Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for *F508del*

Andrea Lopez[a,*], Conor Daly[b], Gabriela Vega-Hernandez[b], Gordon MacGregor[c], Jaime L. Rubin[a]

[a] *Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, USA*
[b] *Vertex Pharmaceuticals (Europe) Limited, 2 Kingdom Street, London, W2 6BD, UK*
[c] *Department of Respiratory Medicine, NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, 84 Glasgow Street, Glasgow, G4 0SF, UK*

ARTICLE INFO

Article history:
Received 24 August 2022
Revised 31 January 2023
Accepted 6 February 2023
Available online xxx

Keywords:
Cystic fibrosis
Elexacaftor
Long-term health outcomes
Ivacaftor
Microsimulation modeling
Tezacaftor

ABSTRACT

Background: A series of phase 3 clinical trials have demonstrated that elexacaftor plus tezacaftor plus ivacaftor (ELX/TEZ/IVA) is safe and efficacious in people with cystic fibrosis (pwCF) aged ≥12 years with ≥1 *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The impact of this treatment on lifetime clinical outcomes and survival, however, has yet to be assessed.

Methods: We used a person-level microsimulation model to estimate the survival and lifetime clinical benefits of ELX/TEZ/IVA treatment versus other CFTR modulator combinations (tezacaftor plus ivacaftor [TEZ/IVA] or lumacaftor plus ivacaftor [LUM/IVA]) or best supportive care (BSC) alone in pwCF aged ≥12 years who are homozygous for *F508del-CFTR*. Disease progression inputs were derived from published literature; clinical efficacy inputs were derived from an indirect treatment comparison conducted using relevant phase 3 clinical trial data and extrapolations of clinical data.

Results: The median projected survival for pwCF homozygous for *F508del-CFTR* treated with ELX/TEZ/IVA was 71.6 years. This was an increase of 23.2 years versus TEZ/IVA, 26.2 years versus LUM/IVA, and 33.5 years versus BSC alone. Treatment with ELX/TEZ/IVA also reduced disease severity as well as the number of pulmonary exacerbations and lung transplants. In a scenario analysis, the median projected survival for pwCF initiating ELX/TEZ/IVA between the ages of 12 and 17 years was 82.5 years, an increase of 45.4 years compared with BSC alone.

Conclusions: The results from our model suggest ELX/TEZ/IVA treatment may substantially increase survival for pwCF, with early initiation potentially allowing pwCF to achieve near-normal life expectancy.

1. Introduction

Cystic fibrosis (CF) is a rare, autosomal recessive disease that affects >83,000 adults and children worldwide [1]. CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene that decrease the quantity and/or function of CFTR protein [2]. CF is a chronic, multisystemic disease that is associated with severe symptom burden, frequent complications and hospitalizations, and premature mortality [3,4]. Although survival has increased over the past six decades, the median age at death for people with CF (pwCF) in the UK was 36 years in 2020 [5].

Existing treatments for CF are broadly classified as either supportive care, in which CF-related symptoms and complications (e.g., physical airway clearance therapy, bronchodilators, inhaled mucolytics, and antibiotics) are managed, or CFTR modulator therapy, in which small molecules target the underlying cause of the disease [4]. CFTR modulators represent a major advance in the treatment of CF by providing significant improvements in pulmonary and extrapulmonary outcomes, and modifying the course of disease by slowing progression and improving survival relative to supportive care alone [6–9]. Current CFTR modulators include potentiators, such as ivacaftor (IVA), that enhance channel gating, and correctors, such as lumacaftor (LUM), tezacaftor (TEZ), and elexacaftor (ELX), that improve CFTR protein processing and traf-

Abbreviations: BSC, best supportive care; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; ELX, elexacaftor; IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbations; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; pwCF, people with cystic fibrosis; TEZ, tezacaftor; WFAZ, weight-for-age z-score.

* Corresponding author.
E-mail address: Andrea_Lopez@vrtx.com (A. Lopez).

https://doi.org/10.1016/j.jcf.2023.02.004

Please cite this article as: A. Lopez, C. Daly, G. Vega-Hernandez et al., Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del, Journal of Cystic Fibrosis, https://doi.org/10.1016/j.jcf.2023.02.004

ficking [10]. The CFTR dual modulator combinations LUM plus IVA (LUM/IVA) and TEZ plus IVA (TEZ/IVA) have been shown to be safe and effective in treating pwCF homozygous for the *F508del-CFTR* genotype (i.e., with two *F508del-CFTR* alleles), which is the most common form of *CFTR* mutation among pwCF.

More recently, a triple-combination regimen of ELX plus TEZ plus IVA (ELX/TEZ/IVA) was shown to be highly efficacious and safe in pwCF with at least one *F508del* allele, which includes the population homozygous for *F508del-CFTR* [11–13]. Across several phase 3 clinical trials, ELX/TEZ/IVA has demonstrated meaningful and unprecedented clinical benefits for pwCF, including significant improvements in lung function, respiratory symptoms, nutritional status, and health-related quality of life, as well as substantial reductions in the frequency of pulmonary exacerbations (PEx) [11–13]. These clinical benefits have exceeded those reported with other CFTR modulator combinations, including TEZ/IVA, for pwCF homozygous for *F508del-CFTR* [12,13]. Notably, a recent open-label study concluded that the rapid, robust, and clinically meaningful improvements in lung function achieved with ELX/TEZ/IVA were maintained for up to 2 years of continued use [14].

Due to its relatively recent regulatory approval and availability, the impact of ELX/TEZ/IVA on the lifetime survival of pwCF has not yet been evaluated. Here, we developed an individual person-level microsimulation model to estimate the effects of ELX/TEZ/IVA plus current best supportive care (BSC) versus other CFTR modulators (TEZ/IVA, LUM/IVA) plus BSC and BSC alone on survival and other relevant clinical outcomes in pwCF aged ≥12 years homozygous for *F508del-CFTR*.

