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Patient-reported outcomes in patients with cystic fibrosis with a *G551D* mutation on ivacaftor treatment: results from a cross-sectional study

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Abstract

Background: Clinical studies demonstrate that ivacaftor (IVA) improves health-related quality of life (HRQoL) in patients aged ≥ 6 years with cystic fibrosis (CF). The real-world impact of IVA and standard of care (SOC) in groups of patients with *G551D* and *F508del* mutations, respectively, was assessed using a survey comprising disease-specific and generic HRQoL measures.

Methods: Patients with CF aged ≥ 12 years, or aged 6–11 years with caregiver support, with either (1) a *G551D* mutation and receiving IVA (*G551D/IVA*) for ≥ 3 months, or (2) homozygous for *F508del* and receiving SOC before lumacaftor/IVA availability (*F508del/SOC*), were eligible to participate in a cross-sectional survey. Demographic and clinical characteristics, and HRQoL measures were compared between patient groups, and multiple regression analyses were conducted.

Results: After differences in patient demographic and clinical characteristics were controlled for, significantly better scores were observed in the *G551D/IVA* group than in the *F508del/SOC* group on multiple domains of the validated Cystic Fibrosis Questionnaire-Revised and the EuroQol 5-dimensions 5-level questionnaire.

Conclusions: *G551D/IVA* patients reported better HRQoL than *F508del/SOC* patients on generic and disease-specific measures in a real-world setting.

Keywords: Patient-reported outcomes, Work productivity, Ivacaftor, Cystic fibrosis, *G551D-CFTR*

Background

Cystic fibrosis (CF) is a chronic, progressive, life-shortening disease that affects the ability of patients to function in many areas of daily living [1, 2]. There is growing evidence that patient-reported outcomes (PROs) can serve as valuable indicators of the benefit of treatment and its impact on health-related quality of life (HRQoL), as they represent direct measures of how a patient feels and functions [3, 4]. Evaluation of such measures is becoming increasingly important for patients with chronic disease, such as CF, which necessitates complex

management regimens and imposes a considerable burden on patients and their caregivers [1, 5, 6].

The Cystic Fibrosis Questionnaire-Revised (CFQR) is a disease-specific, validated tool that encompasses general domains of HRQoL as well as domains specific to CF [7, 8]. The EuroQol 5-dimensions 5-level questionnaire (EQ-5D-5L) is a generic measure that provides a single index value of health status and permits comparisons between treatments across different medical conditions [4, 9, 10]. The EQ-5D-5L is a widely accepted measure for assessing utilities, which is recommended by the National Institute for Health and Care Excellence in the United Kingdom (UK), and is a standardized assessment that can be used across a variety of diseases [11]. Other PROs, such as the Work Productivity and Activity Impairment Questionnaire (WPAI) [12, 13],

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take productivity losses into consideration, which may provide additional context for the impact of treatment on patients and their caregivers in the real world.

The treatment benefit of ivacaftor (IVA) in patients with CF with a *G551D* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene has been established in Phase 3 studies [14–16]. Improvements in lung function, body weight, and HRQoL, as measured by the CFQ-R Respiratory Symptoms domain, were observed through 48 weeks [14, 15]; these benefits were sustained for nearly 3 years in an open-label extension study [16]. An additional analysis using Phase 3 data further demonstrated broad HRQoL benefits of IVA across multiple domains of the CFQ-R [17]. However, the majority of HRQoL data with IVA have been derived from clinical trials [14–17], whereas HRQoL data from real-world studies are limited [18]. We therefore sought to expand on these studies by determining the impact of IVA on HRQoL using the CFQ-R and EQ-5D-5L, and work productivity using the WPAI. We also sought to compare outcomes for patients with the *G551D-CFTR* mutation on ≥ 1 allele who were receiving treatment with IVA (*G551D/IVA* group) in the real-world setting with those for patients homozygous for the *F508del-CFTR* mutation who were receiving standard of care (SOC) (*F508del/SOC* group) treatment prior to availability of lumacaftor (LUM)/IVA.

