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ORIGINAL ARTICLE

# Real-life efficacy and safety of elexacaftor/tezacaftor/ivacaftor on severe cystic fibrosis lung disease patients

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## Abstract

Elexacaftor/tezacaftor/ivacaftor (ETI) is a cystic fibrosis (CF) transmembrane conductance regulator modulator, which has shown efficacy in CF patients (≥6 years) with ≥1 Phe508del mutation and a minimal function mutation. In October 2019, ETI became available on compassionate use basis for Dutch CF patients with severe lung disease. Our objective was to investigate safety and efficacy of ETI in this patient group in a real-life setting. A multicenter longitudinal observational study was conducted to examine changes in $FEV_1$, BMI, and adverse events at initiation and 1, 3, 6, and 12 months after starting ETI. The number of exacerbations was recorded in the 12 months before and the 12 months after ETI treatment. Patients eligible for compassionate use had a $FEV_1$ <40% predicted. Wilcoxon signed-rank test analyzed changes over time. Twenty subjects were included and followed up for up to 12 months after starting ETI. Treatment was well tolerated with mild side effects reported, namely, rash (15%) and stomach ache (20%) with 80% resolving within 1 month. Mean absolute increase of $FEV_1$ was 11.8/13.7% ($p \leq .001$) and BMI was 0.49/1.87 kg/m$^2$ ($p < .001$–0.02) after 1/12 months, respectively. In comparison to the number of exacerbations pretrial, there was a marked reduction in exacerbations after initiation. Our findings show long-term effects of treatment with ETI in patients with severe CF lung disease in a real-life setting. Treatment with ETI is associated with increased lung function and BMI, less exacerbations, and only mild side effects.

**KEYWORDS**
cystic fibrosis, elexacaftor/tezacaftor/ivacaftor, modulators, sputum

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; ETI, Elexacaftor/tezacaftor/ivacaftor; GGT, gamma-glutamyl transferase; $ppFEV_1$, percent predicted forced expiratory volume in 1 s.

## 1 | INTRODUCTION

Cystic fibrosis (CF) is a recessively inherited, progressive, multiorgan disease that is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene: an ion channel facilitating chloride transport. The protein can be missing, misfolded, or malfunctioning depending on the different classes of mutations.[1] The Phe508del mutation is the most common, approximately 85% of CF patients have at least one copy, for the Netherlands this is 90.8%.[2,3]

Patients with a Phe508del mutation are eligible for CFTR modulators: small molecules that act to correct (correctors) or restore (potentiators) the defective CFTR protein. Recently, a combination of two correctors and a potentiator, elexacaftor/tezacaftor/ivacaftor (ETI), has been proven safe and effective for patients who are either homozygous or heterozygous for the Phe508del mutation in large phase III trials.[4,5] These trials showed that the treatment with ETI resulted in substantial improvements in lung function, sweat chloride concentration, respiratory-related quality of life, and nutritional parameters when compared with placebo or tezacaftor/ivacaftor. These trials led to the compassionate use program and early access to ETI for CF patients with severe lung disease in Europe. While the trial results are very promising, patients' eligibility for phase III trials was dependent on having a percent predicted forced expiratory volume in 1 s ($ppFEV_1$) of 40%–90%. Consequently, this could lead to misrepresentation of patients with severe lung disease.[4,5] In addition, long-term assessment of efficacy was limited with a maximum follow-up of 24 weeks.

This study evaluated the safety and efficacy of ETI in patients with CF who have at least one Phe508del CFTR mutation and had severe lung disease ($ppFEV_1$ <40%) in a prospective, real-life, observational study with a long-term (12 months) follow-up. We hypothesized that CF patients with severe lung disease are likely to benefit from ETI treatment.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and subjects

This study was a two centers observational study, aimed at evaluating the efficacy and safety of ETI treatment in a real-life setting in the Netherlands. The Institutional Research Board of the Academic Medical Center approved the study (#2019_179). Patients were recruited from the Amsterdam Medical Centres and the Radboud University Medical Center between 2019 and 2020. Written informed consent was obtained from all patients, or in the case of minors, from their legal guardian, before data collection.

