



# Long-term effectiveness of dual CFTR modulator treatment of cystic fibrosis

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Long-term effectiveness of dual CFTR modulator therapies on FEV<sub>1</sub> decline, BMI and intravenous antibiotic treatment duration is less pronounced in a real-world setting than reported in previous clinical trials <https://bit.ly/3QippTi>

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## Abstract

**Background** Although short-term efficacy of lumacaftor/ivacaftor and tezacaftor/ivacaftor is clearly established in clinical trials, data on long-term effectiveness is limited. This registry-based cohort study assessed real-world longitudinal outcomes of F508del-homozygous people with cystic fibrosis (pwCF) ≥12 years, up to 3 years after the introduction of dual cystic fibrosis transmembrane conductance regulator (CFTR) modulators.

**Methods** Annual data (2010–2019) were retrieved from the Dutch Cystic Fibrosis Registry. Longitudinal trends of per cent predicted forced expiratory volume in 1 s (FEV<sub>1</sub> % pred) decline, body mass index (BMI), BMI Z-score and intravenous antibiotic treatment duration before and after CFTR modulator initiation were assessed with linear and negative binomial mixed models.

**Results** We included 401 participants (41.9% female, baseline age 24.5 years (IQR 18.0–31.5 years), baseline mean±SD FEV<sub>1</sub> 70.5±23.4% pred). FEV<sub>1</sub> decline improved from –1.36% pred per year to –0.48% pred per year after modulator initiation (change: 0.88% pred, 95% CI: 0.35–1.39%, p=0.001). This change was even 1.40% pred per year (95% CI: –0.0001–2.82%, p=0.050) higher in participants with baseline FEV<sub>1</sub> <40% pred. In adults, annual BMI trend was not altered (change: 0.10 kg·m<sup>-2</sup>·year<sup>-1</sup>, 95% CI: –0.01–0.21, p=0.079). Annual BMI Z-score in children reversed from –0.08 per year before modulator treatment to 0.06 per year afterwards (change: 0.14 per year, 95% CI: 0.06–0.22, p<0.001). Intravenous antibiotic treatment duration showed a three-fold reduction in the first year after modulator initiation (incidence rate ratios (IRR): 0.28, 95% CI: 0.19–0.40, p<0.001), but the annual trend did not change in the subsequent years (IRR: 1.19, 95% CI: 0.94–1.50, p=0.153).

**Conclusion** Long-term effectiveness of dual CFTR modulator therapies on FEV<sub>1</sub> decline, BMI and intravenous antibiotic treatment duration is less pronounced in a real-world setting than in clinical trials and varies considerably between pwCF and different baseline FEV<sub>1</sub> levels.

## Introduction

Over the last decade, the treatment landscape of cystic fibrosis (CF) has drastically changed with the arrival of cystic fibrosis transmembrane conductance regulator (CFTR) modulators [1]. Lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) were the first two dual therapies that became available for people with CF (pwCF) who are homozygous for the F508del mutation. Lumacaftor and tezacaftor are small molecules that enhance the processing and trafficking of mature CFTR protein to the cell membrane [2], whereas ivacaftor augments the channel opening probability [3]. The first phase III randomised controlled trials (RCTs) that supported the licensing of LUM/IVA were conducted in pwCF



homozygous for F508del older than 12 years of age with a baseline per cent predicted forced expiratory volume in 1 s (FEV<sub>1</sub> % pred) between 40% and 90%. These RCTs demonstrated a mean absolute improvement of 2.6–4% pred FEV<sub>1</sub>, an increase in body mass index (BMI) and a reduction of pulmonary exacerbation rate and intravenous (*i.v.*) antibiotic use after 24 weeks of treatment [4]. A few years later, phase III RCTs with TEZ/IVA showed a comparable short-term efficacy, albeit with substantially less side-effects than LUM/IVA [5].

Subsequently, the original phase III open-label extension trials provided the first evidence of long-term efficacy of LUM/IVA and TEZ/IVA. These trials showed a mean estimated FEV<sub>1</sub> decline between –1.3% pred and –0.8% pred per year after 120 weeks of CFTR modulator treatment, compared to –2.3% pred to –2.1% pred in matched historical controls. Furthermore, the absolute change from baseline BMI continued to increase whereas pulmonary exacerbation rate and *i.v.* antibiotic use remained substantially lower [6, 7].

Especially in chronic diseases like CF, collection of long-term data on the effectiveness of new treatments is important, given the strictly controlled conditions and inclusion criteria as well as a relatively short follow-up in RCTs [8]. Currently, real-world evidence of the long-term benefits after the first year of treatment with LUM/IVA and TEZ/IVA is still limited. No real-world studies have been published yet that include a large group of pwCF homozygous for F508del with different ages and disease stages, covering important clinical outcomes after 1 year of CFTR modulator treatment. Patient registries such as the Dutch Cystic Fibrosis Registry (NCFR), which is part of the European Medicines Agency (EMA)-approved European Cystic Fibrosis Society Patient Registry (ECFSPR), play a key role in the acquisition of long-term real-world evidence of new treatments.