Methods

Patients with CF who were ≥ 12 years of age and caregivers of patients aged 6–11 years were recruited to participate in this cross-sectional, observational study in 5 countries (France, the UK, Germany, Australia, and Ireland). The final study report date was October 2, 2014. Patients were screened by the site coordinators at the time of clinic visits to confirm study eligibility and to collect demographic and clinical characteristics. Patients who were eligible for the study were diagnosed with CF, had ≥ 1 *G551D* mutation, and were receiving IVA with treatment exposure for ≥ 3 months, or were homozygous for the *F508del* mutation and receiving SOC (not exposed to or receiving IVA and prior to the availability of LUM/IVA). Patients were excluded from the study if they were participating in an interventional clinical trial, experiencing a pulmonary exacerbation at their clinic visit, or unable or unwilling to provide consent (adults/caregivers) or assent (minors). A study screening form, completed by clinic staff, reported demographic and clinical patient data, such as percent predicted forced expiratory volume in 1 s (ppFEV₁), height, weight, *CFTR* mutations, select key comorbidities (i.e. presence of anxiety, attention deficit hyperactivity disorder, depression, diabetes, cancer, infertility, end-stage liver disease, pulmonary hypertension, osteoporosis, pancreatic insufficiency, pancreatitis, chronic rhinosinusitis/

nasal polyps, and rectal prolapse), and current CF treatment including IVA.

Patients or their caregivers who qualified and consented to participate in the study completed a one-time survey at the time of their clinic visit comprising the CFQ-R [7, 8], EQ-5D-5L [9, 10], and WPAI [12, 13]. Three distinct age-specific versions of the survey were used for patients aged 6–11 years, 12–13 years, and ≥ 14 years. The survey was completed by the patients themselves with the following exceptions: patients aged 6–11 years (caregivers completed the survey) and patients aged ≥ 12 years (completed by the patient, with some assistance from the caregiver, as appropriate).

The CFQ-R measures HRQoL in general domains of Vitality, Health Perceptions, Physical Functioning, Emotional Functioning, Social Functioning, and Role Functioning, and CF-specific domains of Body Image, Eating, Treatment Burden, and Respiratory and Digestive Symptoms [7, 8]. The EQ-5D-5L has a descriptive system that measures general health status in 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression, and a visual analog scale (VAS) that records an individual's self-rated health on a scale of 0–100 [10]. Both the CFQ-R and EQ-5D-5L have been validated in CF [7, 8, 10]. The WPAI is designed to measure the effect of general health and symptom severity on work/school productivity and regular activities during the past 7 days; it has been validated in respiratory disease, but not in CF [12, 13].

Demographic and clinical characteristics of the *G551D/IVA* and *F508del/SOC* patient groups were compared, with *t*-tests for numeric variables and χ^2 tests for categorical variables. Multivariate regression analyses were conducted for outcomes on the CFQ-R, EQ-5D-5L, and WPAI to compare *G551D/IVA* and *F508del/SOC* groups, adjusting for differences observed between groups in sex, ppFEV₁, and number of comorbidities. Multiplicity was not controlled for. Least squares (LS) estimated means were presented as adjusted mean values. *P* values < 0.05 were considered statistically significant in all analyses.

Central ethics approval of the study protocol was obtained in the UK and France, while institution-specific ethics approval was obtained at each of the participating institutions from Germany, Australia, and Ireland.

Results

Demographic and clinical characteristics of 209 survey respondents (72 in the *G551D/IVA* group and 137 in the *F508del/SOC* group) at study entry are shown in Table 1. In the *G551D/IVA* group, of the 72 surveys, 60 were completed by patients aged ≥ 12 years and 12 by caregivers for children aged 6–11 years. In the *F508del/SOC* group, of the 137 surveys, 116 were completed by patients aged ≥ 12 years and 21 by caregivers for