There were no inclusion or exclusion criteria other than being applicable for the compassionate use program and willingness to participate. The compassionate use program required patients to meet the following criteria: (1) $ppFEV_1$ is <40% for a minimum of 2 months before the date of completion of the ETI request form and/or (2) documentation of being active on a lung transplant waiting list or documentation of being evaluated for lung transplantation, but deemed unsuitable because of contraindications.

All patients were invited for regular three monthly outpatient clinic visits, including clinical assessment and pulmonary function tests. Study visits were combined with regular visits at treatment initiation and at 3, 6, and 12 months after starting treatment; if a patient also presented at the outpatient clinic at 1 month, the data were collected as well. Weight, height, BMI, and $ppFEV_1$ were recorded at each visit. Patients were invited to fill in the CFQ-R questionnaire: a quality-of-life questionnaire with 12 domains, an increase of four points was considered clinically significant.[6] Patients were offered the choice between paper and digital version. Adverse events were reported by patient or physician, and recorded in an electronic case report form. The number of exacerbations was recorded in the 12 months prior and the 12 months post ETI initiation. Clinical laboratory assessment at each visit included, but was not limited to, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) according to the ETI guidance documentation.

### 2.2 | Statistics

Data were presented as percentage and number, *N* (%); median (interquartile range [IQR]); or mean ± SD. Intragroup comparisons of change in $ppFEV_1$, BMI, and CFQ-R respiratory domain score (from baseline to 1, 3, 6, and 12 months of follow-up) were performed using the Wilcoxon paired test, according to an intention to treat analysis. The individual patient response was defined as an increase per day, as calculated by the individual slope from a mixed effect model. Individual slopes were entered in a heatmap to group patients between high and low responders based on relative *z* score. The comparison of the paired McNemar's test was used to assess a change in frequencies over time. A $p < .05$ was considered statistically significant. All analyses were performed using Rstudio version 3.6.2 (SAS Institute, Inc.).

## 3 | RESULTS

### 3.1 | Patient population

In total, 20 of the 21 invited patients were included; one patient was excluded as COVID-19 restrictions made it impossible to perform baseline measurements. One patient was lost to follow-up due to transfer to another hospital, all other patients finished the 12 months follow-up. Patient characteristics are described in Table 1. Six patients were on the transplant list, all of them had their status changed to inactive due to the effect of ETI.

### 3.2 | Efficacy

Treatment with ETI resulted in significant increase in absolute change in $ppFEV_1$ at 1 month, with a mean increase of 11.8% point

**TABLE 1** Baseline patient characteristics, reported as *n* (%) or mean ± SD

| | *N* = 20 | |
|---|---|---|
| Twelve-month follow-up—*n* (%) | 19 | (85.0) |
| Lost to follow-up—*n* (%) | 1 | (5.0) |
| Treatment discontinued—*n* (%) | 0 | (0) |
| Female sex—*n* (%) | 12 | (63.2) |
| Age | | |
| Age in years—mean ± SD | 20.5 | ±8.1 |
| 12 to <18 years—*n* (%) | 6 | (30.0) |
| Heterozygous F508del—*n* (%) | 8 | (42.1) |
| CFRD—*n* (%) | 8 | (42.1) |
| Pancreatic insufficiency—*n* (%) | 14 | (73.7) |
| Body mass index (kg/m$^2$)—mean ± SD | 18.5 | ±3.0 |
| ppFEV$_1$—mean ± SD | 31.3 | ±5.1 |
| ppFVC—mean ± SD | 53.1 | ±15.9 |
| CFTR modulator history—*n* (%) | | |
| Naïve | 9 | (45) |
| Lumacaftor/ivacaftor | 2 | (10) |
| Tezacaftor/ivacaftor | 9 | (45) |
| Medication—*n* (%) | | |
| Acetylcysteine | 2 | (10.0) |
| Hypertonic saline | 7 | (35.0) |
| Dornase alfa | 15 | (75.0) |
| Bronchodilator | 11 | (55.0) |
| Corticosteroid inhalation | 6 | (30.0) |
| Inhaled antibiotics | 10 | (50.0) |
| Oral antibiotics | 12 | (60.0) |
| Ursodeoxycholic acid | 4 | (20.0) |
| Pancreatic enzymes | 18 | (90.0) |
| Vitamins | 18 | (90.0) |
| H2-receptor antagonists | 4 | (20.0) |
| Proton pump inhibitors | 9 | (45.0) |
| Other medication | 4 | (20.0) |
| Chronic infection—*n* (%)[a] | | |
| *Achromobacter* species | 5 | (27.8) |
| *Aspergillus fumigatus* | 5 | (27.8) |
| *Burkholderia* species | 2 | (11.1) |
| *Haemophilus influenzae* | 3 | (16.7) |
| *Pseudomonas aeruginosa* | 6 | (33.3) |
| *Staphylococcus aureus* | 7 | (38.9) |