In this study, we aimed to assess real-world longitudinal changes in FEV<sub>1</sub> decline, BMI and annual duration of *i.v.* antibiotic treatment in people with CF homozygous for F508del, up to 3 years after the introduction of the dual CFTR modulating therapies LUM/IVA and TEZ/IVA, using NCFR data.

## Materials and methods

### Study design and population

In this registry-based observational cohort study, we used longitudinal data from the NCFR between 2010 and 2019. The NCFR retrospectively collects annualised clinical data of pwCF who are treated in one of the seven Dutch CF centres and who provided informed consent for the collection and use of their data for research. This nationwide informed consent procedure is part of an agreement between the Dutch CF Foundation and the Dutch CF centres, which was approved by the local Institutional Review Boards (IRBs) when the NCFR was initiated. The use of clinical data for this research project was considered as exempt from the Dutch Act for Medical Research Involving Human Subjects by the IRB of the University Medical Center Utrecht, the Netherlands, and was approved by the NCFR Steering Group. The NCFR covers 95% of pwCF in The Netherlands and is part of the EMA-approved ECFSPR. All Dutch pwCF homozygous for F508del aged 12 years and older who received LUM/IVA treatment before January 2018 were eligible for this study, regardless of a transition to TEZ/IVA or treatment discontinuation, either temporary or permanent. Participant data were censored after lung transplantation, death or lost to follow-up. No exclusion criteria were specified.

### Study parameters

Longitudinal changes in FEV<sub>1</sub> % pred, BMI, BMI Z-score and annual duration of *i.v.* antibiotic treatment after commencement with LUM/IVA were considered as clinical outcomes. The NCFR collects annual best FEV<sub>1</sub> % pred measurements, calculated according to the Global Lung Initiative (GLI) guideline [9], which were used to assess the mean annual change in FEV<sub>1</sub> % pred before and after CFTR modulator initiation. Annual weight and height measurements were used to calculate BMI in adults of 19 years and older, whereas BMI Z-scores standardised for age and sex were calculated according to the World Health Organisation (WHO) Growth Reference for children below 19 years [10]. Duration of annual *i.v.* antibiotic treatment was calculated in total number of days per year. Baseline was defined by the first start date of LUM/IVA as registered in the NCFR. If applicable, date of transition to TEZ/IVA was collected. CFTR modulator treatment status at each measurement timepoint was dichotomised as treatment=no before baseline and treatment=yes after baseline. Data regarding sex, age and presence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in annual sputum cultures were also collected.

### Statistical analysis

Descriptive statistics were used to summarise baseline characteristics of the study population.

A linear mixed effects model was used to assess longitudinal trends in FEV<sub>1</sub> % pred before and after CFTR modulator initiation. Following the same approach, linear mixed model analyses of BMI and BMI Z-score were performed in data subsets including measurements at an age above and below 19 years, respectively. Changes in the annual duration of *i.v.* antibiotic treatment were analysed with a negative binomial mixed effects model. Detailed model specifications are provided in the supplementary material.

To facilitate a comparison of real-world data with data from controlled registration trials, subgroup analyses in participants with a baseline FEV<sub>1</sub> between 40% and 90% pred were performed for each model. For FEV<sub>1</sub> and *i.v.* antibiotic treatment duration, we also compared longitudinal trends of participants with a baseline FEV<sub>1</sub> <40% and ≥90% pred to the group with a FEV<sub>1</sub> between 40% and 90% pred at baseline and between adults >18 years and adolescents of 12–18 years. This was not performed for BMI and BMI Z-score because these subgroups were already divided by age category according to the WHO reference standard and were therefore too small to allow for a subgroup analysis with multiple baseline FEV<sub>1</sub> groups. Finally, additional subgroup analyses were conducted for each model to compare longitudinal and acute changes after CFTR modulator treatment between participants who transitioned to TEZ/IVA and participants who continued with LUM/IVA and between females and males.

To adjust for potential confounders, age and sex were included as covariates in the models, where appropriate.

The proportion of missing data was highest for the annual duration of *i.v.* antibiotic treatment (32.2%), followed by 4.1% of FEV<sub>1</sub> % pred measurements, 0.5% of BMI Z-scores in children <19 years and 0.2% of BMI in adults ≥19 years.

To adjust for missing data, all models with FEV<sub>1</sub> % pred, BMI and BMI Z-score as outcomes were assessed using Bayesian methods which allow for a joint imputation and analysis of incomplete datasets. Changes in the duration of *i.v.* antibiotic treatment were analysed using maximum likelihood estimation methods without imputation of missing data, which is a robust method for missing outcome data.

Estimations of the Bayesian models were displayed as coefficients with corresponding 95% confidence intervals and p-values. p-values <0.05 were considered statistically significant.

Statistical packages *jointAI* and *lme4* of R for Mac version 4.1.1 were used for the analyses.

## Results

### Study population

A total of 401 pwCF with the F508del/F508del mutation were included in this study. Baseline characteristics are summarised in table 1. Median follow-up time before and after CFTR modulator initiation was 7.9 years (IQR: 7.5–7.9 years) versus 2.1 years (IQR: 2.1–2.2 years), respectively. Censoring occurred in 13 (3.2%) participants due to lung transplantation (n=11) or death (n=2). Approximately half (51.9%) of the study population transitioned from LUM/IVA to TEZ/IVA between 2018 and 2019, after mean±SD 2.0±0.6 years of initial LUM/IVA treatment. Last measured FEV<sub>1</sub> before CFTR modulator initiation was between 40% and 90% pred in 257 (64.1%) of the participants.