Table 1 Demographic and clinical characteristics

Characteristic	Overall (N = 209)	G551D/IVA patient group (n = 72)	F508del/SOC patient group (n = 137)	P value ^a
Age, mean (SD), years	24.3 (12.1)	23.9 (13.9)	24.6 (11.1)	0.70
Range	6–62	6–62	6–52	
Missing, n	6	3	3	
Age group (years), n (%)				
6–11	33 (15.8)	12 (16.7)	21 (15.3)	
12–17	39 (18.7)	18 (25.0)	21 (15.3)	0.19
≥18	137 (65.6)	42 (58.3)	95 (69.3)	
Sex, n (%) ^b				
Male	108 (56.0)	27 (39.7)	81 (64.8)	< 0.01
Female	85 (44.0)	41 (60.3)	44 (35.2)	
Missing, n	16	3	12	
ppFEV ₁ (%), mean (SD)	73.9 ^c (28.0)	79.8 (25.6)	70.7 ^d (28.8)	< 0.05
ppFEV ₁ <70, n (%)	85 (40.7) ^e	24 (33.3)	61 (44.5) ^e	0.12
ppFEV ₁ (%), n; mean (SD)				
<40	32; 29.3 (6.6)	6; 28.8 (4.5)	26; 29.3 (7.0)	0.87
40–69	51; 54.5 (8.7)	18; 57.4 (7.9)	33; 52.9 (8.7)	0.07
70–89	50; 79.2 (6.0)	16; 78.6 (6.6)	33; 79.5 (5.7)	0.60
≥90	74; 103.0 (10.5)	31; 103.4 (9.7)	43; 102.6 (11.1)	0.74
Number of comorbidities, mean (SD)	1.9 ^f (1.2)	1.5 ^g (1.1)	2.0 (1.2)	< 0.01
Patients with ≥1 comorbidity, n (%)	192 (92.3)	60 (84.5)	132 (96.4)	< 0.01
History of lung transplant, n (%)				
Yes	3 ^f (1.4)	0 ^g (0.0)	3 (2.2)	0.55
No	205 ^f (98.6)	71 ^g (100.0)	134 (97.8)	
Waiting for lung transplant, n (%)				
Yes	3 ^f (1.4)	0 ^g (0.0)	3 (2.2)	0.55
No	205 ^f (98.6)	71 ^g (100.0)	134 (97.8)	
BMI				
Aged ≥19 years, n; mean (SD), kg/m ²	126; 21.6 (3.3)	36; 22.2 (3.2)	90; 21.3 (3.3)	0.16
Aged <19 years, n; mean (SD) z-score	59; 0.001 (0.87)	25; 0.004 (0.82)	34; -0.0009 (0.92)	0.98

BMI Body mass index, IVA Ivacaftor, ppFEV₁ Percent predicted forced expiratory volume in 1 s, SD Standard deviation, SOC Standard of care

^aP values presented are for comparison of the G551D/IVA group with the F508del/SOC group

^bPercentages are derived from the available sample

^cn=207

^dn=135

^eBaseline data was missing for 2 patients

^fn=208

^gn=71

children aged 6–11 years. Overall, the mean (standard deviation [SD]) patient age was 24.3 (12.1) years and 56% of patients were male (Table 1). Some differences were observed between groups. Age was similar between the two groups but the G551D/IVA group had a significantly higher proportion of females than the F508del/SOC group (60.3% vs. 35.2%, respectively; $P < 0.01$). The G551D/IVA group also had a significantly higher mean ppFEV₁ than the F508del/SOC group (79.8 vs. 70.7 percentage points, respectively;

$P < 0.05$), significantly fewer patients with pancreatic insufficiency (80.3% vs. 92.0%; $P < 0.05$), significantly fewer mean number of comorbidities (1.5 vs. 2.0; $P < 0.01$), and significantly lower proportion of patients with ≥1 comorbidity (84.5% vs. 96.4%; $P < 0.01$) (Table 1). Individual comorbidities for which significant differences were observed between G551D/IVA and F508del/SOC groups included pancreatitis (2.8% vs. 0.0%; $P < 0.05$) and nasal polyp formation (8.5% vs. 19.0%; $P < 0.05$). Body mass index (BMI) for those

aged ≥ 19 years was similar between the groups, as was BMI z-score for those aged < 19 years.

The mean (SD) duration of IVA exposure was 21.8 (15.1) months. Patient recruitment and duration of IVA exposure varied by country, as shown in Table 2.

Using an analysis of covariance model controlled for differences in ppFEV₁, sex, and number of comorbidities at the time of their clinic visit, patients in the *G551D*/IVA group had significantly higher LS mean CFQ-R scores than patients in the *F508del*/SOC group in the following scales: Respiratory Symptoms (75.4 vs. 62.5; $P < 0.0001$), Digestive Symptoms (85.5 vs. 78.0; $P < 0.05$), Eating (91.1 vs. 84.2; $P < 0.05$), Treatment Burden (65.3 vs. 54.8; $P < 0.01$), and Physical Functioning (74.6 vs. 66.6; $P < 0.05$) (Fig. 1). Patients in the *G551D*/IVA group also had significantly higher LS mean CFQ-R scores than patients in the *F508del*/SOC group in the 6–11-year and the ≥ 14 -year versions of the Weight (80.7 vs. 64.2; $P < 0.01$), Health Perceptions (67.6 vs. 58.6; $P < 0.01$), and Vitality (63.5 vs. 55.9; $P < 0.05$) (Fig. 1) domains. For the EQ-5D-5L, significantly better LS mean index scores and VAS scores were also observed in the *G551D*/IVA group than in the *F508del*/SOC group after controlling for differences in ppFEV₁, sex, and number of comorbidities (Table 3). Within individual domains of the EQ-5D-5L, significantly better scores of Mobility, Usual Activities, Pain/Discomfort, and Anxiety/Depression were observed for the *G551D*/IVA group, whereas Self-Care was not

