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.

REFERENCES

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