### Lung function decline

Overall, we observed a moderate acute change in the estimated FEV<sub>1</sub> at baseline (FEV<sub>1</sub> at baseline: 70.97% pred, 95% CI: 68.52–73.42%) after CFTR modulator initiation (change: 1.51% pred, 95% CI: 0.56–2.46%, p=0.002). The mean annual FEV<sub>1</sub> decline improved from –1.36% pred per year to –0.48% pred per year after CFTR modulator initiation (change: 0.88% pred, 95% CI: 0.35–1.39%, p=0.001; figure 1a and table 2).

The acute impact of CFTR modulator treatment was slightly higher in the subgroup of participants with a baseline FEV<sub>1</sub> between 40% and 90% pred, with an acute change from baseline FEV<sub>1</sub> of 2.59% pred (95% CI: 1.40–3.78%, p<0.001; supplementary table S1a). The magnitude of change in FEV<sub>1</sub> decline was comparable to the change in the entire cohort (change: 0.81% pred per year, 95% CI: 0.11–1.50%, p=0.026; supplementary table S1a and figure S1a).

In participants with a baseline FEV<sub>1</sub> <40% pred, the acute improvement in FEV<sub>1</sub> was not significantly different from those with a FEV<sub>1</sub> 40%–90% pred before CFTR modulator initiation (difference: –1.24% pred, 95% CI: –4.25–1.78%, p=0.420; supplementary table S1a). As illustrated in supplementary figure S1b, the mean change in FEV<sub>1</sub> decline after CFTR modulator initiation was even 1.40% pred per year

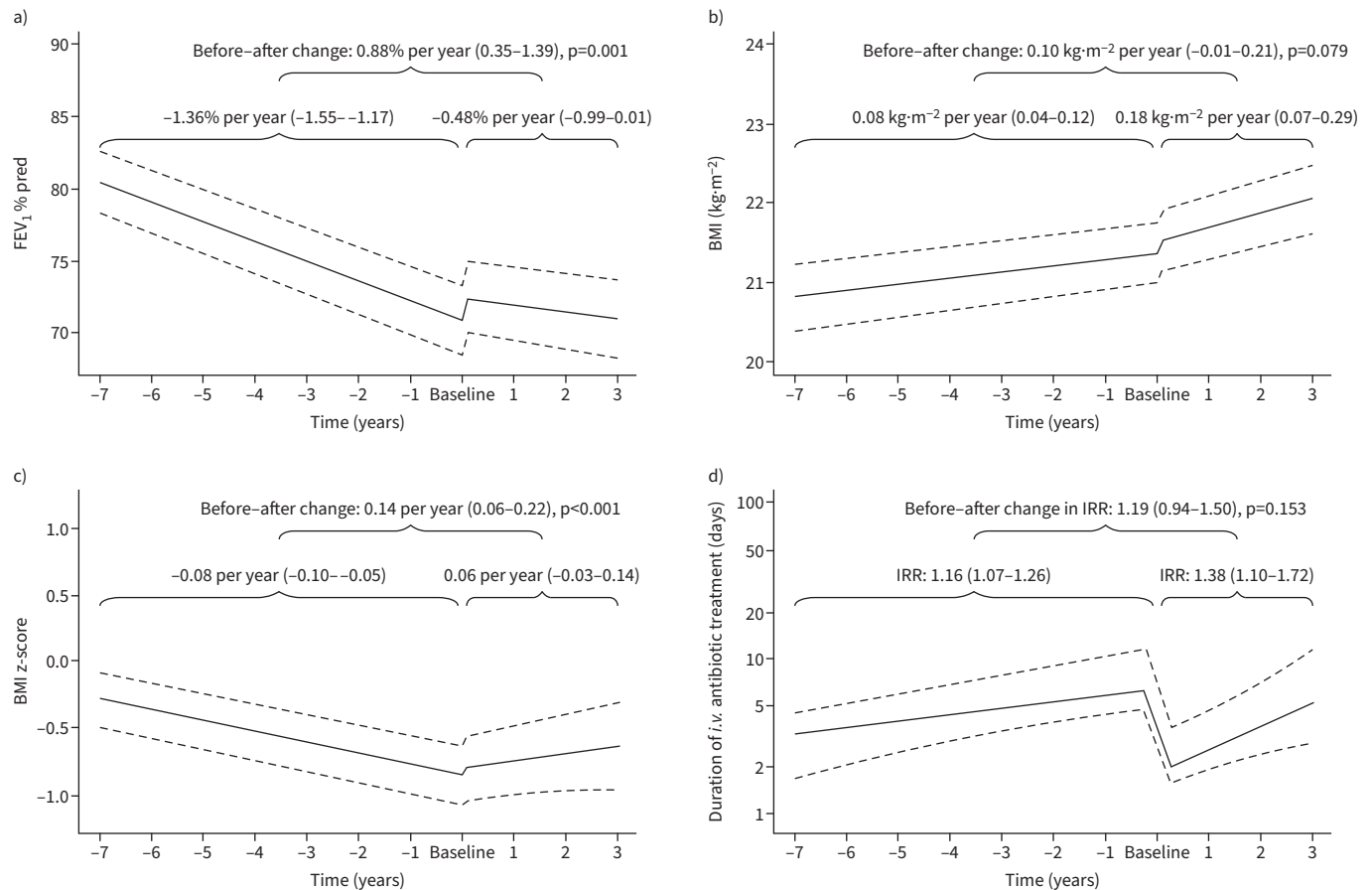
**TABLE 1** Baseline characteristics (n=401)