significantly different between the groups (Fig. 2). In adjusted analyses of the WPAI, LS mean scores for School Productivity Loss and Daily Activity Impairment were numerically lower in the *G551D*/IVA group than in the *F508del*/SOC group, although differences between groups did not reach statistical significance (Table 3).

Discussion

This cross-sectional observational study demonstrated that treatment with IVA in patients with CF and a *G551D* mutation was associated with multiple HRQoL benefits on disease-specific and generic and validated PRO measures compared with patients with CF who were homozygous for *F508del* and receiving SOC. This study was designed to evaluate outcomes following IVA exposure for a longer period of time than the usual follow-up period of randomized controlled trials, with the mean duration of IVA exposure being 21.8 months. Better outcomes on the CFQ-R in multiple domains and on the EQ-5D-5L using both index and VAS scores were observed in the *G551D*/IVA group. These findings lend additional real-world support to the HRQoL benefit of IVA previously described in clinical trials [14–17].

In recent years, there has been mounting interest from regulatory authorities as well as funding authorities to evaluate HRQoL, efficacy, and safety in real-world settings, necessitating continued demonstration of health outcomes. In particular, measures that can generate a single index value to allow for comparisons across a disease state that contribute to cost analysis are needed [4]. Data on EQ-5D-5L scores are instrumental in health technology assessments (HTA) in several countries around the world [11]. In this analysis, significant differences between the *G551D*/IVA and *F508del*/SOC groups were observed on the EQ-5D-5L using both the index score and VAS. Although a minimum clinically important difference has not yet been established in CF, in chronic obstructive pulmonary disease, the mean estimates of the minimum clinically important difference for the utility index and EuroQol-VAS have been estimated at 0.051 (range 0.037–0.063) and 6.9 (range 6.5–8.0), respectively [19]. This is in line with the difference of 0.09 observed in this study. It should be noted that children with CF and their parents tend to develop coping mechanisms early in life and often establish a ‘new normal’ in their minds. This is sometimes reflected in high EQ-5D-5L scores, as seen in this study, and can make it difficult to identify differences in treatment effects using the EQ-5D-5L. Despite this, the statistically significant difference in the tool measures shown here mark a notable finding in this area.

With respect to the subscales on the EQ-5D-5L, we saw better scores for Mobility, Usual Activities, Pain/Discomfort, and Anxiety/Depression in the *G551D*/IVA