Abbreviations: CFRD, CF-related liver disease; CFTR, CF transmembrane conductance regulator; H2, histamine 2; ppFEV$_1$, percent predicted forced expiratory volume in 1 s; ppFVC, percent predicted forced vital capacity.

[a]Potentially >1 cultured pathogen per patient.

relative to baseline ($p = .001$). Sustained increase in absolute change in ppFEV$_1$ was seen through 3, 6, and 12 months, with a mean increase of 11.7%, 14.4%, and 13.7%, respectively, to baseline ($p \leq .001$) (Figure 1A). No significant difference was seen between visits at 3, 6, and 12 months (Table S1). All patients, in both heterozygous and homozygous Phe508del patient groups, showed an increase in ppFEV$_1$ from baseline during follow-up, it was not possible to perform any statistics to compare the two groups (Figure 1B). Individual responses ranged from 0.3% to 7.8% point increase per 100 days (Table S2).

Treatment with ETI resulted in a significant increase in absolute change in BMI after 1 month, with a mean increase of 0.49 kg/m$^2$ relative to baseline ($p = .017$). A sustained increase in absolute change in BMI was seen through 3, 6, and 12 months, with a mean increase of 1.11, 1.58, and 1.87 kg/m$^2$, respectively, to baseline ($p \leq .002$) (Figure 1C). There was a statistically significant difference between all visits except one; there was no significant difference between 6 and 12 months (Table S1). Nineteen patients showed an increase in BMI from baseline during follow-up, one homozygous Phe508del patient did not show an increase in BMI after initiation of ETI treatment (Figure 1D).

The CFQ-R respiratory domain score improved significantly through follow-up, with a mean increase of 32.3 points relative to baseline ($p = 0.002$) (Figure 2A). Similar results were found for the physical, treatment, health, social, and body domain scores, with a statistically significant increase of 27.9, 15.5, 25.1, 17.34, 9.93 points relative to baseline, respectively (Figure 2A and Table S3). The score on the CFQ-R question, "In the last two weeks, have you had to cough up mucus," significantly increased ($p \leq .007$) over time, indicating that patients had to cough up less mucus (Figure 3A). The same is reflected by the patients' ability to produce sputum for culture during their outpatient visit, this was 80% at the initiation visit, and reduced to 60% after 3 months ($p = .03$), 44% after 6 months ($p = .05$), and 58% after 12 months ($p = 0.01$).

The number of exacerbations per patient in 1 year after ETI initiation (mean 0.19 ± 0.4) was significantly lower ($p < 0.001$) compared to the number before ETI initiation (mean 2.89 ± 1.6). The same is true for number of exacerbations in 1 year that lead to hospitalizations, this was 1.41 ± 1.4 before and 0 ± 0 after ETI initiation ($p = 0.001$) (Figure 2B).

