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Original research article

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Please cite this article as: Muilwijk D, Zomer-van Ommen DD, Gulmans VAM, *et al*. Long-term effectiveness of dual CFTR modulator treatment of Cystic Fibrosis. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00204-2022).

Long-term effectiveness of dual CFTR modulator treatment of Cystic Fibrosis

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KEYWORDS

Cystic Fibrosis, F508del/F508del, CFTR modulators, long-term effectiveness, real-world study

TAKE-HOME MESSAGE

Long-term effectiveness of dual CFTR modulator therapies on ppFEV1 decline, BMI and intravenous antibiotic treatment duration is less pronounced in a real-world setting than reported in previous clinical trials.

ABSTRACT

Background: Although short-term efficacy of lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) 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 CF (pwCF) ≥12 years, up to three years after the introduction of dual CFTR modulators.

Methods: Annual data (2010-2019) were retrieved from the Dutch Cystic Fibrosis Registry. Longitudinal trends of percent predicted forced expiratory volume in 1s (ppFEV1) 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 ppFEV1 70.5% (SD:23.4%)). ppFEV1 decline improved from -1.36%/year to -0.48%/year after modulator initiation (change: 0.88%, CI:0.35–1.39%, p=0.001). This change was even 1.40%/year (CI -0.0001–2.82%, p=0.050) higher in participants with baseline ppFEV1<40%. In adults, annual BMI trend was not altered (change: 0.10 kg/m²/year, CI:-0.01–0.21, p=0.079). Annual BMI Z-score in children reversed from -0.08/year before modulator treatment to 0.06/year afterwards (change: 0.14/year, CI:0.06–0.22, p<0.001). Intravenous antibiotic treatment duration showed a three-fold reduction in the first year after modulator initiation (IRR: 0.28, CI:0.19–0.40, p<0.001), but the annual trend did not change in the subsequent years (IRR: 1.19, CI:0.94–1.50, p=0.153).

Conclusion: Long-term effectiveness of dual CFTR modulator therapies on ppFEV1 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 ppFEV1 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 randomized 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 percent predicted forced expiratory volume in 1s (ppFEV1) between 40% and 90%. These RCTs demonstrated an average absolute improvement of 2.6-4% ppFEV1, an increase in body mass index (BMI) and a reduction of pulmonary exacerbation rate and intravenous (IV) 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 an average estimated ppFEV1 decline between -1.3% and -0.8% per year after 120 weeks of CFTR modulator treatment, compared to -2.3% to -2.1% in matched historical controls. Furthermore, the absolute change from baseline BMI continued to increase whereas pulmonary exacerbation rate and IV 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 one 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 ppFEV1 decline, BMI and annual duration of IV antibiotic treatment in people with CF homozygous for F508del, up to three years after the introduction of the dual CFTR modulating therapies LUM/IVA and TEZ/IVA, using NCFR data.

MATERIALS & 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 annualized clinical data of pwCF who are treated in one of the seven Dutch CF centers 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 centers, 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 ppFEV1, BMI, BMI Z-score and annual duration of IV antibiotic treatment after commencement with LUM/IVA were considered as clinical outcomes. The NCFR collects annual best ppFEV1 measurements, calculated according to the Global Lung Initiative (GLI) guideline [9], which were used to assess the average annual change in ppFEV1 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 standardized for age and sex were calculated according to the World Health Organization (WHO) Growth Reference for children below 19 years [10]. Duration of annual IV 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 dichotomized as treatment=no before baseline and treatment=yes after baseline. Data regarding sex, age and presence of *Pseudomonas Aeruginosa* (PA) and *Staphylococcus Aureus* (SA) in annual sputum cultures were also collected.

Statistical analysis

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

A linear mixed effects model was used to assess longitudinal trends in ppFEV1 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 IV antibiotic treatment were analyzed with a negative binomial mixed effects model. Detailed model specifications are provided in the online supplements.

To facilitate a comparison of real-world data with data from controlled registration trials, subgroup analyses in participants with a baseline ppFEV1 between 40-90% were performed for each model. For ppFEV1 and IV antibiotic treatment duration, we also compared longitudinal trends of participants with a baseline ppFEV1 <40% and ≥90% to the group with a ppFEV1 between 40-90% 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 ppFEV1 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 IV antibiotic treatment (32.2%), followed by 4.1% of ppFEV1 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 ppFEV1, 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 IV antibiotic treatment were analyzed 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 summarized in Table 1. Median follow-up time before and after CFTR modulator initiation was 7.9 years (IQR: 7.5-7.9 years) vs. 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 on average 2.0 years (SD: 0.6 years) of initial LUM/IVA treatment. Last measured ppFEV1 before CFTR modulator initiation was between 40-90% in 257 (64.1%) of the participants.

Lung function decline

Overall, we observed a moderate acute change in the estimated ppFEV1 at baseline (ppFEV1 at baseline: 70.97%, 95% CI: 68.52 – 73.42%) after CFTR modulator initiation (change: 1.51%, 95% CI: 0.56 – 2.46, p=0.002). The average annual ppFEV1 decline improved from -1.36% per year to -0.48% per year after CFTR modulator initiation (change: 0.88%, 95% CI: 0.35 – 1.39%, p=0.001); Figure 1a & Table 2).

The acute impact of CFTR modulator treatment was slightly higher in the subgroup of participants with a baseline ppFEV1 between 40-90%, with an acute change from baseline ppFEV1 of 2.59% (95% CI: 1.40 – 3.78%, p<0.001; Supplementary table 1a). The magnitude of change in ppFEV1 decline was comparable to the change in the entire cohort (change: 0.81% per year, 95% CI: 0.11 – 1.50%, p=0.026; Supplementary table 1a and Supplementary figure 1a).

In participants with a baseline ppFEV1 <40%, the acute improvement in ppFEV1 was not significantly different from those with a ppFEV1 40-90% before CFTR modulator initiation (difference: -1.24, 95% CI: -4.25 – 1.78, p=0.420; Supplementary table 1a). As illustrated in Supplementary figure 1b, the average change in ppFEV1 decline after CFTR modulator initiation was even 1.40% per year

higher (95% CI -0.0001 - 2.82%, p=0.050; Supplementary table 1a) than in the participants with a baseline ppFEV1 40-90%.

In the group with baseline ppFEV1 ≥90%, a longitudinal decline of ppFEV1 was not observed (Supplementary table 1a). Additional subgroup analyses did not show any differences in acute or longitudinal ppFEV1 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 1b-1d).