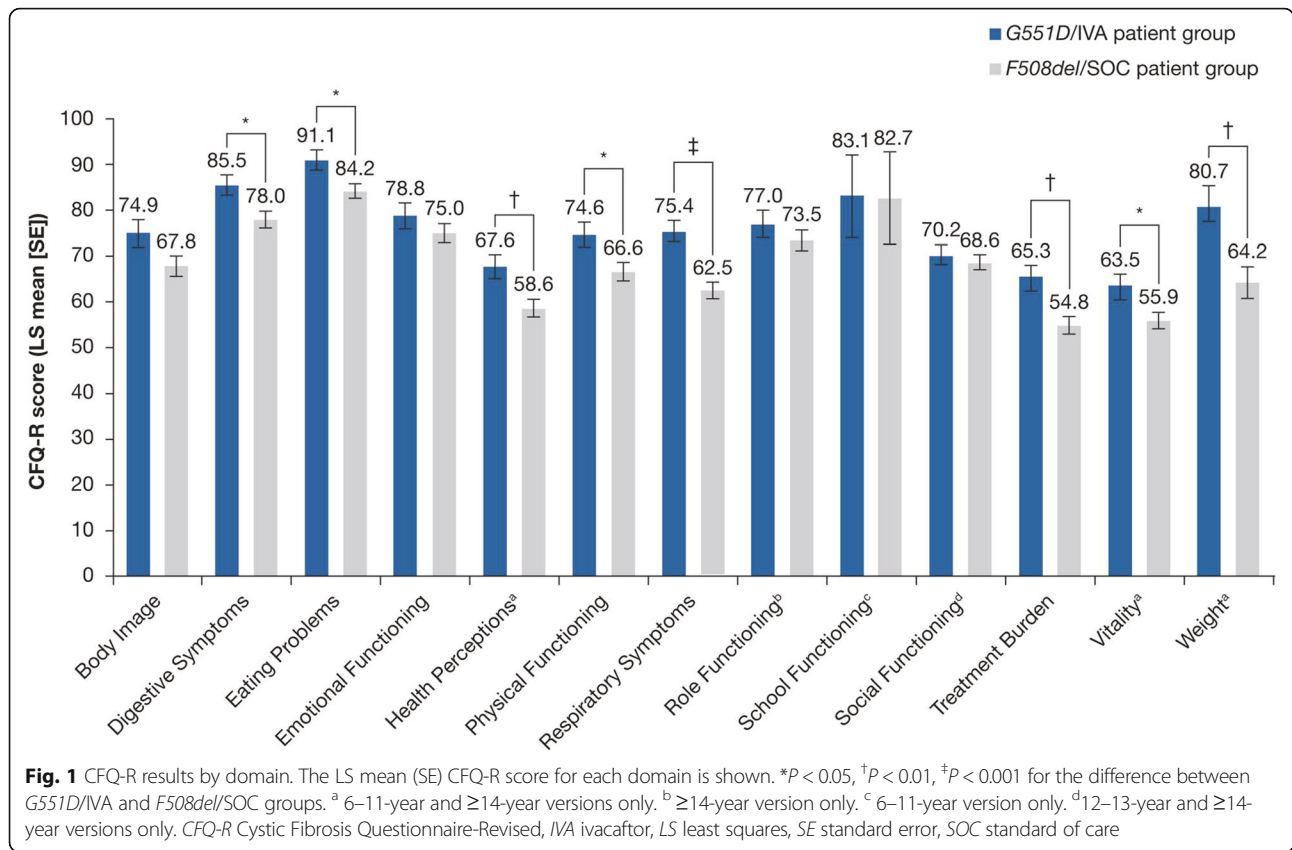
Table 2 Patient cohorts by country with duration of IVA exposure

Country	Overall	<i>G551D</i> /IVA patient group	<i>F508del</i> /SOC patient group
All countries, <i>N</i>	209	72 ^a	137
IVA exposure, mean (SD), months	NA	21.8 (15.1)	NA
France, <i>n</i> (%)	61 (29.2)	10 (13.9)	51 (37.2)
IVA exposure, mean (SD), months	NA	15.9 (8.4)	NA
United Kingdom, <i>n</i> (%)	54 (25.8)	33 (45.8)	21 (15.3)
IVA exposure, mean (SD), months	NA	18.1 ^b (11.4)	NA
Germany, <i>n</i> (%)	47 (22.5)	14 (19.4)	33 (24.1)
IVA exposure, mean (SD), months	NA	19.6 (9.6)	NA
Australia, <i>n</i> (%)	38 (18.2)	12 (16.7)	26 (19.0)
IVA exposure, mean (SD), months	NA	35.6 (24.1)	NA
Ireland, <i>n</i> (%)	9 (4.3)	3 (4.2)	6 (4.4)
IVA exposure, mean (SD), months	NA	30.0 (0.0)	NA

IVA Ivacaftor, NA Not applicable, SD Standard deviation, SOC Standard of care

^aDuration on ivacaftor exposure was missing for 6 patients

^b*n* = 27



group than in the F508del/SOC group. Although no difference in Self-Care was seen, previous observations in CF have also showed little impact on this scale [4, 10]. However, Pain/Discomfort and Anxiety/Depression scales have consistently been found to be highly impacted among patients with CF [4, 10]. These scales may be particularly informative in CF and warrant further study. Depression and anxiety have been reported at higher rates among patients with CF and their caregivers than in the general community [20]. Psychological symptoms in

patients with CF have been associated with lower lung function, worse nutritional status, poorer adherence, lower HRQoL, and more frequent hospitalization [21]. Thus, the Cystic Fibrosis Foundation and the European Cystic Fibrosis Society developed a consensus statement for screening and treating depression and anxiety, recommending use of the Patient Health Questionnaire 9- and Generalized Anxiety Disorder 7-item scales for annual screening [21]. In our study, between-group differences were not significant on psychosocial domains of the CFQ-