Patients were grouped into high and low responders for treatment with ETI (Figure 4A). Characteristics of the groups, including data on pathogen cultures during the last visit, are described in Table S4, no parameters where significantly different between groups. All children were clustered in the high responders group. Patients with a *Burkholderia* infection were more often clustered in the low responders group, while patients with an *Aspergillus fumigatus* infection were more often clustered in the high responders group. The majority of patients were either low or high responders on all outcome parameters. However, for some individuals, treatment with ETI had a larger effect on the quality of life (according to CFQ) and a lower effect on the clinical parameters (Figure 4A, column 6), and vice versa (columns 6, 15). Increase in ppFEV$_1$ was correlated to an increase in FVC (R: 0.91, 95% CI: 0.78–0.97), an increase in BMI (R: 0.56, 95% CI: 0.49–0.53), as well as an increase in the health CFQ-R domain (R: 0.49, 95% CI: 0.04–0.77) (Figure 4B).

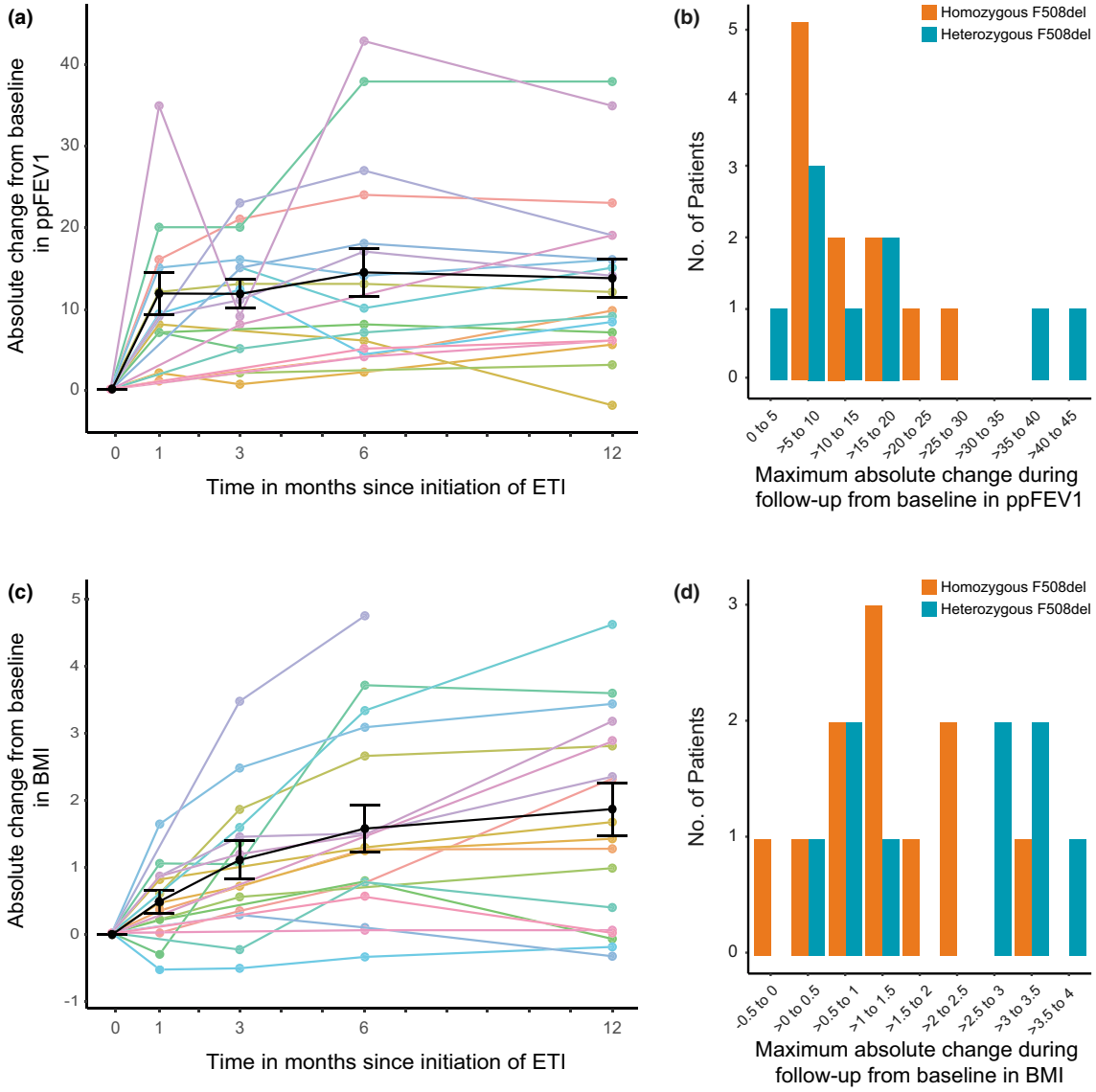


**FIGURE 1** Absolute change from baseline in $ppFEV_1$ and BMI. (A) Absolute change from baseline in $ppFEV_1$ over time, since initiation of ETI treatment. Displayed as mean with error bars indicating standard error of the mean (black), and per individual (color). (B) The maximum absolute change during follow-up from baseline in $ppFEV_1$, per individual. Grouped by genetic mutation. (C) Absolute change from baseline in BMI over time since initiation of ETI treatment, displayed as mean with error bars indicating standard error of the