BMI and BMI Z-scores

In adults of 19 years and older, estimated average baseline BMI (21.37 kg/m², 95% CI: 21.00 – 21.74 kg/m²) did not show an acute change after CFTR modulator initiation (change: 0.08 kg/m², 95% CI: -0.34 – 0.31 kg/m², p=0.097; Table 3). As illustrated in Figure 1b, the increasing annual BMI trend prior to modulator initiation (0.08 kg/m² per year, 95% CI: 0.04 – 0.12 kg/m², p<0.001) was not significantly altered after CFTR modulator initiation (change: 0.10 kg/m² per year, 95% CI: -0.01 – 0.21 kg/m², p=0.079; Table 3), although a trend towards might be suggested.

The subgroup analysis in participants with a baseline ppFEV1 between 40-90% showed similar longitudinal trends, with an average change in annual BMI of 0.13 kg/m² (95% CI: -0.04 – 0.32 kg/m², p=0.058) after CFTR modulator initiation (Supplementary table 2a and Supplementary figure 2a). 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 2b) or between females and males (Supplementary table 2c).

Following WHO growth reference standards [10], BMI Z-scores were calculated for children with an age at baseline of 12-18 years. Estimated average 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 average 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 average 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 ppFEV1 between 40-90% 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 3a and Supplementary figure 2b). 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 3b). The average acute improvement of BMI Z-score 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 3c).

Intravenous antibiotic treatment duration

In the first year after CFTR modulator initiation, the average duration of IV antibiotic treatment became approximately three times lower (IRR 0.28, 95% CI: 0.19 – 0.40, p<0.001) than the average 4.38 days (95% CI: 2.82 – 6.79 days) in the last year preceding CFTR modulator initiation (Table 5). In contrast, the average annual duration of received IV antibiotics was not significantly altered after CFTR modulator initiation (IRR 1.19, 95% CI: 0.94 – 1.50, p=0.153), which increased on average 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 ppFEV1 40-90%, the average duration of received IV 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 4a and Supplementary figure 3a). As shown in Supplementary figure 3b, average trends of participants with a baseline ppFEV1 <40% were comparable to participants with baseline ppFEV1 40-90%, but the average IV antibiotic treatment duration in participants with a ppFEV1 ≥90% at baseline was considerably lower and did not increase after CFTR modulator initiation (Supplementary table 4a). Additional subgroup analyses did not show differences between participants who transitioned to TEZ/IVA or continued LUM/IVA treatment, between females and males or between adults and adolescents (Supplementary tables 4b-4d).

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 three 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 endpoints in pwCF with a baseline ppFEV1 between 40-90% [4–7], our results emphasized that real-world effectiveness is less pronounced, with considerable differences in long-term trends among pwCF and a ppFEV1 below 40% or above 90% upon CFTR modulator initiation.

Real-world improvement of annual ppFEV1 decline was slightly lower than the 1% change in ppFEV1 decline estimated by the long-term open label extension trial data [6, 7], as demonstrated by an average change of 0.81% and 0.88% per year after CFTR modulator initiation in both the subgroup with baseline ppFEV1 40-90% and in the entire cohort, respectively. In contrast with the short-term trials [4, 5], the acute change of ppFEV1 after modulator initiation was limited in the entire cohort. However, we did observe an acute improvement of 2.59% in the subgroup of participants with a baseline ppFEV1 between 40-90% that approximated the original trial results [4–7].

Interestingly, the average acute improvement of ppFEV1 in participants with a baseline ppFEV1 <40% was not significantly different from the group with a pre-modulator ppFEV1 40-90%. Moreover, the improvement of ppFEV1 decline was even higher in those with ppFEV1 <40% before CFTR modulator initiation. Similar short-term improvements in pwCF and severe lung disease were already reported in subgroup analyses of clinical trials and several case series [11], but these benefits in long-term ppFEV1 changes have not yet been demonstrated in this subgroup.

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 average duration of IV antibiotic use in the first year after modulator initiation, the average duration of IV antibiotic treatment continued to increase again in the subsequent years.

Taken together, the results of this study emphasize that translation of clinical trial results into daily clinical practice can be difficult, especially in chronic diseases like CF, as 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 e.g. severe or limited lung disease (ppFEV1 <40% and >90%) or people with CF-related co-morbidities 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 one 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 seven years before CFTR modulator treatment and up to three 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 compared to the initial trials. Most studies reported a moderate change from baseline ppFEV1 [13, 14] and a moderate change in ppFEV1 decline after one [16, 17] or two 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 ppFEV1 measurements [19] might be explained by

the inclusion of annual best ppFEV1 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 (non-linear) 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 IV 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 on 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 dornase 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 endpoints such as ppFEV1 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 IV 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, dornase 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 was considered as limited.

In conclusion, this real-world study showed that long-term ppFEV1 decline improved up to three 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. IV 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 ppFEV1 levels.

ACKNOWLEDGEMENTS

We thank all people with CF who consented with the collection of their data by the NCFR and the use of this data for research. We also thank all collaborating Dutch CF Centers for their effort to provide the data to the NCFR, in particular the members of the Dutch CF Registry Steering Group: J. Altenburg, MD PhD, Amsterdam University Medical Centers; S.W.J. Terheggen-Lagro, MD PhD, Emma Children's Hospital, Amsterdam University Medical Centers; H.G.M. Heijerman, MD PhD, University Medical Center Utrecht, K.M. de Winter-de Groot, MD PhD, Wilhelmina Children's Hospital, University Medical Center Utrecht; M. Bakker, MD, Erasmus University Medical Center

Rotterdam, R.A.S. Hoek, MD, Erasmus University Medical Center Rotterdam; H.M. Janssens, MD PhD, Sophia Children's Hospital, Erasmus University Medical Center Rotterdam; R. van der Meer, MD, Haga Teaching Hospital The Hague, M. Nuijsink, MD PhD, Juliana Children's Hospital, Haga Teaching Hospital The Hague; H. van der Vaart, MD PhD, University Medical Center Groningen; G.H. Koppelman, MD PhD, Beatrix Children's Hospital, University Medical Center Groningen; L.H. Conemans, MD, Maastricht University Medical Center+ Maastricht; M.A.G.E. Bannier, MD, Maastricht University Medical Center+ Maastricht; P.J.F.M. Merkus, MD PhD, Amalia Children's Hospital, Radboud University Medical Center Nijmegen; J.J. Noordhoek, MA MSc, Dutch Cystic Fibrosis Foundation; all in The Netherlands.

FUNDING

This research received no external funding.