Table 3 EQ-5D-5L and WPAI results

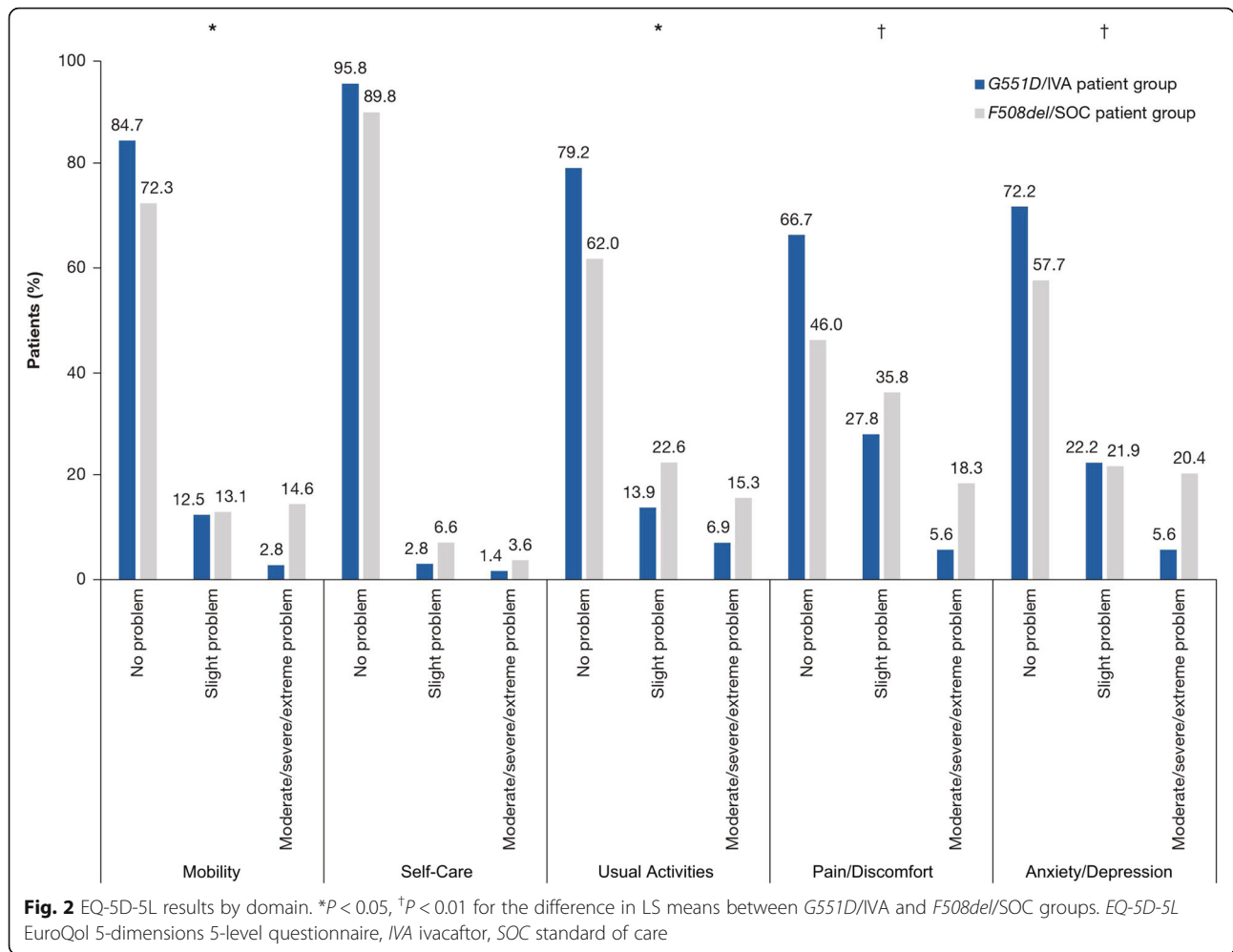
	G551D/IVA patient group	F508del/SOC patient group	P value
EQ-5D-5L			
Index score (0–1), n; LS mean (SE)	72; 0.90 (0.02)	137; 0.81 (0.02)	< 0.01
VAS score (0–100), n; LS mean (SE)	72; 75.7 (1.8)	135; 70.0 (1.4)	0.0136
WPAI			
School, n ^a	41	53	
Productivity loss, n; LS mean (SE) ^b	27; 24.62 (6.69)	32; 34.57 (6.73)	0.3242
Daily activities, n	70	135	
Activity impairment, LS mean (SE) ^c	21.63 (2.95)	28.30 (2.19)	0.08