mean (black), and per individual (color). (D) The maximum absolute change during follow-up from baseline in BMI, per individual. Grouped by genetic mutation. BMI, body mass index; ETI, elexacaftor/tezacaftor/ivacaftor; $ppFEV_1$, percent of predicted forced expiratory volume in 1 s.

### 3.3 | Safety

Table 2 provides an overview of adverse events reported during the study. Eleven (55%) patients had at least one therapy-related adverse event, excluding pulmonary exacerbations, which were not seen as an adverse event, but as a symptom of the disease. Stomach ache (20%) and rash (15%) were the most common presentation. All adverse events were reported as either mild or moderate in severity with the large majority resolving during the study. No serious adverse events occurred. No patients discontinued the treatment.

Based on the experience with ETI treatment, including the phase III trials, data related to aminotransferase levels were reviewed. Elevated levels of ALT or AST occurred in 8 (40%) and 4 (20%) patients, respectively. No patient had an elevated aminotransferase level greater than three times the upper limit of normal during the follow-up period.

Additional observations included elevated levels of GGT and ALP in 4 (20%) and 9 (45%) patients, respectively. Less patients had elevated white blood cell counts after treatment with ETI ($p < .001$): 2 (10%) patients had elevated levels during follow-up, compared to 7 (35%) patients at baseline. Similar results were shown for elevated C-reactive protein levels ($p < .001$): 2 (10%) patients had elevated levels during follow-up, compared to 14 (70%) patients at baseline.