<b>CFTR modulator treatment, n (%)</b>	
Lumacaftor/ivacaftor (LUM/IVA)	401 (100)
Transition to tezacaftor/ivacaftor (TEZ/IVA)	208 (51.9)
Time (years) to transition from LUM/IVA to TEZ/IVA, mean±sd	2.0±0.6
<b>Death, n (%)</b>	2 (0.5)
<b>Lung transplantation, n (%)</b>	11 (2.7)
<b>Sex, n (%)</b>	
Male	233 (58.1)
Female	168 (41.9)
<b>Age (years), median (IQR)</b>	24.5 (18.0–31.5)
<b>Age 12–18 years, n (%)</b>	116 (28.9)
<b>Age &gt;18 years, n (%)</b>	285 (71.1)
<b>Missing, n (%)</b>	0
<b>FEV<sub>1</sub> % pred, mean±sd</b>	70.5±23.4
<b>FEV<sub>1</sub> &lt;40% pred, n (%)</b>	51 (12.7)
<b>FEV<sub>1</sub> 40–70% pred, n (%)</b>	128 (31.9)
<b>FEV<sub>1</sub> 70–90% pred, n (%)</b>	129 (32.2)
<b>FEV<sub>1</sub> ≥90% pred, n (%)</b>	90 (22.4)
<b>Missing, n (%)</b>	3 (0.8)
<b>BMI adults (kg·m<sup>-2</sup>) ≥19 years, mean±sd</b>	21.4±2.5
<b>Missing, n (%)</b>	5 (1.8)
<b>BMI Z-score children 12–19 years, mean±sd</b>	−0.5±0.8
<b>Missing, n (%)</b>	0
<b>Received intravenous antibiotic treatment, n (%)</b>	
Yes	149 (37.3)
No	201 (50.0)
Missing	51 (12.7)
<b>Duration of intravenous antibiotic treatments in days, median (IQR)</b>	23 (17–42)
<b><i>Pseudomonas aeruginosa</i> sputum culture status, n (%)</b>	
Positive	179 (44.6)
Negative	209 (52.2)
Missing	13 (3.2)
<b><i>Staphylococcus aureus</i> sputum culture status, n (%)</b>	
Positive	196 (48.9)
Negative	192 (47.9)
Missing	13 (3.2)
<b>Cystic fibrosis-related diabetes, n (%)</b>	
Yes	156 (38.9)
No	234 (58.4)
Missing	11 (2.7)
<b>Cystic fibrosis-related liver disease, n (%)</b>	
Yes	89 (22.2)
No	255 (63.6)
Missing	57 (14.2)

Definitions: age was calculated at the date of CFTR modulator initiation (baseline). FEV<sub>1</sub> % pred, BMI, BMI Z-score, number and duration of received intravenous antibiotic treatment, *Pseudomonas aeruginosa* and *Staphylococcus aureus* sputum culture status, CF-related diabetes and CF-related liver disease status reported at the last annual measurement preceding CFTR modulator initiation. The median duration of intravenous treatments was calculated for the 149 participants who received intravenous antibiotics in the last year prior to CFTR modulator initiation. BMI: body mass index. CFTR: cystic fibrosis transmembrane conductance regulator; FEV<sub>1</sub> % pred: % predicted forced expiratory volume in 1 s; IQR: interquartile range.

higher (95% CI: −0.0001–2.82%, p=0.050; supplementary table S1a) than in the participants with a baseline FEV<sub>1</sub> 40%–90% pred.

In the group with baseline FEV<sub>1</sub> ≥90% pred, a decline of FEV<sub>1</sub> was not observed (supplementary table S1a). Additional subgroup analyses did not show any differences in acute or longitudinal FEV<sub>1</sub> changes after CFTR modulator initiation between participants who transitioned to TEZ/IVA or continued LUM/IVA treatment, between females and males or between adults and adolescents (supplementary tables S1b–d).