AUTHOR CONTRIBUTIONS

Conceptualization: D.M. and C.K.v.d.E.; methodology: D.M., M.J.C.E. and C.K.v.d.E.; data curation: D.M. and D.D.Z.v.O; formal analysis: D.M. and M.J.C.E.; resources: D.D.Z.v.O and V.A.M.G.; writing—original draft preparation: D.M., D.D.Z.v.O. and C.K.v.d.E.; writing—review and editing: D.M., D.D.Z.v.O., V.A.M.G., M.J.C.E. and C.K.v.d.E.; visualization: D.M. and M.J.C.E.; supervision: M.J.C.E and C.K.v.d.E. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

C.K.v.d.E. reports grants from Vertex, Eloxx, Proteostasis, Galapagos NV, ProQR, Gilead, TEVA, GSK and Nutricia (money to institution), outside of the submitted work. All other authors have nothing to disclose.

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TABLES

Table 1. Baseline characteristics (n=401)

CFTR modulator treatment, n (%)	
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)
Death, n (%)	2 (0.5)
Lung transplantation, n (%)	11 (2.7)
Sex, n (%)	
Male	233 (58.1)
Female	168 (41.9)
Age (years), median (IQR)	24.5 (18.0 – 31.5)
Age 12-18 years, n (%)	116 (28.9)
Age > 18 years, n (%)	285 (71.1)
Missing, n (%)	0
ppFEV1pp (%), mean (SD)	70.5 (23.4)
ppFEV1 <40%, n (%)	51 (12.7)
ppFEV1 40-70%, n (%)	128 (31.9)
ppFEV1 70-90%, n (%)	129 (32.2)
ppFEV1 ≥90%, n (%)	90 (22.4)
Missing, n (%)	3 (0.8)
BMI adults (kg/m²) ≥ 19 years, mean (SD)	21.4 (2.5)
Missing, n (%)	5 (1.8)
BMI Z-score children 12-19 years, mean (SD)	-0.5 (0.8)
Missing, n (%)	0

Received intravenous antibiotic treatment, n (%)	
Yes	149 (37.3)
No	201 (50.0)
Missing	51 (12.7)
Duration of intravenous antibiotic treatments (days), median (IQR)	23 (17 – 42)
Pseudomonas Aeruginosa sputum culture status, n (%)	
Positive	179 (44.6)
Negative	209 52.2)
Missing	13 (3.2)
Staphylococcus Aureus sputum culture status, n (%)	
Positive	196 (48.9)
Negative	192 (47.9)
Missing	13 (3.2)
Cystic Fibrosis-related diabetes, n (%)	
Yes	156 (38.9)
No	234 (58.4)
Missing	11 (2.7)
Cystic Fibrosis-related liver disease, n (%)	
Yes	89 (22.2)
No	255 (63.6)
Missing	57 (14.2)

Abbreviations: BMI: body mass index. CFTR: Cystic fibrosis transmembrane conductance regulator. ppFEV1: percent predicted forced expiratory volume in 1s.

Definitions: age was calculated at the date of CFTR modulator initiation (baseline). ppFEV1, 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.

Table 2. Bayesian linear mixed effects model estimates of ppFEV1 (n=401, Years of observation=3844)

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

Interpretation: the intercept represents the average ppFEV1 of the study population at the time of CFTR modulator initiation (baseline). The coefficient of time (in years) reflects the average annual ppFEV1 decline in the years before CFTR modulator initiation. The coefficient CFTR modulator indicates the acute change in average ppFEV1 after CFTR modulator initiation, whereas time : CFTR modulator represents the change in annual ppFEV1 decline in the years after CFTR modulator initiation compared to the years before. # Coefficients were adjusted for the main effects of sex, age at baseline and the interaction effect of age at baseline with time.

*Significance level $p<0.05$.

Table 3. Bayesian linear mixed effects model estimates of BMI in adults ≥ 19 years (n=312, Years of observation=2317)

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

Interpretation: the intercept represents the average BMI at the time of CFTR modulator initiation (baseline) in adults of 19 years and older. The coefficient of time indicates the average 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. # 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#	95% CI	P-value
Intercept	-0.60	-0.73 – -0.47	<0.001	-0.85	-1.08 – -0.62	<0.001
Time	-0.06	-0.09 – -0.05	<0.001*	-0.08	-0.11 – -0.05	<0.001*
CFTR modulator	0.003	-0.15 – 0.15	0.959	0.05	-0.10 – 0.19	0.537
Time : CFTR Modulator	0.13	0.05 – 0.21	0.002*	0.14	0.06 – 0.22	<0.001*

Interpretation: the intercept represents the average BMI Z-score at the time of CFTR modulator initiation (baseline) in children under 19 years (according to WHO growth reference standards). The coefficient of time indicates the average 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. # 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.

Table 5. Negative binomial mixed effects model estimates of the duration of IV antibiotic treatment (n=364, Years of observation=2805)

	Unadjusted coefficient	IRR	95% CI (IRR)	P-value	Adjusted coefficient#	IRR	95% CI (IRR)	P-value
Intercept	1.76	5.83	3.97 – 8.56	<0.001	1.48	4.38	2.82 – 6.79	<0.001
Time	0.15	1.16	1.07 – 1.26	<0.001*	0.15	1.16	1.07 – 1.26	<0.001*
CFTR modulator	-1.28	0.28	0.19 – 0.40	<0.001*	-1.28	0.28	0.19 – 0.40	<0.001*
Time : CFTR Modulator	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 (IRR) are transformed back to the original scale. The IRR of the intercept represents the average duration of received IV 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 IV antibiotics before CFTR modulator treatment. The IRR of CFTR modulator reflects the acute change in the duration of IV antibiotics in the first year after CFTR modulator initiation, whereas time : CFTR