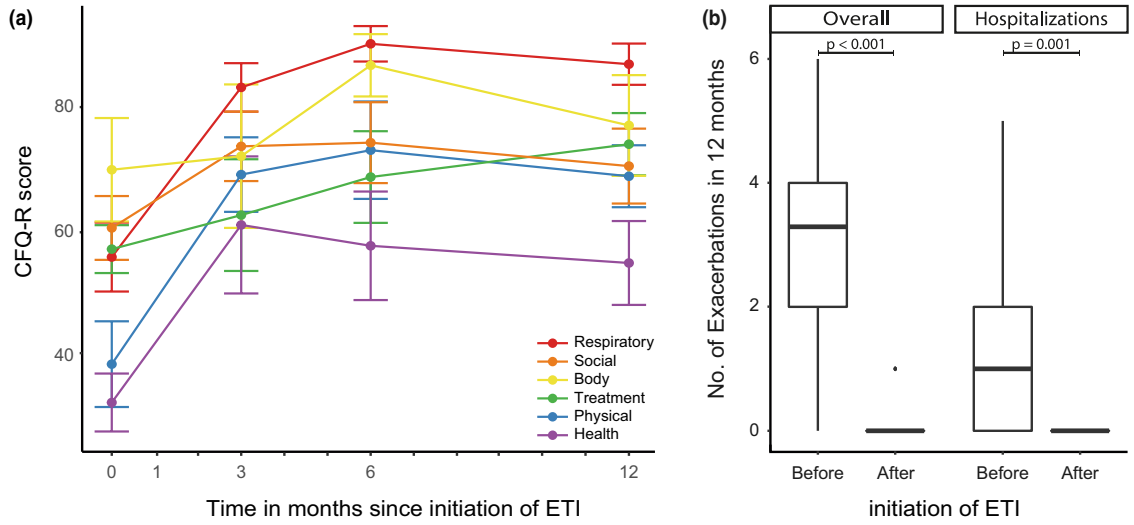


**FIGURE 2** CFQ-R score and exacerbations. (A) The CFQ-R score per domain normalized from 1 to 100, 100 being the maximum score indicating a higher quality of life. (B) Occurrence of exacerbations during study period. Exacerbations that lead to hospitalizations are marked in dark gray.

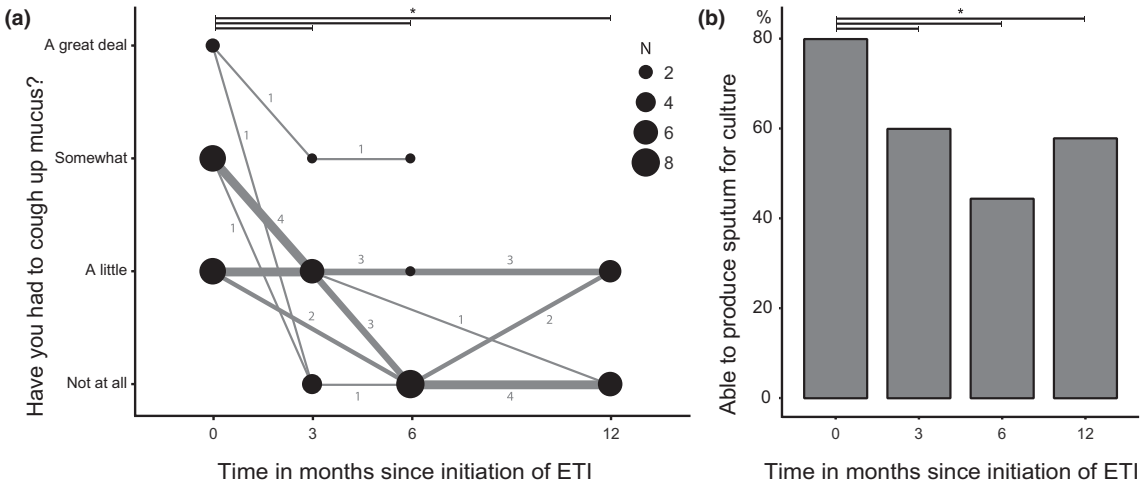


**FIGURE 3** CFQ-R and sputum. (A) Answers to the CFQ-R question "During the past 2 weeks—Have you had to cough up mucus?" lines represent paired answers form the same participant. Not all samples are paired due to missing data. (B) Ability to expectorate sputum for clinical cultures during the outpatient clinic visits. *$p \leq .05$.

## 4 | DISCUSSION

In this study, we examined the 12 months safety and efficacy of ETI in a real-life setting for CF patients with ppFEV$_1$ <40%. The study showed an increased ppFEV$_1$ and BMI, better quality of life, reduced sputum production, and reduced numbers of pulmonary exacerbations. Therapy resulted in mild side effects that resolved quickly. Severe CF lung disease patients tolerated ETI treatment well.

No patients discontinued their treatment in this study. This is in line with the phase III trials for homozygous and heterozygous Phe508del patients who reported a discontinuation rate of 0% and 1%, respectively.[4,5] Thus, severe CF lung disease patients showed similar tolerance to ETI treatment as compared to CF patients with a ppFEV$_1$ >40%. This is unique to ETI and not seen for other CFTR modulators, where severe CF lung disease patients had higher discontinuation rates as compared to the clinical trials.[7–9] This difference is most likely explained by the greater beneficial effect of ETI as compared to alternative CFTR modulators.[10,11] Our findings support the notion that severe CF lung disease patients should receive ETI.