2. Methods

2.1. Model overview

A person-level microsimulation model was developed to estimate the lifetime clinical outcomes and survival of pwCF aged ≥12 years and homozygous for *F508del-CFTR* in the UK. The modeled interventions included ELX/TEZ/IVA, TEZ/IVA, and LUM/IVA, each in combination with BSC, as well as BSC alone. The model framework and underlying survival calculation approach were aligned with those of a previously published model used to predict the long-term clinical outcomes of pwCF in the US treated with LUM/IVA [15], the framework of which has been validated using real-world data from a long-term safety study of pwCF treated with IVA over 5 years [16]. After calibration, 5-year mortality projections from the model closely approximated mortality observed in the study, confirming the model's ability to make accurate long-term projections of CF population survival and the impact of CFTR modulator therapies.

The model used in the current study tracked both disease progression and CFTR modulator treatment benefits for simulated individuals over a lifetime horizon (Fig. 1). Four cohorts of 2000 simulated pwCF were generated and assigned treatment with either ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or BSC alone. All cohorts used the same set of 2000 simulated individuals, ensuring any differences in modeled outcomes between cohorts were attributable to the treatment received rather than differences in baseline characteristics.

A baseline survival probability was assigned to each simulated individual based on age-specific mortality derived from the 2008 UK Cystic Fibrosis Registry, which represents the survival of a CFTR modulator-naive CF population in the UK. Over the individual's modeled lifetime, their survival probability was continuously updated using a Cox proportional hazards model that links survival in pwCF to demographics and clinical characteristics including age, sex, percent predicted forced expiratory volume in 1 second ($ppFEV_1$), annual number of PEx requiring hospitalization and/or treatment with intravenous antibiotics, weight-for-age z-score (WFAZ), and CF-related diabetes (CFRD) [17]. This allowed survival to be influenced by clinical characteristics as they evolved over time. (See Supplementary Fig. S1 and Table S1 for additional details on the model mortality calculations.) Survival differences between the treatment cohorts were driven by differences in $ppFEV_1$, annual number of PEx, and WFAZ, as CFTR modulator treatment has been shown to impact on these three characteristics based on the available clinical evidence. Treatment efficacy inputs for these three characteristics were derived from the relevant CFTR modulator clinical trials, the longer-term open-label extension studies, and extrapolations of clinical data.

2.2. Model inputs

2.2.1. Baseline characteristics

Baseline clinical characteristics were derived from individual person-level baseline data collected from phase 3 clinical trials of CFTR modulators conducted in pwCF aged ≥12 years who were homozygous for *F508del-CFTR* and naive to CFTR modulator treatment at baseline (Table S2) [18–20]. Each individual was randomly assigned a CFRD status (diabetic/non-diabetic) based on the age-specific prevalence reported in the 2019 UK Cystic Fibrosis Registry [19].

2.2.2. CF disease progression

Based on extensive evidence documenting disease progression in pwCF, the model estimated the lifetime decline in lung function, occurrence of PEx and lung transplantation, and development of CFRD in the absence of CFTR modulation for each simulated individual over time. Age-specific estimates of annual $ppFEV_1$ decline were based on rates observed in a retrospective cohort study of pwCF homozygous for *F508del-CFTR* [21]. The model predicted the occurrence of PEx based on age and $ppFEV_1$ using a published mathematic relationship in which the annual rate of PEx was found to increase with lower $ppFEV_1$ [22].

Consistent with clinical guidelines and observed transplantation rates among pwCF in the UK, the model assumed 24.5% of simulated individuals whose $ppFEV_1$ dropped below 30 would receive a lung transplant [19,23,24]. Lung transplantation altered the risk for mortality based on observed post-transplant survival rates among adults with CF [25].

Some individuals developed CFRD during the lifetime simulation based on age- and sex-specific incidences of diabetes for pwCF in the UK [26]. The risk for developing CFRD was conservatively assumed to be equal for individuals receiving a CFTR modulator and those receiving BSC alone, although several long-term studies have shown reductions in the incidence of diabetes with CFTR modulator use [7,9,27].

2.2.3. CFTR modulator treatment efficacy

The microsimulation model required placebo-adjusted estimates of clinical efficacy for CFTR modulators because the assignment of baseline survival probability was based on a CFTR modulator-naive population. In the absence of a placebo control group in the clinical trials of ELX/TEZ/IVA conducted in pwCF homozygous for *F508del-CFTR*, an indirect treatment comparison was conducted to estimate placebo-adjusted efficacy to inform model inputs. A detailed description of the methodology, including an illustration of the network used to conduct the analysis, and the associated results are provided in the Supplementary Materials (Fig. S2 and Table S3).

Simulated individuals receiving a CFTR modulator were assumed to experience an acute increase in $ppFEV_1$ and WFAZ over the first 24 weeks of the model simulation, to reflect the improvements observed in phase 3 clinical trials [12,18,20]. Model inputs were based on statistically significant placebo-adjusted estimates

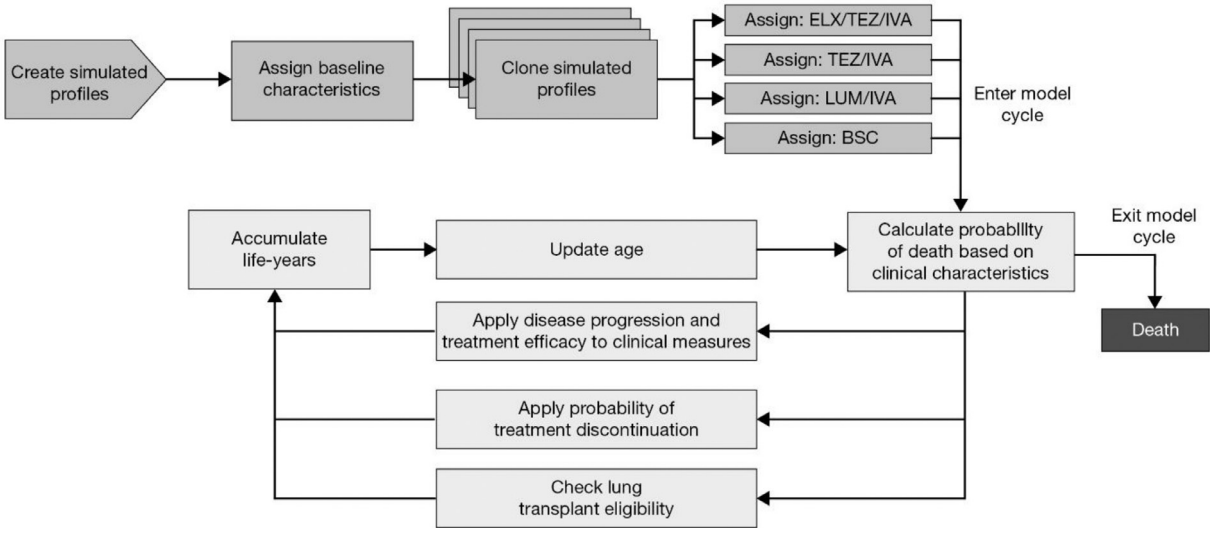

Fig. 1. Simulation model structure.
Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; LUM/IVA = lumacaftor plus ivacaftor; TEZ/IVA = tezacaftor plus ivacaftor.