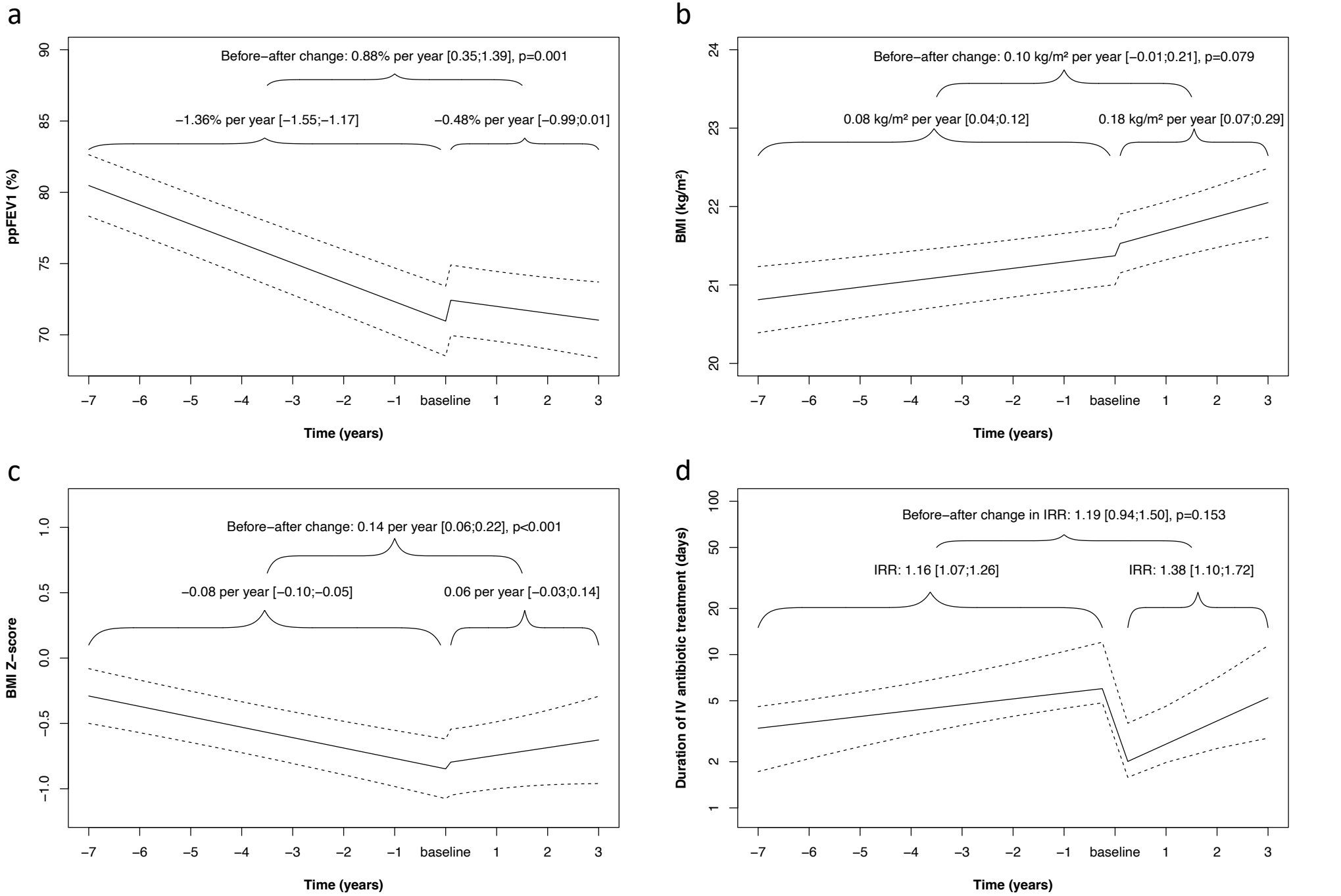
modulator treatment indicates the relative change of IV antibiotic treatment in the years after modulator initiation compared to the annual trend before CFTR modulator use. # Coefficients and IRRs were adjusted for sex and age at baseline. * Significance level $p<0.05$.

FIGURE LEGENDS

Figure 1. Longitudinal time trends of clinical outcomes before and after CFTR modulator initiation.

Estimated longitudinal trends of percent predicted forced expiratory volume in 1s (ppFEV1), body mass index (BMI), BMI Z-score and annual intravenous (IV) 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 shown between square brackets. **Panel 1a**: average ppFEV1 decline before CFTR modulator treatment was -1.36% per year (95% CI: -1.55;-1.17%), which changed with 0.88% per year (95% CI: 0.35;1.39%, p=0.001) after CFTR modulator initiation (Table 2). The calculated ppFEV1 decline after modulator initiation (-0.48% per year, 95% CI: -0.99;0.01%) was added to the figure to illustrate the difference in ppFEV1 decline before and after CFTR modulator initiation. **Panel 1b**: in adults ≥ 19 years, BMI gradually increased over time with 0.08 kg/m² per year (95% CI: 0.04;0.12 kg/m²) before CFTR modulator treatment. This annual BMI trend did not significantly change (change: 0.10 kg/m² per year (95% CI: -0.01;0.21 kg/m², p=0.079) in the years after modulator initiation (Table 3). The calculated BMI after modulator initiation (0.18 kg/m² per year, 95% CI: 0.07;0.29 kg/m²) was added to the figure to illustrate the difference in BMI before and after CFTR modulator initiation. **Panel 1c**: In children < 19 years, BMI Z-score initially decreased over time before CFTR modulator initiation, with an average of -0.08 per year (95% CI: -0.10;-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. **Panel 1d**: the average annual duration of IV antibiotic treatment (in days) increased with 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 average duration of IV antibiotics was observed, leading to a three-times lower (IRR 0.28, 95% CI: 0.19 – 0.40, p<0.001) duration of IV

antibiotic treatment compared to the years before CFTR modulator initiation. In the years after CFTR modulator initiation, the annual average duration of IV 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.


a
Before–after change: 0.88% per year [0.35;1.39], p=0.001
–1.36% per year [–1.55;–1.17]
–0.48% per year [–0.99;0.01]
ppFEV1 (%)
90
85
80
75
70
–7
–6
–5
–4
–3
–2
–1
baseline
1
2
3
Time (years)
b
Before–after change: 0.10 kg/m² per year [–0.01;0.21], p=0.079
0.08 kg/m² per year [0.04;0.12]
0.18 kg/m² per year [0.07;0.29]
BMI (kg/m²)
24
23
22
21
20
Time (years)
c
Before–after change: 0.14 per year [0.06;0.22], p<0.001
–0.08 per year [–0.10;–0.05]
0.06 per year [–0.03;0.14]
BMI Z–score
1.0
0.5
0.0
–0.5
–1.0
Time (years)
d
Before–after change in IRR: 1.19 [0.94;1.50], p=0.153
IRR: 1.16 [1.07;1.26]
IRR: 1.38 [1.10;1.72]
Duration of IV antibiotic treatment (days)
100
50
20
10
5
2
1
Time (years)

SUPPLEMENTARY TABLES & FIGURE LEGENDS

Supplementary table 1a. Bayesian linear mixed effects model estimates of ppFEV1.