**FIGURE 1** Longitudinal time trends of clinical outcomes before and after cystic fibrosis transmembrane conductance regulator (CFTR) modulator initiation. Estimated longitudinal trends of per cent predicted forced expiratory volume in 1 s (FEV<sub>1</sub> % pred), body mass index (BMI), BMI Z-score and annual intravenous (*i.v.*) antibiotic treatment duration. Time ranges from -7 years before to +3 years after CFTR modulator initiation, with time=0 (baseline) defined by the start date of CFTR modulator treatment. Dashed lines represent 95% confidence intervals, which are also given in parentheses. **a)** Mean FEV<sub>1</sub> decline before CFTR modulator treatment was -1.36% pred per year (95% CI: -1.55 to -1.17%), which changed by 0.88% pred per year (95% CI: 0.35-1.39%, p=0.001) after CFTR modulator initiation (table 2). The calculated FEV<sub>1</sub> decline after modulator initiation (-0.48% pred per year, 95% CI: -0.99-0.01%) was added to the figure to illustrate the difference in FEV<sub>1</sub> decline before and after CFTR modulator initiation. **b)** In adults ≥19 years, BMI gradually increased over time by 0.08 kg·m<sup>-2</sup> per year (95% CI: 0.04-0.12 kg·m<sup>-2</sup>) before CFTR modulator treatment. This annual BMI trend did not significantly change (change: 0.10 kg·m<sup>-2</sup> per year (95% CI: -0.01-0.21 kg·m<sup>-2</sup>, p=0.079)) in the years after modulator initiation (table 3). The calculated BMI after modulator initiation (0.18 kg·m<sup>-2</sup> per year, 95% CI: 0.07-0.29 kg·m<sup>-2</sup>) was added to the figure to illustrate the difference in BMI before and after CFTR modulator initiation. **c)** In children <19 years, BMI Z-score initially decreased over time before CFTR modulator initiation, by a mean of -0.08 per year (95% CI: -0.10 to -0.05). This annual trend significantly changed into an increasing trend (change: 0.14 per year (95% CI: 0.06-0.22, p<0.001)) in the years after CFTR modulator initiation (table 4). The calculated BMI Z-score after modulator initiation (0.06 per year, 95% CI: 0.03-0.14) was added to the figure to illustrate the difference in BMI Z-score before and after CFTR modulator initiation. **d)** The mean annual duration of *i.v.* antibiotic treatment (in days) increased by 16% (IRR: 1.16, 95% CI: 1.07-1.26, p<0.001) in the years preceding CFTR modulator treatment. In the year of CFTR modulator initiation, a drop in the mean duration of *i.v.* antibiotics was observed, leading to a three-times lower (IRR 0.28, 95% CI: 0.19-0.40, p<0.001) duration of *i.v.* antibiotic treatment compared to the years before CFTR modulator initiation. In the years after CFTR modulator initiation, the mean annual duration of *i.v.* treatment did not significantly change (change in IRR: 1.19, 95% CI: 0.94-1.50, p=0.153; table 5). The calculated IRR after modulator initiation (IRR: 1.84, 95% CI: 1.10-1.72) was added to the figure to illustrate the trend after CFTR modulator initiation.

#### BMI and BMI Z-scores

In adults of 19 years and older, estimated baseline BMI (21.37 kg·m<sup>-2</sup>, 95% CI: 21.00-21.74 kg·m<sup>-2</sup>) did not show an acute change after CFTR modulator initiation (change: 0.08 kg·m<sup>-2</sup>, 95% CI: -0.34-0.31 kg·m<sup>-2</sup>, p=0.097; table 3). As illustrated in figure 1b, the increasing annual BMI trend prior to modulator initiation (0.08 kg·m<sup>-2</sup> per year, 95% CI: 0.04-0.12 kg·m<sup>-2</sup>, p<0.001) was not significantly altered after CFTR modulator initiation (change: 0.10 kg·m<sup>-2</sup> per year, 95% CI: -0.01-0.21 kg·m<sup>-2</sup>, p=0.079; table 3).

**TABLE 2** Bayesian linear mixed effects model estimates of per cent predicted forced expiratory volume in 1 s (FEV<sub>1</sub> % pred) (n=401, years of observation=3844)

	Unadjusted coefficient	95% CI	p-value	Adjusted coefficient <sup>#</sup>	95% CI	p-value
<b>Intercept</b>	69.09	66.78–71.39	<0.001	70.97	68.52–73.42	<0.001
<b>Time</b>	–1.35	–1.54 – –1.15	<0.001*	–1.36	–1.55 – –1.17	<0.001*
<b>CFTR modulator</b>	1.51	0.49–2.48	0.002*	1.51	0.56–2.46	0.002*
<b>Time : CFTR modulator</b>	0.86	0.31–1.41	0.002*	0.88	0.35–1.39	0.001*

Interpretation: the intercept represents the mean FEV<sub>1</sub> % pred of the study population at the time of CFTR modulator initiation (baseline). The coefficient of time (in years) reflects the mean annual FEV<sub>1</sub> % pred decline in the years before CFTR modulator initiation. The coefficient CFTR modulator indicates the acute change in mean FEV<sub>1</sub> % pred after CFTR modulator initiation, whereas time : CFTR modulator represents the change in annual FEV<sub>1</sub> % pred decline in the years after CFTR modulator initiation compared to the years before. CFTR: cystic fibrosis transmembrane conductance regulator. <sup>#</sup>: coefficients were adjusted for the main effects of sex, age at baseline and the interaction effect of age at baseline with time; \*: significance level p<0.05.

The subgroup analysis in participants with a baseline FEV<sub>1</sub> between 40% and 90% pred showed similar longitudinal trends, with a change in annual BMI of 0.13 kg·m<sup>-2</sup> (95% CI: –0.04–0.32 kg·m<sup>-2</sup>, p=0.058) after CFTR modulator initiation (supplementary table S2a and figure S2a). In addition, no significant differences were demonstrated in acute or longitudinal changes after CFTR modulator initiation in participants who transitioned to TEZ/IVA compared to participants who continued LUM/IVA treatment (supplementary table S2b) or between females and males (supplementary table S2c).