Table 1
Model inputs.

Parameter	Value		Source
Disease progression			
Annual rate of $ppFEV_1$ decline (pp per year) in absence of CFTR modulator treatment			
Aged 12–13 years	−1.32		[21]
Aged 13–18 years	−2.37		
Aged 18–25 years	−2.52		
Aged ≥25 years	−1.86		
Annual rate of PEx			
Aged <18 years	$8.5938 * \exp(-0.035 * ppFEV_1)$		[22,28]
Aged ≥18 years	$3.7885 * \exp(0.026 * ppFEV_1)$		
Lung transplant			
$ppFEV_1$ threshold for lung transplant	30		[23,24]
Probability of transplant	24.5%		[19]
Probability of death post-transplant year 1	14.2%		[25]
Probability of death post-transplant year ≥2	5.4%		
Incidence of diabetes	Male	Female	
Aged 12–19 years	0.039	0.060	[26]
Aged 20–29 years	0.049	0.071	
Aged 30–39 years	0.065	0.072	
Aged ≥40 years	0.051	0.029	

CFTR modulator treatment efficacy and discontinuation	ELX/TEZ/IVA	TEZ/IVA	LUM/IVA	Source
Change in $ppFEV_1$ from baseline to week 24	14.1 pp increase	3.9 pp increase	2.8 pp increase	[12,18,20]
Reduction in rate of $ppFEV_1$ decline relative to BSC alone	90.0%	61.5%	42.0%	[6,29,30]
PEx event rate ratio relative to BSC alone	0.22	0.53	0.44	[11,18,20]
Change in WFAZ from baseline to week 24	0.41 unit increase	0.00 unit increase	0.06 unit increase	[12,18,20]
Discontinuation (per person-year) from baseline to week 24	0.025	0.143	0.152	[12,15,18]

Abbreviations: BSC = best supportive care; CFTR = cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; exp = exponential function; LUM/IVA = lumacaftor plus ivacaftor; PEx = pulmonary exacerbation; pp = percentage point; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; TEZ/IVA = tezacaftor plus ivacaftor; WFAZ = weight-for-age z-score.

of change from baseline derived from the indirect treatment comparison (Table 1) [6,11,12,15,18–26,28–30]. Simulated individuals treated with BSC alone were assumed to have no improvements in $ppFEV_1$ or WFAZ over the first 24 weeks.

In the model, the annual decline in lung function was set to begin after week 24. For simulated individuals treated with a CFTR modulator, a percent reduction was applied to the rates of decline in $ppFEV_1$ observed among untreated individuals in order to capture the effect of CFTR modulators on long-term disease progression. The treatment effects for LUM/IVA and TEZ/IVA (42.0% and 61.5% reduction in the rate of $ppFEV_1$ decline, respectively) were based on published analyses comparing pwCF treated in clinical studies for up to 120 weeks with untreated matched control participants [6,30]. In a similar matched analysis, pwCF treated with ELX/TEZ/IVA demonstrated no loss of lung function on average over a 2-year treatment period, in contrast to declines observed in untreated matched control participants (i.e., 100% reduction in the rate of $ppFEV_1$ decline) [29]. To conservatively allow for some lung function decline over time, a 90% reduction in the rate of $ppFEV_1$ decline was applied to simulated individuals treated with ELX/TEZ/IVA.

Simulated individuals treated with a CFTR modulator were also assumed to experience a reduction in the rate of PEx based on the treatment effect observed in the relevant clinical trials and open-

label extension studies (Table 1). Because the active-controlled clinical trials of ELX/TEZ/IVA in pwCF homozygous for *F508del-CFTR* did not include PEx as an efficacy endpoint, the treatment effect for the model was derived from the pivotal trial of ELX/TEZ/IVA in pwCF with a single *F508del-CFTR* allele [11]. This was a reasonable assumption, given the available evidence confirms consistent treatment effects across the two genotypes [31].

Rates of CFTR modulator discontinuation for the first 24 weeks of the model simulation were based on attrition reported in the relevant phase 3 clinical trials (Table 1) [12,15,18]. Upon discontinuation, simulated individuals were assumed to receive no further benefit of CFTR modulator treatment and to experience the same disease progression (e.g., ppFEV$_1$ decline, rate of PEx) as those receiving BSC alone (i.e., no reductions applied).

2.3. Model analyses

2.3.1. Base case analysis

The model input parameters used in the base case analysis are described in Table 1. Model outputs included median predicted survival, mean residual life-years (years alive in the simulation), proportion of life-years spent at varying levels of disease severity, mean change from baseline in ppFEV$_1$, total number and annual rate of PEx, and the proportion of simulated individuals who receive a lung transplant and mean time to transplantation among those transplanted. Outputs were generated for each treatment cohort. Probabilistic sensitivity analyses were used to generate 95% credible intervals (Bayesian 95% confidence intervals [CIs]) on the point estimates of incremental median predicted survival (Supplementary Table S4). See Supplementary Materials for methods and other results of the sensitivity analyses (Figs. S3–S8).

2.3.2. Scenario analyses

Three scenario analyses were performed to investigate the impact of key model assumptions on survival outcomes: 1) using age-specific cohorts (i.e., simulated individuals entering the model at the ages of 12–17, 18–25, and ≥25 years); 2) varying the long-term impact of ELX/TEZ/IVA on lung function decline from 80% to 100%; 3) using a 10-year model time horizon.