Comparison of effects in participants with baseline FEV1pp <40%, between 40-90% and ≥90% (n=401, Years of observation=3844).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	67.46	65.91 – 69.00	<0.001	68.74	67.05 – 70.41	<0.001
ppFEV1 40-90%	Reference			Reference		
ppFEV1 <40%	-34.30	-37.87 – -30.75	<0.001*	-29.46	-32.74 – -26.19	<0.001*
ppFEV1 ≥90%	29.03	26.20 – 31.86	<0.001*	25.13	22.49 – 27.76	<0.001*
Time	-1.59	-1.82 – -1.36	<0.001*	-1.62	-1.84 – -1.41	<0.001*
Time : ppFEV1 40-90%	Reference			Reference		
Time : ppFEV1 <40%	-1.12	-2.50 – 0.26	0.112	-2.24	-3.58 – -0.90	0.001*
Time : ppFEV1 ≥90%	2.25	1.49 – 3.01	<0.001*	2.87	2.13 – 3.62	<0.001*
CFTR modulator	2.60	1.42 – 3.78	<0.001*	2.59	1.40 – 3.78	<0.001*
CFTR modulator : ppFEV1 40%-90%	Reference			Reference		
CFTR modulator : ppFEV1 <40%	-1.30	-4.30 – 1.69	0.395	-1.24	-4.25 – 1.78	0.420
CFTR modulator : ppFEV1 ≥90%	-4.12	-6.41 – -1.82	0.002*	-4.07	-6.36 – -1.77	<0.001*
Time : CFTR modulator	0.75	0.05 – 1.43	0.039*	0.81	0.11– 1.50	0.026*
Time : CFTR modulator : ppFEV1 40-90%	Reference			Reference		
Time : CFTR modulator : ppFEV1 <40%	1.50	0.10 – 2.92	0.035*	1.40	-0.0001 – 2.82	0.050*
Time : CFTR modulator : ppFEV1 ≥90%	-0.60	-1.97 – 0.7	0.389	-0.63	-2.01 – 0.76	0.368

Definitions and abbreviations: percent predicted forced expiratory volume in 1 s (ppFEV1), lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), Cystic Fibrosis Transmembrane conductance Regulator (CFTR). Time in years. # Adjusted for sex, age at baseline and the interaction effect between age at baseline with time. * Significance level < 0.05.

Supplementary table 1b. Bayesian linear mixed effects model estimates of ppFEV1.

Comparison of effects in participants who transitioned to TEZ/IVA and participants who continued LUM/IVA treatment (n=401, Years of observation=3844).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	66.33	63.16 – 69.48	<0.001	70.20	67.25 – 73.14	<0.001
Continuation LUM/IVA	Reference			Reference		
Transition TEZ/IVA	5.22	0.98 – 9.48	0.017*	1.64	-1.95 – 5.21	0.365
Time	-1.22	-1.51 – -0.94	<0.001*	-1.28	-1.56 – -1.00	<0.001*
Time : continuation LUM/IVA	Reference			Reference		
Time : transition TEZ/IVA	-0.28	-0.74 – 0.18	0.234	-0.17	-0.63 – 0.29	0.462
CFTR modulator	1.81	0.41 – 3.21	0.011*	1.79	0.37 – 3.21	0.014*
CFTR modulator : continuation LUM/IVA	Reference			Reference		
CFTR modulator : transition TEZ/IVA	-0.56	-2.47 – 1.34	0.562	-0.52	-2.46 – 1.39	0.593
Time : CFTR Modulator	1.01	0.22 – 1.80	0.016*	1.03	0.22 – 1.83	0.013*
Time : CFTR modulator : continuation LUM/IVA	Reference			Reference		
Time : CFTR modulator : transition TEZ/IVA	-0.26	-1.30 – 0.79	0.629	-0.27	-1.34 – 0.80	0.612

Adjusted for sex, age at baseline and the interaction effect between age at baseline and time. * Significance level < 0.05.

Supplementary table 1c. Bayesian linear mixed effects model estimates of ppFEV1.

Comparison of effects in females and males (n=401, Years of observation=3844).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	68.12	65.20 – 71.06	<0.001	70.89	68.39 – 73.38	<0.001
Male sex	Reference			Reference		
Female sex	2.30	-2.04 – 6.62	0.300	0.19	-3.37 – 3.75	0.918
Time	-1.35	-1.61 – -1.09	<0.001*	-1.38	-1.64 – -1.13	<0.001*
Time : male sex	Reference			Reference		
Time : female sex	0.01	-0.50 – 0.51	0.973	0.08	-0.42 – 0.58	0.762
CFTR modulator	1.43	0.15 – 2.70	0.028*	1.38	0.11 – 2.64	0.033*
CFTR modulator : male sex	Reference			Reference		
CFTR modulator : female sex	0.26	-1.67 – 2.19	0.797	0.32	-1.63 – 2.26	0.749
Time : CFTR Modulator	0.55	0.23 – 1.62	0.013*	0.97	0.27 – 1.65	0.011*
Time : CFTR modulator : male sex	Reference			Reference		
Time : CFTR modulator : female sex	-0.16	-1.24 – 0.91	0.767	-0.22	-1.29 – 0.86	0.685

Adjusted for age at baseline and the interaction effect between age at baseline and time. * Significance level < 0.05.

Supplementary table 1d. Bayesian linear mixed effects model estimates of ppFEV1.

Comparison of effects in adults >18 years and adolescents of 12-18 years (n=401, Years of observation=3844).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	86.22	82.66 – 89.77	<0.001	85.57	81.69 – 89.48	<0.001
Adolescents	Reference			Reference		
Adults	-24.08	-28.19 – -20.01	<0.001*	-24.01	-28.14 – -19.91	<0.001*
Time	-1.55	-1.91 – -1.18	<0.001*	-1.11	-1.91 – -1.18	<0.001*
Time : adolescents	Reference			Reference		
Time : adults	0.29	-0.18 – 0.75	0.215	0.29	-0.17 – 0.76	0.215
CFTR modulator	0.15	-1.60 – 1.91	0.881	0.14	-1.61 – 1.88	0.893
CFTR modulator : adolescents	Reference			Reference		
CFTR modulator : adults	1.95	-0.15 – 4.01	0.070	1.95	-0.14 – 4.04	0.067
Time : CFTR Modulator	0.48	-0.47 – 1.49	0.314	0.50	-0.46 – 1.45	0.289
Time : CFTR modulator : adolescents	Reference			Reference		
Time : CFTR modulator : adults	0.57	-0.59 – 1.72	0.334	0.55	-0.58 – 1.70	0.342

Adjusted for sex. * Significance level < 0.05.

Supplementary table 2a. Bayesian linear mixed effects model estimates of BMI in adults ≥ 19 years.

Subgroup analysis in participants with baseline ppFEV1 40-90% (n=214, Years of observation=1564)

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	21.35	21.03 – 21.66	<0.001	21.27	20.85 – 21.69	<0.001
Time	0.05	0.01 – 0.09	0.021*	0.06	0.02 – 0.11	0.008*
CFTR modulator	0.12	-0.05 – 0.30	0.175	0.14	-0.04 – 0.32	0.121
Time : CFTR Modulator	0.08	-0.04 – 0.20	0.212	0.13	-0.004 – 0.26	0.058

Definitions and abbreviations: body mass index (BMI) in kg/m². # Adjusted for sex, age at baseline and the interaction effect between age at baseline and time and between age at baseline, time and CFTR modulator treatment. * Significance level < 0.05.

Supplementary table 2b Bayesian linear mixed effects model estimates of BMI in adults ≥ 19 years.