CF Cystic fibrosis, EQ-5D-5L EuroQol 5-dimensions 5-level questionnaire, IVA Ivacaftor, LS Least squares, SE Standard error, SOC Standard of care, VAS Visual analog scale, WPAI Work Productivity Activity and Impairment Questionnaire

^aA total of 29 students were excluded because they were not in school over the past 2 weeks for reasons other than CF or had missing data

^bProductivity loss: combination of absenteeism and presenteeism representing the percentage of overall impairment due to CF

^cActivity impairment: percentage impact of CF on daily activities



R questionnaire, suggesting that the CFQ-R questionnaire is less capable of capturing the psychosocial benefits of therapy with CFTR modulators. The role of pain in CF is less well studied, but recent reports indicate that pain is associated with depression, anxiety, lower HRQoL, and increased risk of pulmonary exacerbations and death [22, 23] and could relate to a decrease in the patient’s ability to participate in airway clearance activities, or pain could be a potential marker of increased inflammation and/or disease severity. More research is needed to evaluate pain and its effect on HRQoL and other health parameters, as well as to further assess pain management strategies [22, 23].

The benefits associated with IVA on the CFQ-R after a mean (SD) exposure of 21.8 (15.1) months were generally consistent with those observed using data from the Phase 3 STRIVE study [17]. Benefits on the Respiratory Symptoms domain were notable; a nearly 13-point difference was found between the G551D/IVA and F508del/SOC groups in adjusted analyses, exceeding the minimum clinically important difference of 4 points for the Respiratory

Symptoms domain of the CFQ-R [24]. Furthermore, these data are consistent with the observational GOAL study, in which real-world patients with G551D mutations treated with IVA for 6 months showed a 7.4-point improvement from baseline in the CFQ-R Respiratory Symptoms domain [18].

Benefits on other CF-specific scales, including Weight, Digestive Symptoms, Eating, and Treatment Burden, were also observed. The between-group difference in Weight score of 16.5 points was particularly notable. Higher scores on general health domains of Physical Functioning, Health Perception, and Vitality were seen, although we did not see higher scores in Social Functioning, as seen in Phase 3 clinical trials [17].

In chronic diseases such as CF, lost productivity can contribute to the overall burden of disease. Additionally, work productivity data are considered in HTAs in several countries, and are considered a relevant and meaningful parameter to evaluate and report because they can further reinforce the value of an intervention from a patient and societal perspective, and can justify social

funding for interventions that deliver societal value. The WPAI is a PRO tool that can assess productivity losses and general activity impairment but, to our knowledge, has not been previously validated in CF. Our findings show that school productivity loss was significantly lower and activity impairment was numerically lower in the *G551D/IVA* group than in the *F508del/SOC* group. While these results are encouraging, they are based on a subgroup of the study population and further research including a larger group of patients is needed.

Several limitations of this cross-sectional, observational study should be noted. The outcomes assessed were compared in patients with different genotypes. There has been debate in the literature regarding whether patients with class III (e.g. *G551D*) genotypes have disease severity similar to that of patients with class II (e.g. *F508del*) genotypes. Whereas some studies have shown less severe disease in patients with class III than with class II genotypes, others have found these genotypes to be generally comparable [25–29], although variation in the size of the studies may account for some of the differences reported. The observational nature of the study does not allow for the differences in HRQoL between groups to be directly attributed to IVA, in particular because only one group was exposed to this therapy. For patients in the *F508del/SOC* group, the exact nature of SOC was not defined, nor were potential differences in the components of what is regarded as SOC in different countries taken into account.

In our sample, we observed differences between groups, such as the *G551D/IVA* group having a higher proportion of female patients, higher ppFEV₁ values, and fewer comorbidities than the *F508del/SOC* group. These differences may relate to the fact that the patients within the *G551D/IVA* group were treated with IVA. The significantly lower rate of pancreatic insufficiency seen in the *G551D/IVA* group, for example, may be associated with IVA treatment, since patient clinical characteristics were collected at the time of the survey when patients were long established on therapy. Furthermore, 3 patients with lung transplants were included in the *F508del/SOC* group. Ideally, such patients should have been excluded by the study protocol. However, as they constitute only 2.3% of the *F508del/SOC* group, and their inclusion likely favors the *F508del/SOC* group, we do not envisage that their exclusion would have substantially changed the results. In addition, excluding these patients may favor the results of the *G551D/IVA* group. Our analysis controlled for differences in patient demographic and clinical characteristics between groups; nevertheless, underlying differences between genotypes that could not be accounted for may still exist. In addition, this was an international multicenter study; therefore, available treatment options and corresponding patient burden may