3. Results

3.1. Base case analysis

The projected survival curves for pwCF aged ≥12 years who are homozygous for *F508del-CFTR* and are treated with ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or BSC alone are shown in Fig. 2. The median projected survival for the cohort of individuals treated with BSC alone was 38.1 years (95% CI: 36.3, 40.6), approximately 45 years less than the life expectancy for the general UK population (approximately 83 years) [32]. The median projected survival for the cohort treated with ELX/TEZ/IVA was 71.6 years (95% CI: 58.9, 77.2); this was an increase of 33.5 years (95% CI: 20.8, 39.5) versus BSC alone, 26.2 years (95% CI: 12.9, 32.9) versus LUM/IVA, and 23.2 years (95% CI: 9.3, 30.4) versus TEZ/IVA.

In addition to increasing overall survival, treatment with ELX/TEZ/IVA was associated with substantial improvements in other key clinical outcomes (Table 2). The model predicted that individuals homozygous for *F508del-CFTR* receiving ELX/TEZ/IVA would spend more of their lifetime with higher lung function versus those receiving BSC alone (50.5% of life-years spent with mild disease vs only 7.0% for those treated with BSC alone) and substantially less time with severe lung disease (0.8% of life-years vs 46.8% for BSC alone). Despite additional years of survival, the model predicted individuals homozygous for *F508del-CFTR* receiving ELX/TEZ/IVA would have 13 fewer PEx over a lifetime compared with individuals receiving BSC alone. The model also predicted that treatment with ELX/TEZ/IVA would substantially decrease the need for lung transplantation, with 0.1% of the ELX/TEZ/IVA cohort receiving a lung transplant versus 9.6% of the BSC-alone cohort, and double the time to the procedure among those transplanted (24.5 vs 12.0 years, respectively).

The model predicted that the clinical improvements provided by ELX/TEZ/IVA would also be substantially greater than those provided by TEZ/IVA and LUM/IVA (Table 2). ELX/TEZ/IVA was predicted to increase the proportion of life spent with mild lung disease (ppFEV$_1$ ≥70%) more than threefold compared with the other CFTR modulator treatment options (3.7 times vs TEZ/IVA; 5.1 times vs LUM/IVA), and to reduce the annual rate of PEx by nearly 75%.

3.2. Scenarios analyses

Results from the age-specific baseline cohort scenarios indicated that initiating treatment with a CFTR modulator at younger ages would lead to greater survival benefits (Fig. 3). For all CFTR modulator combinations, the greatest survival benefit versus BSC alone was achieved when initiating treatment aged 12–17 years (mean age: 14.9 years), the youngest cohort studied here. Median projected survival for the cohort of individuals homozygous for *F508del-CFTR* initiating ELX/TEZ/IVA treatment aged 12–17 years was 82.5 years, which was a 45.4-year increase compared with the cohort treated with BSC alone. The median predicted survival increment with ELX/TEZ/IVA versus BSC alone was 40.2 years in the cohort initiating treatment aged 18–24 years and 21.0 years in those initiating treatment aged ≥25 years. Similar improvements were seen with ELX/TEZ/IVA versus TEZ/IVA and LUM/IVA (Fig. 3).

Increasing the reduction in the rate of lung function decline with ELX/TEZ/IVA to 100% (indicating preserved lung function for the duration of the model horizon) increased the median projected survival for the cohort to 75.4 years, a 26.9-year increase over TEZ/IVA, 30.0-year increase over LUM/IVA, and 37.2-year increase over BSC alone (Figs. S3–S5). Decreasing the ELX/TEZ/IVA reduction in rate of decline to 80% still resulted in very meaningful survival benefits, with an 18.6-year increase in median survival versus TEZ/IVA, a 21.7-year increase versus LUM/IVA, and a 28.9-year increase versus BSC alone (Figs. S3–S5).

The scenario utilizing a shorter model horizon demonstrated the substantial clinical benefits achieved within the first 10 years of initiating CFTR modulator treatment (Table S5). After 10 years of treatment, a greater proportion of individuals in the ELX/TEZ/IVA cohort were alive (87%) compared with the TEZ/IVA (77%), LUM/IVA (75%), and BSC (64%) cohorts. The projected mean change in ppFEV$_1$ from model baseline to 10 years was also substantially higher among those treated with ELX/TEZ/IVA (12.2 points higher than baseline) compared with BSC alone (13.9 points lower than baseline) and the other treatment cohorts (2.2 and 5.9 points lower than baseline with TEZ/IVA and LUM/IVA, respectively).

4. Discussion

The magnitude of improvements in clinical and patient-reported outcomes achieved with ELX/TEZ/IVA have established ELX/TEZ/IVA as a new benchmark for CFTR modulator therapy and the current standard of care for treating pwCF with at least one *F508del-CFTR* allele. Because lung function has been identified as a key predictor of long-term survival [17], the unprecedented and significant improvements demonstrated in the clinical trial program [11–13] suggest that ELX/TEZ/IVA treatment may provide a lifetime therapeutic benefit for pwCF. We, therefore, set out to estimate the potential lifetime clinical benefits for pwCF aged ≥12 years and homozygous for *F508del-CFTR* treated with ELX/TEZ/IVA,