Comparison of effects in participants who transitioned to TEZ/IVA and participants who continued LUM/IVA treatment (n=312, Years of observation=2317).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient	95% CI	P-value
Intercept	21.46	21.10 – 21.82	<0.001	21.40	21.00 – 21.81	<0.001
Continuation LUM/IVA	Reference			Reference		
Transition TEZ/IVA	-0.14	-0.66 – 0.38	0.604	-0.08	-0.60 – 0.44	0.765
Time	0.05	0.004 – 0.09	0.033*	0.07	0.02 – 0.11	0.005*
Time : continuation LUM/IVA	Reference			Reference		
Time : transition TEZ/IVA	0.03	-0.06 – 0.12	0.572	0.04	-0.05 – 0.13	0.350
CFTR modulator	0.28	0.01 – 0.44	0.038*	0.22	0.001 – 0.44	0.049*
CFTR modulator : continuation LUM/IVA	Reference			Reference		
CFTR modulator : transition TEZ/IVA	-0.20	-0.52 – 0.12	0.219	-0.20	-0.54 – 0.12	0.227
Time : CFTR Modulator	0.10	-0.04 – 0.25	0.147	0.14	-0.003 – 0.28	0.055
Time : CFTR modulator : continuation LUM/IVA	Reference			Reference		
Time : CFTR modulator : transition TEZ/IVA	-0.08	-0.28 – 0.12	0.434	-0.08	-0.27 – 0.10	0.387

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 < 0.05.

Supplementary table 2c Bayesian linear mixed effects model of BMI in adults ≥ 19 years.

Comparison of effect estimates in females and males (n=312, Years of observation=2317).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient	95% CI	P-value
Intercept	21.69	21.35 – 22.03	<0.001	21.32	20.95 – 21.69	<0.001
Male sex	Reference			Reference		
Female sex	-0.77	-1.29 – -0.25	0.004*	-0.71	-1.22 – -0.19	0.007*
Time	0.07	0.02 – 0.11	0.002*	0.09	0.05 – 0.14	<0.001*
Time : male sex	Reference			Reference		
Time : female sex	-0.04	-0.14 – 0.06	0.443	-0.04	-0.14 – 0.05	0.360
CFTR modulator	0.26	0.06 – 0.48	0.012*	0.26	0.05 – 0.48	0.016*
CFTR modulator : male sex	Reference			Reference		
CFTR modulator : female sex	-0.29	-0.62 – 0.03	0.078	-0.30	-0.63 – 0.03	0.078
Time : CFTR Modulator	0.03	-0.10 – 0.17	0.653	0.07	-0.07 – 0.20	0.330
Time : CFTR modulator : male sex	Reference			Reference		
Time : CFTR modulator : female sex	0.08	-0.12 – 0.29	0.432	0.08	-0.11 – 0.27	0.406

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 < 0.05.

Supplementary table 3a. Bayesian linear mixed effects model estimates of BMI Z-score in children < 19 years.

Subgroup analysis in participants with baseline ppFEV1 40-90% (n=147, Years of observation=941)

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient#	95% CI	P-value
Intercept	-0.71	-0.87 – -0.55	<0.001	-0.82	-1.09 – -0.54	<0.001
Time	-0.07	-0.10 – -0.05	<0.001*	-0.08	-0.12 – -0.05	<0.001*
CFTR modulator	-0.07	-0.28 – 0.14	0.502	0.01	-0.21 – 0.22	0.924
Time : CFTR Modulator	0.08	-0.04 – 0.19	0.181	0.09	-0.02 – 0.20	0.113

Definitions and abbreviations: BMI Z-score was normalized for age and sex and according to the WHO growth reference standard. # 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.

Supplementary table 3b Bayesian linear mixed effects model estimates of BMI Z-score in children < 19 years.

Comparison of effects in participants who transitioned to TEZ/IVA and participants who continued LUM/IVA treatment (n=225, Years of observation=1552).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient	95% CI	P-value
Intercept	-0.71	-0.89 – -0.53	<0.001	-0.87	-1.11 – -0.64	<0.001
Continuation LUM/IVA	Reference			Reference		
Transition TEZ/IVA	0.19	-0.001 – 0.38	0.051	0.12	-0.09 – 0.32	0.253
Time	-0.05	-0.08 – -0.01	0.011*	-0.07	-0.10 – -0.03	<0.001*
Time : continuation LUM/IVA	Reference			Reference		
Time : transition TEZ/IVA	-0.04	-0.08 – 0.005	0.083	-0.02	-0.07 – 0.02	0.283
CFTR modulator	0.16	-0.11 – 0.44	0.242	0.14	-0.17 – 0.44	0.375
CFTR modulator : continuation LUM/IVA	Reference			Reference		
CFTR modulator : transition TEZ/IVA	-0.17	-0.47 – 0.13	0.271	-0.11	-0.45 – 0.24	0.520
Time : CFTR Modulator	0.02	-0.21 – 0.26	0.862	0.11	-0.07 – 0.30	0.228
Time : CFTR modulator : continuation LUM/IVA	Reference			Reference		
Time : CFTR modulator : transition TEZ/IVA	0.11	-0.15 – 0.37	0.398	0.03	-0.18 – 0.23	0.786

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.

Supplementary table 3c Bayesian linear mixed effects model estimates of BMI Z-score in children < 19 years.

Comparison of effects in females and males (n=225, Years of observation=1552).

	Unadjusted coefficient	95% CI	P-value	Adjusted coefficient	95% CI	P-value
Intercept	-0.58	-0.73 – -0.42	<0.001	-0.83	-1.05 – -0.60	<0.001
Male sex	Reference			Reference		
Female sex	-0.05	-0.24 – 0.15	0.639	-0.05	-0.24 – 0.14	0.594
Time	-0.07	-0.10 – -0.04	<0.001*	-0.07	-0.09 – -0.04	<0.001*
Time : male sex	Reference			Reference		
Time : female sex	0.002	-0.04 – 0.05	0.919	0.004	-0.04 – 0.05	0.853
CFTR modulator	-0.14	-0.29 – 0.02	0.086	-0.11	-0.29 – 0.08	0.270
CFTR modulator : male sex	Reference			Reference		
CFTR modulator : female sex	0.33	0.09 – 0.56	0.007*	0.33	0.06 – 0.61	0.018*
Time : CFTR Modulator	0.10	-0.04 – 0.23	0.161	0.12	0.02 – 0.23	0.023*
Time : CFTR modulator : male sex	Reference			Reference		
Time : CFTR modulator : female sex	0.01	-0.19 – 0.21	0.898	0.03	-0.13 – 0.19	0.717

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.

Supplementary table 4a Negative binomial mixed effects model estimates of the duration of IV antibiotic treatment.