The current study showed an increase in FEV$_1$ for both homozygous and heterozygous patient cohorts. In addition, our study has shown that these improvements were sustained for up to 12 months for both groups with severe lung disease. This is in line with the postapproval study of Nichols et al.[12] who showed similar results for 6 months after initiation. Furthermore, the study by Carnovale et al. studied the 48 weeks effect of ETI, but only included homozygous patients.[13] They showed a 14.48% point increase at 48 weeks, compared to 13.7% point increase displayed in

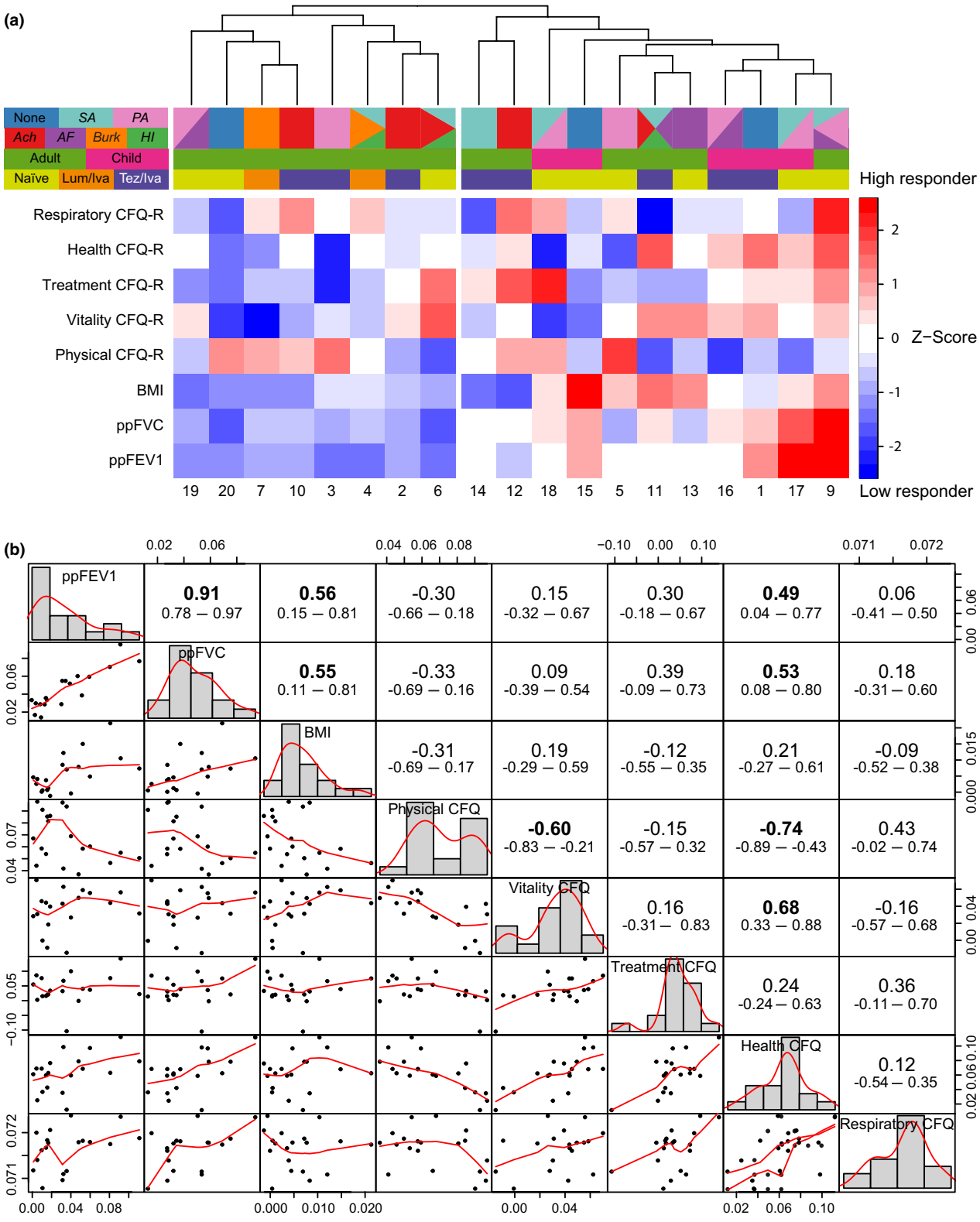


**FIGURE 4** Heatmap and correlation matrix of maximum response per outcome measures. (A) Heatmap of individual response per outcome measure. Each column represents an individual patient; each row represents a different numerical outcome measure. Fill colors range from "blue" being low responders to "red" being high responders. The upper colored bars describe whether a patient had an infection at baseline, if a patient is adult, and if they have a CFTR modulator history. (B) Correlation matrix of different numerical outcome measures. The top-right boxes depict the correlation coefficient, including 95% confidence interval, the bottom-left a scatterplot of the outcomes, the diagonal show a histogram of each outcome measure. Ach, *Achromobacter*; AF, *Aspergillus fumigatus*; BMI, body mass index; Burk, *Burkholderia*; HI, *Haemophilus influenzae*; Lum/Iva, lumacaftor/ivacaftor; PA, *Pseudomonas aeruginosa*; ppFEV$_1$, percent of predicted forced expiratory volume in 1 s; ppFVC, percent of predicted forced vital capacity; SA, *Staphylococcus aureus*; Tez/Iva, tezacaftor/ivacaftor.

TABLE 2 Adverse events

| | 0–3 months | | >3 months | |
|---|---|---|---|---|
| | *N* | (%) | *N* | (%) |
| Rash | 3 | (15) | | |
| Dry/irritated eyes | 2 | (10) | 2 | (10) |
| Hair loss | 1 | (5) | | |
| Hypercholesterolemia | | | 1 | (5) |
| Abnormal blood sugar | 2 | (10) | | |
| Stomach ache | 4 | (20) | | |
| Flatulence | 1 | (5) | | |
| Diarrhea | 2 | (10) | | |
| Discolored stool | 2 | (10) | | |
| Headache | 2 | (10) | | |
| Dizziness | 2 | (10) | | |

this study. Thus, this study validates that the effect of ETI maintains for 12 months in both homozygous and heterozygous severe CF lung disease patients.

