor.

CONCLUSIONS
In conclusion, the results of this real-world observational study based on analysis of data from the US

| Table 3 Absolute change in the mean number of PEx and hospitalisations from pretreatment baseline for all ages |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Absolute change* from pretreatment baseline     | PEx                                             | Hospitalisations                                 |
| n      | Mean (SD) | P value†    | n      | Mean (SD) | P value†    |
| 12 months after treatment initiation            | 340     | −0.08 (0.62) | 0.026  | 340     | −0.10 (0.68) | 0.010  |
| >12 to 24 months after treatment initiation     | 268     | −0.07 (0.60) | 0.036  | 268     | −0.09 (0.73) | 0.030  |
| >24 to 36 months after treatment initiation     | 230     | −0.08 (0.56) | 0.025  | 230     | −0.11 (0.67) | 0.012  |

*Absolute change could be calculated only among participants with non-missing data in the 12-month pretreatment interval and 12-month post-treatment interval specified.
†P values were obtained from a Wilcoxon signed-rank test and were not adjusted for multiple comparisons.
CFFPR support the long-term effectiveness of ivacaftor in people with CF and an R117H variant. This study used data collected by the US CFFPR, the largest national CF registry in the world with broad coverage of the CF population. Key clinical outcomes were evaluated among all CFFPR participants with an R117H variant who had a record of ivacaftor initiation during the study enrolment period and were ages ≥2 years, with no additional inclusion or exclusion criteria. Therefore, these study results may be considered generalisable to people with CF and an R117H variant in the USA and informative to the broader population of people with CF and an R117H variant globally.

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Contributors MH, TF, DC and NV designed the study, and data were collected by JO and AE. All authors participated in the analysis and interpretation of study data. The manuscript was drafted by MH, TF and NV, and all authors contributed to critical revision of the manuscript for important intellectual content and gave final approval of the manuscript for publication. MH is the guarantor.

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Competing interests MH, TF, ML, JS and NV are employees of Vertex Pharmaceuticals and may own stock or stock options in that company. DC is a former employee of Vertex Pharmaceuticals and may own stock or stock options in that company. JO and AE are employees of the Cystic Fibrosis Foundation.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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