vary across different countries/sites [30]. Furthermore, we saw some imbalances in recruitment across different countries, which differed by group. Although systematic recruitment was attempted, data may reflect patients only in the centers studied, and, as such, these results may not be fully generalizable. As with any cross-sectional, observational study, the data do not capture change over time or treatment effects. However, they do highlight the importance of assessing PROs longitudinally in patients, before and during treatment with a new CFTR modulator therapy. With the growing importance of PROs as a measure of the benefit of therapy from the patients' own perspectives, we would suggest that future longitudinal trials of CFTR modulators in patients with CF should include relevant PROs in their study design. Although resource constraints make routine administration of the CFQ-R impractical in the real-world clinic setting, the simplicity and low costs associated with the EQ-5D-5L confer potential for more widespread use and capture of longitudinal data.

Conclusions

In summary, patients with CF and a *G551D-CFTR* mutation on ≥ 1 allele and receiving IVA in real-world settings reported better generic and disease-specific HRQoL, better school productivity, and better symptomatology than patients with CF who are homozygous for *F508del-CFTR* and receiving SOC (without LUM/IVA) in multiple domains. These data support further longitudinal, multicenter assessments to continue to investigate real-world benefits with IVA in patients with CF and a *G551D-CFTR* mutation.

Abbreviations

BMI: Body mass index; CF: Cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: Cystic fibrosis transmembrane conductance regulator; EQ-5D-5L: EuroQol 5-dimensions 5-level questionnaire; HRQoL: Health-related quality of life; HTA: Health technology assessment; IVA: Ivacaftor; LS: Least squares; LUM: Lumacaftor; ppFEV₁: Percent predicted forced expiratory volume in 1 s; PRO: Patient-reported outcome; SD: Standard deviation; SE: Standard error; SOC: Standard of care; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire

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Authors' contributions

All authors contributed to the design of the study, provided an interpretation of the data, critically reviewed the manuscript drafts, provided final approval of the manuscript to be submitted, and are accountable for accuracy and integrity of the manuscript. All authors have read and approved the manuscript, and ensure that this is the case. SCB made substantial contributions to the conception and design of the work; the

acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. JGM made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. SM made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. JM made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. MF made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. EDF made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. SN made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. NK made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; substantial revisions to the draft; approved the submitted version; agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Central ethics approval of the study protocol was obtained in the UK (national approval via the National Research Ethics Service Committee South Central, reference no. 14/SC/0297) and France (ethics exemption provided by the *Comité de Protection des Personnes*), while institution-specific ethics approval was obtained at each of the participating institutions from Germany (institutional ethics review committee at Universitätsklinikum Jena [reference no. not available]), and approval by the Ethics Commission of LMU Munich, reference no. 390-14), Australia (local institutional review board at Princess Margaret Hospital, Scientific Advisory Sub-committee, reference no. 2014096/EP, and Human Research Ethics Committee of Prince Charles Hospital, Metro North Hospital and Health Services, reference no. HREC/14/QPCH/113), and Ireland (Temple St Children's University Hospital, Ethics Committee, Department of Research, reference no. 14.042).

Written informed participant consent was obtained by participants or their guardians. All participants, or their parent or guardian if aged younger than 18 years, provided written informed consent, or assent where appropriate, before enrolment.

Consent for publication

Not applicable.

Competing interests

SCB is a site principal investigator, advisory board member, and writing group member; he has received travel support from Vertex Pharmaceuticals Incorporated to attend investigator meetings. He also has been a site principal investigator and received travel support from Galapagos and Flatley to attend investigator meetings and attended advisory board meetings for AbbVie/Galapagos. JGM has participated in clinical trials and has received funding for investigator-initiated research and advisory boards for Vertex Pharmaceuticals Incorporated. GM has received funding for investigator-led research, participated in clinical trials, and attended paid advisory board meetings for Vertex Pharmaceuticals Incorporated. SM is a former advisory board member and has received funding and travel support from Vertex Pharmaceuticals Incorporated. JM has participated in clinical trials and received funding for advisory boards from Vertex Pharmaceuticals Incorporated. MF is a consultant for Vertex Pharmaceuticals Incorporated. EDS is a former employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. SN is an employee of Decision Resources Group, has provided consulting services for Vertex Pharmaceuticals Incorporated, and has received funding to execute the observational study discussed in this manuscript. NK is an employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company.

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