Following WHO growth reference standards [10], BMI Z-scores were calculated for children with an age at baseline of 12–18 years. Estimated BMI Z-score at baseline –0.85 (95% CI: –0.08 – –0.62) did not show an acute change after modulator initiation (change: 0.05, 95% CI: –0.10–0.19, p=0.537; table 4). Figure 1c shows that the annual trend of BMI Z-score improved with 0.14 per year (95% CI: 0.06–0.22, p<0.001) to 0.06 per year in children below 19 years of age, which was in contrast with the decreasing trend prior to CFTR modulating treatment (–0.08 per year, 95% CI: –0.10 – –0.05, p<0.001; table 4).

Trends of BMI Z-score in the subgroup with a baseline FEV<sub>1</sub> between 40% and 90% pred were similar to the overall trends, although the longitudinal change after CFTR modulator initiation was slightly smaller compared to the entire cohort (change: 0.09 per year, 95% CI: –0.02–0.20, p=0.113; supplementary table S3a and figure S2b). Again, no significant differences were observed in acute or longitudinal changes after CFTR modulator initiation between participants who transitioned to TEZ/IVA and participants who continued LUM/IVA treatment (supplementary table S3b). The mean acute improvement of BMI Z-score

**TABLE 3** Bayesian linear mixed effects model estimates of body mass index (BMI) in adults ≥19 years (n=312, years of observation=2317)

	Unadjusted coefficient	95% CI	p-value	Adjusted coefficient <sup>#</sup>	95% CI	p-value
<b>Intercept</b>	21.40	21.12–21.67	<0.001	21.37	21.00–21.74	<0.001
<b>Time</b>	0.06	0.03–0.31	<0.001*	0.08	0.04–0.12	<0.001*
<b>CFTR modulator</b>	0.14	–0.02–0.31	0.086	0.14	–0.03–0.31	0.097
<b>Time : CFTR modulator</b>	0.06	–0.03–0.15	0.217	0.10	–0.01–0.21	0.079

Interpretation: the intercept represents the mean BMI at the time of CFTR modulator initiation (baseline) in adults of 19 years and older. The coefficient of time indicates the mean annual change in BMI in the years before modulator initiation. The coefficient of CFTR modulator reflects the acute change in BMI after modulator initiation, whereas time : CFTR modulator represents the change in annual BMI in the years after CFTR modulator initiation compared to the years before. CFTR: cystic fibrosis transmembrane conductance regulator. <sup>#</sup>: coefficients were adjusted for the main effects of sex, age at baseline, the interaction effect of age at baseline with time and the interaction effect of age at baseline with time and CFTR modulator treatment; \*: significance level p<0.05.

**TABLE 4** Bayesian linear mixed effects model estimates of BMI Z-score in children <19 years (n=225, years of observation=1552)

	Unadjusted coefficient	95% CI	p-value	Adjusted coefficient <sup>#</sup>	95% CI	p-value
<b>Intercept</b>	-0.60	-0.73 – -0.47	<0.001	-0.85	-1.08 – -0.62	<0.001
<b>Time</b>	-0.06	-0.09 – -0.05	<0.001*	-0.08	-0.11 – -0.05	<0.001*
<b>CFTR modulator</b>	0.003	-0.15–0.15	0.959	0.05	-0.10–0.19	0.537
<b>Time : CFTR modulator</b>	0.13	0.05–0.21	0.002*	0.14	0.06–0.22	<0.001*

Interpretation: the intercept represents the mean BMI Z-score at the time of CFTR modulator initiation (baseline) in children under 19 years (according to World Health Organization growth reference standards). The coefficient of time indicates the mean annual change in BMI Z-score in the years before modulator initiation. The coefficient of CFTR modulator reflects the acute change in BMI Z-score after modulator initiation, whereas time : CFTR modulator represents the change in annual BMI Z-score in the years after CFTR modulator initiation compared to the years before. BMI: body mass index. CFTR: cystic fibrosis transmembrane conductance regulator. <sup>#</sup>: coefficients were adjusted for the main effects of sex, age at baseline, the interaction effect of sex with time and the interaction effect of age at baseline with time; \*: significance level p<0.05.

after CFTR modulator initiation was 0.33 (95% CI: 0.06–0.61, p=0.018) higher in females compared to males, whereas longitudinal trends were comparable between sexes (supplementary table S3c).

#### Intravenous antibiotic treatment duration

In the first year after CFTR modulator initiation, the mean duration of *i.v.* antibiotic treatment became approximately three times lower (incidence rate ratios (IRR) 0.28, 95% CI: 0.19–0.40, p<0.001) than the mean 4.38 days (95% CI: 2.82–6.79 days) in the last year preceding CFTR modulator initiation (table 5). In contrast, the mean annual duration of received *i.v.* antibiotics was not significantly altered after CFTR modulator initiation (IRR 1.19, 95% CI: 0.94–1.50, p=0.153), which increased with 16% per year (IRR 1.16, 95% CI: 1.07–1.26, p<0.001) in the years before CFTR modulator initiation (table 5 and figure 1d).