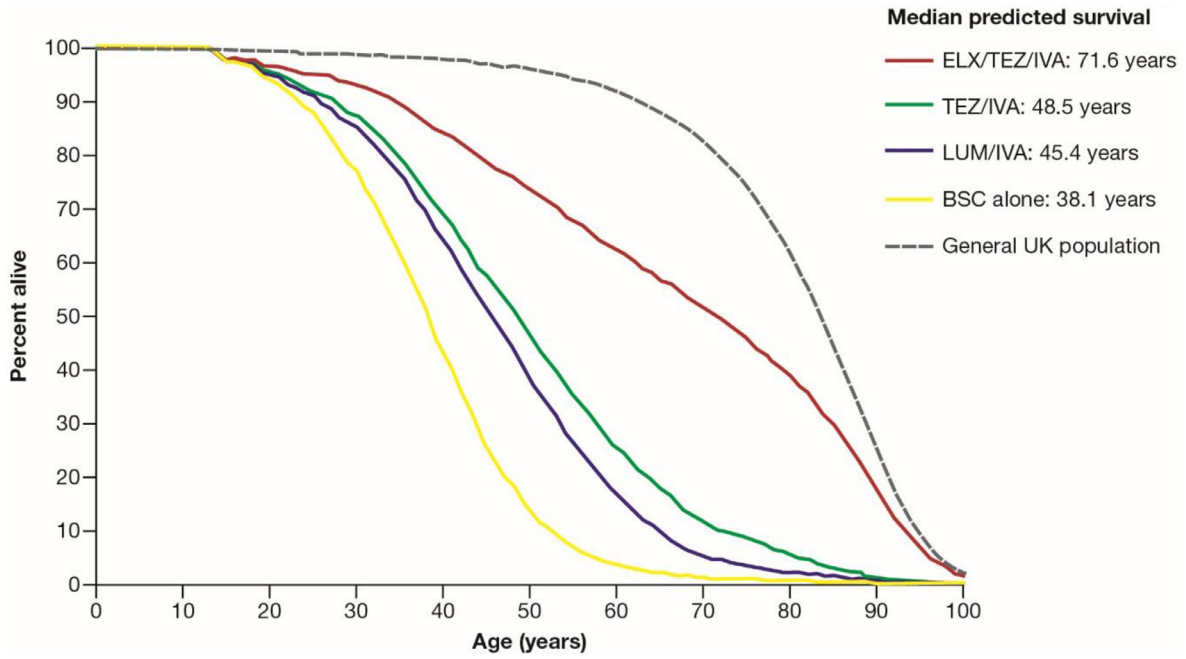

Fig. 2. Projected survival for pwCF homozygous for *F508del-CFTR* who receive ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or BSC alone (base case analysis).
Note: The general population mortality curve was estimated from age- and sex-specific UK life-table data [32]. Curves for BSC alone and CFTR modulators were estimated by applying the Kaplan–Meier product limit formula to the simulation results (see Supplementary Materials).
Abbreviations: BSC = best supportive care; CFTR = cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; LUM/IVA = lumacaftor plus ivacaftor; pwCF = people with cystic fibrosis; TEZ/IVA = tezacaftor plus ivacaftor.

Table 2
Projected lifetime clinical outcomes for pwCF treated with ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or BSC alone (base case analysis).

	ELX/TEZ/IVA	TEZ/IVA	LUM/IVA	BSC
Median age of death, years (95% CI)	71.6 (58.9, 77.2)	48.5 (44.0, 54.2)	45.4 (42.6, 50.2)	38.1 (36.3, 40.6)
Mean age of death, years	67.4	49.8	46.3	38.9
Mean residual life-years	43.0	25.9	22.5	15.6
Proportion of life-years spent with $ppFEV_1$, %				
≥70%	50.5	13.7	10.0	7.0
≥40% to <70%	48.7	61.0	54.2	46.2
<40%	0.8	25.4	35.9	46.8
Mean change in $ppFEV_1$, %	+5.7	−15.7	−21.2	−25.2
Total number of PEx	6.4	14.7	12.2	19.1
Annual rate of PEx, per person-year	0.15	0.59	0.57	1.35
Proportion undergoing lung transplant, %	0.1	5.3	8.0	9.6
Mean time to lung transplant among those transplanted, years	24.5	26.4	22.9	12.0

Abbreviations: BSC = best supportive care; CI = confidence interval; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; LUM/IVA = lumacaftor plus ivacaftor; PEx = pulmonary exacerbations; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; pwCF = people with cystic fibrosis; TEZ/IVA = tezacaftor plus ivacaftor.

as well as the incremental survival benefit over treatment with TEZ/IVA, LUM/IVA, or BSC alone. To do so, we used an adapted version of a well-established, validated, person-level simulation model that translates improvements in $ppFEV_1$, PEx rate, and nutritional status observed with the use of CFTR modulators to long-term health outcomes.

The results of our simulation model illustrate the substantial long-term benefits that pwCF homozygous for *F508del-CFTR* may experience over a lifetime when treated with ELX/TEZ/IVA, including improved survival and reduced disease progression and severity. The median projected survival for pwCF homozygous for *F508del-CFTR* treated with ELX/TEZ/IVA was 71.6 years, which is a three-decade increase compared with survival in the absence of CFTR modulator treatment and more than two decades longer than with other available CFTR modulators. These estimates support the potential transformative effects on the health and well-being of pwCF provided by ELX/TEZ/IVA. Furthermore, ELX/TEZ/IVA is expected to decrease healthcare resource utilization based on the projected reductions in the rate of PEx requiring intravenous antibiotics and/or hospitalization and lung transplantation. Early real-world studies of ELX/TEZ/IVA have shown improvements in lung function that have been substantial enough to influence the status of individual patients in terms of lung transplant planning [33–35]. A number of planned and ongoing real-world studies have the potential to provide further evidence of the impact of ELX/TEZ/IVA on clinical and economic outcomes in the clinical practice setting.

The age-specific scenario analysis further demonstrates the potential survival benefit of ELX/TEZ/IVA treatment, as well as highlighting the importance of early treatment initiation. In the youngest simulated cohort (those aged 12–17 years), who have a higher $ppFEV_1$ at baseline than older cohorts, the acute improvement in $ppFEV_1$ paired with the long-term reduction in $ppFEV_1$ decline provided by ELX/TEZ/IVA led to preserved lung function over the lifetime horizon, which translates into a maximized survival benefit. The median projected survival for this cohort was 82.5 years, which is more than double the survival in the cohort