Comparison of effects in participants with baseline FEV1pp <40%, between 40-90% and >=90% (n=361, Years of observation=2827).

	Unadjusted coefficient	IRR	95% CI (IRR)	P-value	Adjusted coefficient	IRR	95% CI (IRR)	P-value
Intercept	2.01	7.49	4.82 – 11.63	<0.001	1.81	6.16	3.81 – 9.97	<0.001
ppFEV1 40-90%	Reference	Reference			Reference	Reference		
ppFEV1 <40%	1.08	2.96	1.04 – 8.44	0.043*	1.10	3.02	1.04 – 8.77	0.042*
ppFEV1 >=90%	-1.48	0.23	0.09 – 0.55	0.001*	-1.51	0.22		<0.001*
Time	0.09	1.09	0.99 – 1.20	0.080	0.09	1.09	0.99 – 1.20	0.079
Time : ppFEV1 40-90%	Reference	Reference			Reference	Reference		
Time : ppFEV1 <40%	0.02	1.02	0.78 – 1.34	0.879	0.03	1.03	0.78 – 1.35	0.851
Time : ppFEV1 >=90%	0.31	1.36	1.11 – 1.66	0.003*	0.31	1.36	1.11 – 1.66	0.003*
CFTR modulator	-1.19	0.30	0.19 – 0.48	<0.001*	-1.20	0.30	0.19 – 0.47	<0.001*
CFTR modulator : ppFEV1 40%-90%	Reference	Reference			Reference	Reference		
CFTR modulator : ppFEV1 <40%	0.01	1.01	0.34 – 3.01	0.990	0.03	1.03	0.34 – 3.14	0.954
CFTR modulator : ppFEV1 >=90%	-0.08	0.92	0.36 – 2.34	0.866	-0.07	0.93	0.36 – 2.39	0.881
Time : CFTR modulator	0.25	1.29	0.97 – 1.70	0.077	0.26	1.30	0.98 – 1.72	0.071
Time : CFTR modulator : ppFEV1 40-90%	Reference	Reference			Reference	Reference		
Time : CFTR modulator : ppFEV1 <40%	0.12	1.12	0.58 – 2.18	0.730	0.10	1.10	0.56 – 2.16	0.774
Time : CFTR modulator : ppFEV1 >=90%	-1.04	0.35	0.17 – 0.73	0.005*	-1.03	0.36	0.17 – 0.75	0.006*

Definitions and abbreviations: intravenous (IV). Coefficients are on the log-scale. Incidence rate ratios (IRR) are transformed back to the original scale. #

Adjusted for age at baseline and sex. * Significance level < 0.05.

Supplementary table 4b Negative binomial mixed effects model estimates of the duration of IV antibiotic treatment.

Comparison of effects in participants who transitioned to TEZ/IVA and participants who continued LUM/IVA treatment (n=364, Years of observation=2848).

	Unadjusted coefficient	IRR	95% CI (IRR)	P-value	Adjusted coefficient#	IRR	95% CI (IRR)	P-value
Intercept	1.81	6.13	3.43 – 10.97	<0.001	1.54	4.64	2.53 – 8.54	<0.001
Continuation LUM/IVA	Reference	Reference			Reference	Reference		
Transition TEZ/IVA	-0.04	0.96	0.45 – 2.03	0.914	-0.03	0.97	0.46 – 2.07	0.944
Time	0.21	1.23	1.08 – 1.41	0.002*	0.21	1.23	1.08 – 1.41	0.002*
Time : continuation LUM/IVA	Reference	Reference			Reference	Reference		
Time : transition TEZ/IVA	-0.09	0.91	0.77 – 1.08	0.284	-0.09	0.91	0.77 – 1.08	0.277
CFTR modulator	-1.47	0.23	0.13 – 0.41	<0.001*	-1.49	0.23	0.13 – 0.40	<0.001*
CFTR modulator : continuation LUM/IVA	Reference	Reference			Reference	Reference		
CFTR modulator : transition TEZ/IVA	0.31	1.37	0.64 – 2.90	0.415	0.34	1.40	0.66 – 2.97	0.375
Time : CFTR Modulator	0.16	1.18	0.81 – 1.71	0.391	0.17	1.19	0.82 – 1.73	0.361
Time : CFTR modulator : continuation LUM/IVA	Reference	Reference			Reference	Reference		
Time : CFTR modulator : transition TEZ/IVA	-0.01	0.99	0.61 – 1.60	0.969	-0.02	0.98	0.61 – 1.58	0.937

Adjusted for age at baseline and sex. * Significance level < 0.05.

Supplementary table 4c Negative binomial mixed effects model estimates of the duration of IV antibiotic treatment.

Comparison of effects in females and males (n=364, Years of observation=2848).

	Unadjusted coefficient	IRR	95% CI (IRR)	P-value	Adjusted coefficient	IRR	95% CI (IRR)	P-value
Intercept	1.57	4.81	2.85 – 8.12	<0.001	1.51	4.53	2.68 – 7.66	<0.001
Male sex	Reference	Reference			Reference	Reference		
Female sex	0.46	1.58	0.75 – 3.31	0.226	0.50	1.65	0.79 – 3.45	0.186
Time	0.15	1.16	1.03 – 1.30	0.014*	0.15	1.16	1.03 – 1.30	0.015*
Time : male sex	Reference	Reference			Reference	Reference		
Time : female sex	0.001	1.00	0.85 – 1.78	0.984	0.002	1.00	0.85 – 1.78	0.977
CFTR modulator	-1.46	0.23	0.14 – 0.39	<0.001*	-1.45	0.23	0.14 – 0.39	<0.001*
CFTR modulator : male sex	Reference	Reference			Reference	Reference		
CFTR modulator : female sex	0.38	1.47	0.70 – 3.08	0.312	0.37	1.45	0.69 – 3.05	0.325
Time : CFTR Modulator	0.28	1.32	0.96 – 1.80	0.084	0.28	1.32	0.97 – 1.81	0.081
Time : CFTR modulator : male sex	Reference	Reference			Reference	Reference		
Time : CFTR modulator : female sex	-0.24	0.78	0.49 – 1.26	0.313	-0.25	0.78	0.49 – 1.25	0.297

Adjusted for age at baseline. * Significance level < 0.05.

Supplementary table 4d Negative binomial mixed effects model estimates of the duration of IV antibiotic treatment.

Comparison of effects in adults >18 years and adolescents of 12-18 years (n=364, Years of observation=2848).