In the subgroup of participants with baseline FEV<sub>1</sub> 40%–90% pred, the mean duration of received *i.v.* antibiotics in the last year preceding CFTR modulator initiation was slightly higher (6.16 days, 95% CI: 5.32–15.38 days), whereas the longitudinal changes before and after modulator initiation were comparable to the overall results (supplementary table S4a and figure S3a). As shown in supplementary figure S3b, trends of participants with a baseline FEV<sub>1</sub> <40% pred were comparable to participants with baseline FEV<sub>1</sub> 40%–90% pred, but the mean *i.v.* antibiotic treatment duration in participants with a FEV<sub>1</sub> ≥90% pred at baseline was considerably lower and did not increase after CFTR modulator initiation (supplementary table S4a). Additional subgroup analyses did not show differences between participants

**TABLE 5** Negative binomial mixed effects model estimates of the duration of intravenous (*i.v.*) antibiotic treatment (n=364, years of observation=2805)

	Unadjusted coefficient	IRR	95% CI (IRR)	p-value	Adjusted coefficient <sup>#</sup>	IRR	95% CI (IRR)	p-value
<b>Intercept</b>	1.76	5.83	3.97–8.56	<0.001	1.48	4.38	2.82–6.79	<0.001
<b>Time</b>	0.15	1.16	1.07–1.26	<0.001*	0.15	1.16	1.07–1.26	<0.001*
<b>CFTR modulator</b>	-1.28	0.28	0.19–0.40	<0.001*	-1.28	0.28	0.19–0.40	<0.001*
<b>Time : CFTR modulator</b>	0.16	1.18	0.93–1.49	0.170	0.17	1.19	0.94–1.50	0.153

Interpretation: coefficients are on the log-scale. Incidence rate ratios (IRRs) are transformed back to the original scale. The IRR of the intercept represents the mean duration of received *i.v.* antibiotics (in days) of the study population at the time of CFTR modulator initiation (baseline). The IRR of time shows the relative annual change in the duration of *i.v.* antibiotics before CFTR modulator treatment. The IRR of CFTR modulator reflects the acute change in the duration of *i.v.* antibiotics in the first year after CFTR modulator initiation, whereas time : CFTR modulator treatment indicates the relative change of *i.v.* antibiotic treatment in the years after modulator initiation compared to the annual trend before CFTR modulator use. CFTR: cystic fibrosis transmembrane conductance regulator. <sup>#</sup>: coefficients and IRRs were adjusted for sex and age at baseline; \*: significance level p<0.05.

who transitioned to TEZ/IVA or who continued LUM/IVA treatment, between females and males or between adults and adolescents (supplementary tables S4b–d).

### Discussion

This study provided real-world data of the long-term effectiveness of LUM/IVA and TEZ/IVA on important pulmonary outcomes and nutritional status, covering almost 4000 patient-years of observation in pwCF homozygous for F508del, up to 3 years after the introduction of these dual CFTR modulating therapies. Although the pivotal RCTs and open-label extension trials demonstrated a clear efficacy of LUM/IVA and TEZ/IVA on several clinical end-points in pwCF with a baseline FEV<sub>1</sub> between 40% and 90% pred [4–7], our results emphasised that real-world effectiveness is less pronounced, with considerable differences in long-term trends among pwCF and a FEV<sub>1</sub> below 40% pred or above 90% pred upon CFTR modulator initiation.

Real-world improvement of annual FEV<sub>1</sub> decline was slightly lower than the 1% pred change in FEV<sub>1</sub> decline estimated by the long-term open-label extension trial data [6, 7]. This was demonstrated by a mean change of 0.81% pred and 0.88% pred per year after CFTR modulator initiation in both the subgroup with baseline FEV<sub>1</sub> 40%–90% pred and in the entire cohort, respectively. In contrast with the short-term trials [4, 5], the acute change of FEV<sub>1</sub> after modulator initiation was limited in the entire cohort. However, we did observe an acute improvement of 2.59% pred in the subgroup of participants with a baseline FEV<sub>1</sub> between 40% and 90% pred that approximated the original trial results [4–7].

Interestingly, the mean acute improvement of FEV<sub>1</sub> in participants with a baseline FEV<sub>1</sub> <40% pred was not significantly different from the group with a pre-modulator FEV<sub>1</sub> 40%–90% pred. Moreover, the improvement of FEV<sub>1</sub> decline was even higher in those with FEV<sub>1</sub> <40% pred before CFTR modulator initiation. Similar short-term improvements in pwCF and severe lung disease were already reported in subgroup analyses of clinical trials and in several case series [11], but the long-term benefits in this subgroup have not yet been demonstrated before.

In addition, long-term changes in BMI and BMI Z-score in this study were moderate compared to previous trials [6, 7], and despite the acute decrease in the duration of *i.v.* antibiotic use in the first year after modulator initiation, the mean duration of *i.v.* antibiotic treatment continued to increase again in the subsequent years.