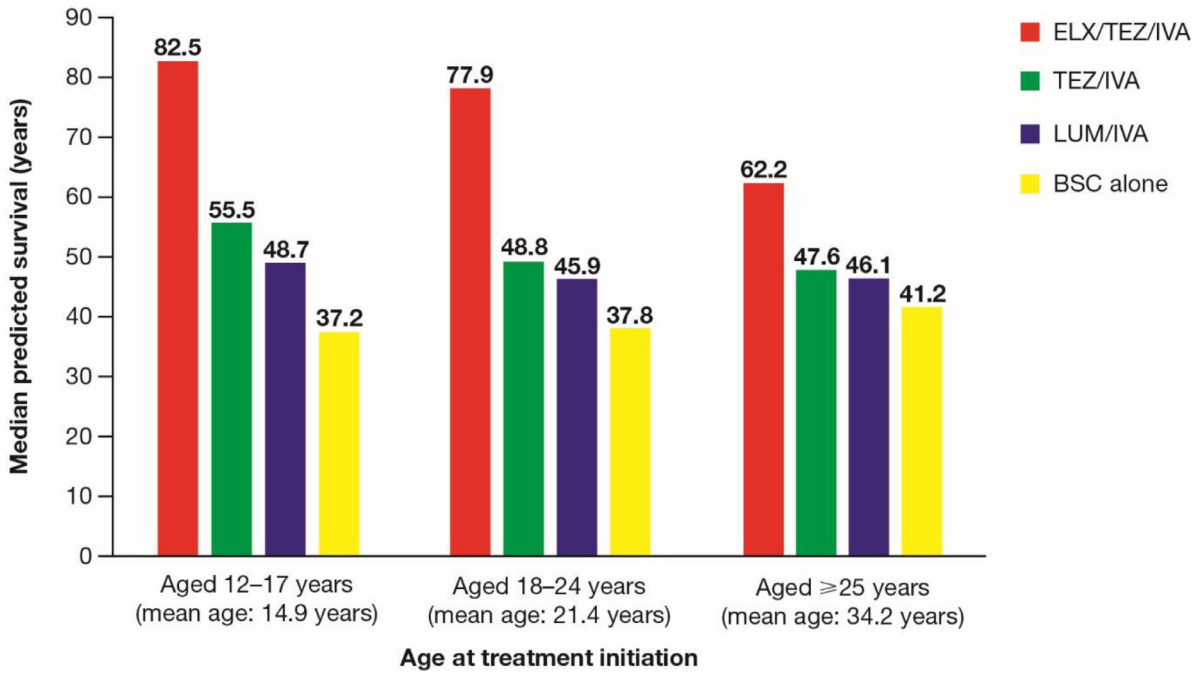

Fig. 3. Median predicted survival with ELX/TEZ/IVA, TEZ/IVA, and LUM/IVA versus BSC alone, by age of treatment initiation.
Abbreviations: BSC = best supportive care; ELX/TEZ/IVA = elexacaftor plus tezacaftor plus ivacaftor; LUM/IVA = lumacaftor plus ivacaftor; TEZ/IVA = tezacaftor plus ivacaftor

treated with BSC alone, approximately three decades longer than in the other CFTR modulator-treated cohorts, and nearly equivalent to the life expectancy of the general UK population [32]. These results contribute to accumulating evidence that early intervention in pwCF is associated with better outcomes later in life. The advent of newborn CF screening, which results in earlier initiation of effective treatment for asymptomatic pwCF, has been shown to prevent CF-related deaths in early childhood and lead to substantial and prolonged clinical benefits, including a reduced mortality risk [36,37]. Furthermore, access to routine care from multidisciplinary CF care teams in infants with CF has been suggested to be the reason for improved health benefits at older ages, including improved lung structure and function, growth, and survival [1,38]. The results of our simulation analysis further demonstrate that early intervention in a progressive disease such as CF is critical to minimizing functional loss and maximizing survival benefits. Further analyses are needed to quantify the potential additional benefit of ELX/TEZ/IVA therapy when initiated in pwCF aged 6–11 years who have at least one *F508del-CFTR* mutation, an age group for which ELX/TEZ/IVA therapy recently received regulatory approval.

The scenario evaluating a 10-year model horizon demonstrates the substantial near-term benefits that ELX/TEZ/IVA treatment may provide. In addition to increasing the proportion of pwCF homozygous for *F508del-CFTR* remaining alive at 10 years, there were considerable reductions in healthcare resource utilization over this time period, including substantially fewer hospitalizations and intravenous antibiotics required to treat PEx and a complete elimination of the need for lung transplantation. A Canadian modeling study published in 2021 also evaluated the potential impact of ELX/TEZ/IVA over a 10-year time horizon [39]. Compared with that study, our model generally produced a greater impact of ELX/TEZ/IVA on mortality (15% reduction in deaths in the Canadian study vs 64% estimated here) and other clinical outcomes. The magnitude of the difference is not unexpected given the Canadian analysis included all pwCF, including those who were not eligible for and did not receive ELX/TEZ/IVA treatment during the study period, and also assumed a substantially lower impact of ELX/TEZ/IVA on lung function decline over time (50% reduction), as the longer-term data on ELX/TEZ/IVA used in the current study were not available at the time of their analysis. Nonetheless, despite different methodologies, patient populations, and model input values, both analyses suggest immense benefits of ELX/TEZ/IVA treatment.

A limitation of our model structure is the use of a Cox proportional hazards equation, which was developed in a CFTR modulator-naive population to estimate the impact of clinical characteristics on survival, and not the impact of treatment, as attempted here [15]. However, the previous model validation demonstrates that changes in clinical outcomes as a result of CFTR modulator treatment can be combined with the Cox proportional hazard equation to generate plausible clinical predictions that match real-world survival benefits [16]. While the aforementioned validation study encourages confidence in model projections, we further note that the available data for validation included only 5 years of follow-up in a US population of pwCF treated with a single CFTR modulator. Further validation and refinement of the model may be warranted as longer-term real-world data for additional CFTR modulators and broader populations become available.

Additionally, the simulation model can only evaluate variables selected for inclusion in the Cox proportional hazards equation [17]. Racial and ethnic disparities, which are important contributors to health outcomes and mortality in the general population [40], were not identified as predictors of survival in the Cox proportional hazards equation and are, therefore, not accounted for in this study. Other inherent limitations of using predictive models include the use of inputs from multiple data sources and extrapolation of observations from clinical trials over longer periods of time and to real-world populations. The modeled survival benefits were generated for a cohort of clinical trial participants; however, because the characteristics of pwCF homozygous for *F508del-CFTR* in the UK Cystic Fibrosis Registry are similar to those for trial participants used for the base-case model population, survival benefits of similar magnitude would be expected for both populations. When UK-specific data were not available, inputs were derived from stud-

ies conducted using the US Cystic Fibrosis Foundation Patient Registry (e.g., rate of lung function decline [21], rate of PEx [22]); the extent to which differences in underlying disease progression differ across countries and, therefore, influence model projections, is unknown. However, sensitivity analyses that varied all key model inputs demonstrate the robustness of this model's survival predictions to plausible changes in inputs (Supplementary Materials). The model assumed that the CFTR modulator treatment effects observed over 2–3 years in clinical settings would apply over the lifetime model horizon. In particular, the estimated reduction in the rate of lung function decline with use of ELX/TEZ/IVA, a key driver of model outcomes, was based on within-group estimates of change in ppFEV$_1$ from a single-arm open-label extension study, which lacked control participants [14]. Analyses may need to be revised as longer-term data become available.