	Unadjusted coefficient	IRR	95% CI (IRR)	P-value	Adjusted coefficient#	IRR	95% CI (IRR)	P-value
Intercept	1.49	4.45	2.21 – 8.95	<0.001	2.25	9.49	4.91 – 18.33	<0.001
Adolescents	Reference	Reference			Reference	Reference		
Adults	0.38	1.46	0.65 – 3.30	0.361	0.36	1.44	0.68 – 3.03	0.341
Time	0.24	1.28	1.10 – 1.48	0.001*	0.22	1.25	1.07 – 1.45	0.005*
Time : adolescents	Reference	Reference			Reference	Reference		
Time : adults	-0.14	0.87	0.73 – 1.04	0.122	-0.10	0.90	0.75 – 1.09	0.284
CFTR modulator	-1.61	0.20	0.10 – 0.40	<0.001*	-1.08	0.34	0.16 – 0.71	0.004*
CFTR modulator : adolescents	Reference	Reference			Reference	Reference		
CFTR modulator : adults	0.48	1.62	0.71 – 3.71	0.252	-0.03	0.97	0.40 – 2.35	0.948
Time : CFTR Modulator	0.04	1.04	0.66 – 1.64	0.855	0.10	1.11	0.68 – 1.79	0.685
Time : CFTR modulator : adolescents	Reference	Reference			Reference	Reference		
Time : CFTR modulator : adults	0.17	1.19	0.70 – 2.02	0.516	0.16	1.17	0.67 – 2.06	0.583

Adjusted for sex. * Significance level < 0.05.

Supplementary figure 1. Comparison of longitudinal ppFEV1 trends before and after CFTR modulator initiation in subgroups with baseline ppFEV1 <40%, between 40-90% and ≥90%.

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 shown between square brackets. **Panel 1a**: The impact of CFTR modulator use in the subgroup with baseline ppFEV1 40-90% was demonstrated by an acute change from baseline ppFEV1 of 2.59% (95% CI: 1.40 – 3.78%, p<0.001) in addition to an improvement in ppFEV1 decline of 0.81% per year, 95% CI: 0.11 – 1.50%, p=0.026); Supplementary table 1a) that was comparable to the main analysis. **Panel 1b**: Compared to the group with baseline ppFEV1 40-90% (black lines), the average estimated change in ppFEV1 decline after CFTR modulator initiation was on average even 1.40% per year higher (95% CI -0.0001 - 2.82%, p=0.050; Supplementary table 1a) in the group with baseline ppFEV1 <40% (grey lines). In the group with baseline ppFEV1 ≥90% (dark blue lines), a longitudinal decline in ppFEV1 was not observed.

Supplementary figure 2. Comparison of longitudinal BMI and BMI Z-score trends before and after CFTR modulator initiation in subgroup with baseline ppFEV1 between 40-90%.

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 reported between square brackets. **Panel 2a**: In adults ≥19 years, BMI trend before and after CFTR modulator initiation in this subgroup was comparable to the observed overall trends, with a change in annual BMI of 0.13 (95% CI: -0.04 – 0.32, p=0.058) after CFTR modulator initiation (Supplementary table 2a). **Panel 2b**: Trends of BMI Z-score in children <19 years were similar to the entire population,

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 3a).

Supplementary figure 3. Comparison of longitudinal trends in IV antibiotic treatment duration before and after CFTR modulator initiation in subgroups with baseline ppFEV1 <40%, between 40-90% and ≥90%.

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 reported between square brackets. **Panel 3a**: trends in the average annual duration of IV antibiotic treatment (in days) were comparable to the overall population, although the average duration of received IV antibiotics in the last year preceding CFTR modulator initiation was slightly higher (6.16 days, 95% CI: 5.32 – 15.38 days; Supplementary table 4a). **Panel 3b**: Compared to the group with baseline ppFEV1 40-90% (black lines), average trends of participants with a baseline ppFEV1 <40% (grey lines) were comparable to participants with baseline ppFEV1 40-90%, but the average IV antibiotic treatment duration in participants with a baseline ppFEV1 ≥90% (dark blue lines) was considerably lower and did not increase after CFTR modulator initiation (Supplementary table 4a).

ONLINE SUPPLEMENTARY MATERIALS & METHODS

Statistical model specification

ppFEV1

A linear mixed effects model was used to assess longitudinal trends in ppFEV1 before and after CFTR modulator initiation. The model included a random intercept per subject and random slopes for time, CFTR modulator treatment status and the interaction between time and CFTR modulator treatment status, using an unstructured covariance matrix. As fixed effects we included time, CFTR modulator treatment status and the interaction between time and CFTR modulator treatment status in the unadjusted model. The fixed effect for time represented ppFEV1 decline in the years before CFTR modulator use and the interaction of time : CFTR modulator treatment reflected ppFEV1 decline after CFTR modulator initiation. Age at baseline (centered to median) and sex were considered as (potential) confounders, as ppFEV1 decline is associated with age [1, 2] and could be different between males and females [3]. We used stepwise forward selection to test these variables as two-way interaction terms with time and as three-way interactions with time : CFTR modulator treatment. The interaction terms that significantly improved model fit, indicating a significant association, were included in the final adjusted model.

For the subgroup analyses, the same linear mixed effects models were built, including additional interaction terms of time, CFTR modulator treatment and time : CFTR modulator treatment with 1) baseline ppFEV1 category (<40%, between 40-90% and ≥90%); 2) age category (adults > 18 years and adolescents 12-18 years); 3) CFTR modulator transition to TEZ/IVA or continuation of LUM/IVA; and 4) female or male sex.

BMI and BMI Z-score

Following the same approach, the analyses of BMI and BMI Z-score were performed in data subsets including measurements at an age above and below 19 years, respectively, based on WHO growth reference guidelines for normalization of BMI Z-score. These linear mixed effects models included a random intercept per subject and random slopes for time and the interaction between time and CFTR modulator treatment status. Time, CFTR modulator treatment status and the interaction between time and CFTR modulator treatment status were added as fixed effects in the unadjusted models. In addition, main effects and statistically significant interaction terms with sex and age at baseline (centered to median) were added to the adjusted models. As the data subsets for BMI and BMI Z-score were already divided by age category and were too small to allow for subgroup analysis with baseline ppFEV1 categories, we only conducted additional subgroup analysis for the transition or continuation of CFTR modulator type and for sex.

IV antibiotic treatment duration

Changes in the annual duration of IV antibiotic treatment were analyzed with a negative binomial mixed effects model. A random intercept per subject was included, assuming an unstructured covariance matrix. As fixed effects in the unadjusted model, we included time, CFTR modulator treatment status and the interaction between time and CFTR modulator treatment status, which reflected the change in duration of IV antibiotic treatment in the years after CFTR modulator initiation. Finally, main effects and statistically significant interaction terms with sex and age at baseline (centered to median) were added to the adjusted models. Similar to ppFEV1, additional subgroup analyses were performed using negative binomial mixed effects models with same structure as the main model.

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