Taken together, the results of this study emphasise that translation of clinical trial results into daily clinical practice can be difficult, especially in chronic diseases like CF. Most of the discrepancies are probably explained by the different populations, design and settings of traditional trials compared to observational real-world studies. This could be related to the relatively short follow-up of RCTs, as well as to the stringent selection criteria which usually exclude people with, for example, severe or limited lung disease (FEV<sub>1</sub> <40% pred and >90% pred) or people with CF-related comorbidities such as diabetes and liver disease. In addition, clinical trial conditions regarding co-medication and treatment adherence are strictly controlled, whereas temporary or permanent treatment discontinuation is more likely to occur in practice [8]. Real-world studies with a long-term follow-up are therefore important to provide additional post-approval data of the impact and sustainability of treatments on the entire heterogeneous population [12].

So far, seven studies have been published that assessed the effectiveness of LUM/IVA in a real-world setting [13–19]. Most of these studies were conducted in small populations, examining different subgroups and outcomes with a follow-up period of 1 year after LUM/IVA initiation and a limited observation period, not exceeding 845 patient-years.

The present study substantially contributes to the existing real-world evidence, because the follow-up period covered on average 7 years before CFTR modulator treatment and up to 3 years after modulator initiation. Moreover, this study included 3844 patient-years of observation of a relatively large and heterogeneous population of F508del-homozygous pwCF aged 12 years and older at different disease stages, which reflects daily clinical practice. In addition, we adjusted for the confounding effect of age, which is known to be associated with rate of lung function decline [20].

Overall, our results were consistent with previous studies that suggested real-world effectiveness to be less pronounced compared to the initial trials. Most studies reported a moderate change from baseline FEV<sub>1</sub> % pred [13, 14] and a moderate change in FEV<sub>1</sub> % pred decline after 1 year [16, 17] or 2 years [18] of follow-up. The discrepancy with a different recently published study that focused on predictors of long-term clinical outcomes using encounter-based FEV<sub>1</sub> measurements [19] might be explained by the inclusion of



annual best FEV<sub>1</sub> measurements in the NCFR. Annual best measurements may provide a better estimation of long-term trends, as this reduces the impact of measurement variability over time compared to multiple repeated measurements. Given the strong (nonlinear) association of lung function decline with age [20, 21], trends were adjusted for age at baseline in this study. The short- and long-term improvement of BMI and nutritional status could be interpreted as modest and was more profound in adolescents [13, 14, 18]. The use of the different reference values for adults and adolescents limits a direct comparison of BMI and BMI Z-score trends between age groups, which has also not been assessed in other real-world studies. Nevertheless, similar differences were reported in the PROGRESS trial, showing an increasing BMI trend in treated pwCF and matched registry controls, whereas BMI Z-score and weight-for-age trend improved after LUM/IVA initiation compared to a decline in matched registry controls [6]. Moreover, LUM/IVA and TEZ/IVA might induce a short-term improvement of pulmonary exacerbations [13, 14] and reduce the use of *i.v.* antibiotics in the first year after treatment initiation in pwCF above 12 years of age, but this improvement was not sustained in the subsequent years [18, 19]. This could indicate that the benefit of dual CFTR modulators on severe pulmonary exacerbations diminishes in the long-term, but it could also be related to a decreasing long-term adherence to modulators or to a reduced prescription or adherence to other co-medication such as domase  $\alpha$ , hypertonic saline and inhaled antibiotics in a real-life setting.

The contrast between short- and long-term changes in this study also illustrates that traditional short-term clinical end-points such as FEV<sub>1</sub> % pred might not always be the best measures to capture treatment benefits, especially when effect sizes are limited, populations are heterogeneous and sample sizes are small, which frequently occurs in rare diseases such as CF. Long-term trials or observational real-world studies might partially overcome this problem because they could reveal an inhibition of disease progression, but alternative approaches will be needed since long-term studies are not always feasible and require sufficient short-term evidence first.

An important limitation of this study was the relatively large proportion of missing data in *i.v.* antibiotic treatment duration, which was not consistently collected in the NCFR throughout the entire study period, particularly in the years before CFTR modulator initiation (2010–2014). Although we used appropriate statistical models to adjust for missing data, we cannot rule out that this might have influenced the results. Even though we did adjust for the most important confounders age and sex, we were not able to include data regarding either treatment discontinuation and side-effects or concomitant treatments such as hydrators, domase  $\alpha$ , azithromycin or other inhaled or oral antibiotics, which might have respectively underestimated or overestimated the reported effectiveness. Due to the transition from LUM/IVA to TEZ/IVA during the observation period, this study provides combined results about the effectiveness of both dual CFTR modulators. Based on the additional subgroup analyses that compared the groups who did and did not switch to TEZ/IVA, the influence of transition was considered as limited.

In conclusion, this real-world study showed that long-term FEV<sub>1</sub> decline improved up to 3 years after the introduction of LUM/IVA and TEZ/IVA, which was also observed for BMI Z-score in children, but not for BMI in adults. Intravenous antibiotic treatment duration was reduced in the first year after modulator initiation, but this duration increased in the subsequent years. Compared to the efficacy reported in previous clinical trials, real-world effectiveness of the dual CFTR modulators is less pronounced and varies considerably between pwCF and different baseline FEV<sub>1</sub> levels.

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