An additional limitation is that the model does not account for the potential future effects of aging in a CF population. Much of current CF research, including the evidence underpinning this model, is focused on pediatric and adolescent CF populations. As life expectancy continues to increase, pwCF may be at increased risk for other diseases, particularly those prevalent in older populations (e.g., cancer, cardiovascular disease) [41–43]. Incorporating increased disease risk for older pwCF into the simulation model could potentially decrease the life expectancy projections reported herein. As further real-world data on the impacts of aging in a CF population become available, refinement and calibration of the model should be conducted.

5. Conclusion

Our analysis predicts that treating pwCF homozygous for *F508del-CFTR* with ELX/TEZ/IVA will likely lead to substantial increases in survival compared with all other available treatment options. In addition to extending life, treatment with ELX/TEZ/IVA is projected to limit the amount of time pwCF homozygous for *F508del-CFTR* spend with moderate and severe disease and reduce healthcare resource utilization, including hospitalizations and lung transplants. Furthermore, our model predicts that early intervention with ELX/TEZ/IVA may allow pwCF to achieve near-normal life expectancy. Results highlight the need for early treatment.

Funding

This work was supported by Vertex Pharmaceuticals Incorporated.

Declaration of Competing Interest

Andrea Lopez, Conor Daly, Gabriela Vega-Hernandez, and Jaime L. Ru- bin are employees of Vertex Pharmaceuticals and might own stock or stock options in the company. Gordon MacGre- gor has no conflicts of interest to declare.

CRediT authorship contribution statement

Andrea Lopez: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Conor Daly:** Conceptualization, Data curation, Validation, Writing – original draft, Writing – review & editing. **Gabriela Vega-Hernandez:** Conceptualization, Writing – review & editing. **Gordon MacGregor:** Conceptualization, Writing – review & editing. **Jaime L. Rubin:** Conceptualization, Writing – review & editing.

Acknowledgments

Editorial coordination and support were provided by Nathan Blow, under the guidance of the authors. Nathan Blow is an employee of Vertex Pharmaceuticals Incorporated and might own stock or stock options in the company. Project management support was provided by Alice Newman, PhD, and editing support was provided by Adam Paton, BA, of Complete HealthVizion, IPG Health Medical Communications, funded by Vertex Pharmaceuticals Incorporated.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.02.004.

References

[1] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, Burgel PR, Tullis E, Castaños C, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8(1):65–124. doi:10.1016/S2213-2600(19)30337-6.
[2] O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373(9678):1891–904. doi:10.1016/S0140-6736(09)60327-5.
[3] Castellani C, Assael BM. Cystic fibrosis: a clinical view. Cell Mol Life Sci 2017;74(1):129–40. doi:10.1007/s00018-016-2393-9.
[4] Paranjape SM, Mogayzel PJ Jr. Cystic fibrosis in the era of precision medicine. Paediatr Respir Rev 2018;25:64–72. doi:10.1016/j.prrv.2017.03.001.
[5] UK Cystic Fibrosis Registry Annual Data Report 2020; 2021 https://www.cysticfibrosis.org.uk/sites/default/files/2021-12/CF_Annual%20Report%202020_V8.pdf accessed June 10, 2022.
[6] Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, De Boeck K, Sawicki GS, Chang P, et al. Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del *CFTR* (EXTEND): an open-label extension study. Lancet Respir Med 2021;9(7):733–46. doi:10.1016/s2213-2600(20)30510-5.
[7] Knox C, Han Z, Wu R, Wang LT, Elbert A, Tian S. Real-world outcomes among patients with cystic fibrosis treated with lumacaftor/ivacaftor (LUM/IVA) in 2017: an interim analysis of data from the US CF Foundation Patient Registry (CFFPR). J Cyst Fibros 2019;18(Suppl 1):S22–3 abs WS12-3.
[8] Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, Konstan MW. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med 2015;192(7):836–42. doi:10.1164/rccm.201503-0578OC.
[9] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, Higgins M, Konstan MW, Sawicki GS, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. J Cyst Fibros 2020;19(1):68–79. doi:10.1016/j.jcf.2019.05.015.
[10] Chaudary N. Triplet CFTR modulators: future prospects for treatment of cystic fibrosis. Ther Clin Risk Manag 2018;14:2375–83. doi:10.2147/TCRM.S147164.
[11] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, Ramsey BW, Taylor-Cousar JL, Tullis E, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381(19):1809–19. doi:10.1056/NEJMoa1908639.
[12] Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, Van Braeckel E, Wainwright CE, Watson D, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for *F508del-CFTR*: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. Lancet Respir Med 2022;10(3):267–77. doi:10.1016/S2213-2600(21)00454-9.
[13] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, Mall MA, Welter JJ, Ramsey BW, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394(10212):1940–8. doi:10.1016/s0140-6736(19)32597-8.
[14] Daines CL, Tullis E, Costa S, Linnemann RW, Mall MA, McKone EF, Polineni D, Quon BS, Ringshausen FC, et al. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one *F508del* allele: 96-week interim results from an open-label extension study. Poster 681 presented at the 35th Annual North American Cystic Fibrosis Conference (Virtual), November 2–5; 2021.
[15] Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, Chandler C, Liou TG. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for *F508del-CFTR* treated with lumacaftor/ivacaftor. Ther Adv Respir Dis 2019;13:1753466618820186. doi:10.1177/1753466618820186.
[16] McGarry L, Lopez A, Chandler C, Pelligra C, Alkhateeb Z, Rubin JL, Liou T. Validation of modeled 5-year survival outcomes among patients with cystic fibrosis (CF) treated with the CF transmembrane conductance regulator modulator (CFTRM) ivacaftor using US CF Foundation Patient Registry (USCFFPR) data. Value Health 2020;23(Suppl 1):S8 abs MS1.
[17] Liou TG, Adler FR, FitzSimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153(4):345–52. doi:10.1093/aje/153.4.345.

[18] Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377(21):2013–23. doi:10.1056/NEJMoa1709846.
[19] UK Cystic Fibrosis Registry Annual Data Report 2019; 2020 https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/2019%20Registry%20Annual%20Data%20report_Sep%202020.pdf accessed May 12, 2022.
[20] Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015;373(3):220–31. doi:10.1056/NEJMoa1409547.
[21] Sawicki G, Konstan MW, McKone E, Moss RB, Lubarsky B, Suthoff E, Millar S, Pasta DJ, Mayer-Hamblett N, et al. Rate of lung function decline in patients with cystic fibrosis (CF) having a residual function gene mutation. Thorax 2017;72(Suppl 3):A222 abs P255.
[22] Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax 2007;62(4):360–7. doi:10.1136/thx.2006.060889.
[23] Royal Brompton Hospital Paediatric Cystic Fibrosis Team Clinical guidelines: care of children with cystic fibrosis. 8th edition; 2020 https://www.rbht.nhs.uk/sites/nhs/files/Cystic%20fibrosis%20guidelines/CF%20G%202020/CF%20guideline%202020%20FINAL_edited.pdf accessed May 12, 2022.
[24] The American Society for Transplant Physicians (ASTP)/American Thoracic Society (ATS)/European Respiratory Society (ERS)/International Society for Heart and Lung Transplantation (ISHLT)International guidelines for the selection of lung transplant candidates. Am J Respir Crit Care Med 1998;158(1):335–9. doi:10.1164/ajrccm.158.1.15812.
[25] The International Society for Heart and Lung Transplantation Slide 26. Adult lung transplants; 2017 https://ishltregistries.org/downloadables/slides/2017/lung_adult.pptx accessed June 10, 2022.
[26] Adler AI, Gunn E, Haworth CS, Bilton D. Characteristics of adults with and without cystic fibrosis-related diabetes. Diabet Med 2007;24(10):1143–8. doi:10.1111/j.1464-5491.2007.02252.x.
[27] Gaines H, Jones KR, Lim J, Medhi NF, Chen S, Scofield RH. Effect of CFTR modulator therapy on cystic fibrosis-related diabetes. J Diabetes Complications 2021;35(6):107845. doi:10.1016/j.jdiacomp.2020.107845.
[28] Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, Armstrong N, Allen A, Severens H, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18(18):1–106. doi:10.3310/hta18180.
[29] Lee T, Sawicki G, Altenburg J, Millar S, Morlando Geiger J, Jennings M, Lou Y, McGarry L, Moskowitz S, et al. Effect of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on annual rate of lung function decline in people with cystic fibrosis. Abstract WS22.04 presented at the 45th European Cystic Fibrosis Conference (ECFS), Amsterdam: The Netherlands; 2022. June 8–11.
[30] Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, Lubarsky B, Rubin J, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med 2017;5(2):107–18. doi:10.1016/S2213-2600(16)30427-1.
[31] Taylor-Cousar JL, Mall MA, Ramsey BW, McKone EF, Tullis E, Marigowda G, McKee CM, Waltz D, Moskowitz SM, et al. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two *F508del* alleles. ERJ Open Res 2019;5(2):0008–2019. doi:10.1183/23120541.00082-2019.
[32] The Human Mortality Database United Kingdom Total Population; 2022 https://www.mortality.org/cgi-bin/hmd/country.php?cntr=GBR&level=2 accessed June 10, 2022.
[33] Bermingham B, Rueschhoff A, Ratti G, Nesmith A, Goodwin D, Gray S, Flume P, Solomon GM, Cohen L, et al. Short-term effect of elexacaftor-tezacaftor-ivacaftor on lung function and transplant planning in cystic fibrosis patients with advanced lung disease. J Cyst Fibros 2021;20(5):768–71. doi:10.1016/j.jcf.2021.05.009.
[34] Burgel P-R, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, Grenet D, Marguet C, Reynaud-Gaubert M, et al. Rapid improvement after starting elexacaftor–tezacaftor–ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. Am J Respir Crit Care Med 2021;204(1):64–73. doi:10.1164/rccm.202011-4153OC.
[35] Uluer AZ, Fowler RE, Mwangi IM, Shin K, Cardoni L, Regan K, Hui M, Marchetti P, Cernadas M, et al. Initiation of triple combination CFTR modulator therapy in patients with advanced cystic fibrosis lung disease. Pediatr Pulmonol 2020;55(Suppl 2):S293 abs 651.
[36] Grosse SD, Rosenfeld M, Devine OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. J Pediatr 2006;149(3):362–6. doi:10.1016/j.jpeds.2006.04.059.
[37] Dankert-Roelse JE, Mérelle ME. Review of outcomes of neonatal screening for cystic fibrosis versus non-screening in Europe. J Pediatr 2005;147(Suppl3):S15–20. doi:10.1016/j.jpeds.2005.08.009.
[38] VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: a review of disease manifestation, progression, and response to early treatment. J Cyst Fibros 2016;15(2):147–57. doi:10.1016/j.jcf.2015.09.008.
[39] Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with cystic fibrosis. J Cyst Fibros 2021;20(2):243–9. doi:10.1016/j.jcf.2020.07.017.
[40] Curtin SC, Arias E. Mortality trends by race and ethnicity among adults aged 25 and over: United States, 2000–2017. NCHS Data Brief 2019;342:1–8.
[41] Hadjiliadis D, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels ABon behalf of the Cystic Fibrosis Colorectal Cancer Screening Task Force. Cystic fibrosis colorectal cancer screening consensus recommendations. Gastroenterology 2018;154(3):736–745.e14. doi:10.1053/j.gastro.2017.12.012.
[42] Rousset-Jablonski C, Reynaud Q, Nove-Josserand R, Ray-Coquard I, Mekki Y, Golfier F, Durieu I. High proportion of abnormal pap smear tests and cervical dysplasia in women with cystic fibrosis. Eur J Obstet Gynecol Reprod Biol 2018;221:40–5. doi:10.1016/j.ejogrb.2017.12.005.
[43] Saunders T, Burgner D, Ranganathan S. Identifying and preventing cardiovascular disease in patients with cystic fibrosis. Nat Cardiovasc Res 2022;1(3):187–8. doi:10.1038/s44161-022-00030-y.