ETI treatment reduced the sputum production during this study. This did not only manifest in the ability of the patients to produce sputum for clinical cultures, but it also had a positive effect in their daily lives. A reduction in sputum production has been mentioned earlier in a case report,[14] but this parameter has not been included as an outcome measure in other studies. It is important to be aware that the ability to produce sputum for clinical cultures does not reflect the ease by which it is expectorated, for which the quality of life question is a better surrogate marker. Furthermore, the amount of sputum produced per clinical sample is not taken into account. The reduced ability to cough up sputum provides diagnostic challenges for pathogen colonization detection, but should be considered a positive effect for the patients.

Large fluctuations are shown between individual responses to ETI treatment for severe CF lung disease patients and discrepancies were seen between the QOL scores and clinical response. We hypothesize that these discrepancies are most likely due to different impacts in daily life. For some patients the treatment made it possible to play more sports, or be more active with their kids, which would increase the QOL scores. For others, the improved lung function did not lead to major changes in their daily lives. Furthermore, we hypothesize that the large fluctuations could be attributed to the severity of structural damage to the lungs. Severe CF lung disease patients display a wide spectrum of structural abnormalities in the lungs as identified on CT scans: this ranges from air trapping to infection and/or inflammation-related changes.[15] Any irreversible lung damage will not be improved by ETI treatment. Thus, the extent of preexisting damage is a potential factor for response to treatment. In this study, we were able to group the patients into high and low responders. While no statistically significant differences were found between groups, it shows a potential correlation between age at ETI initiation and the effect of treatment. In addition, airway pathogen colonization and infection, namely *Burkholderia*, could potentially impair treatment response and explain the fluctuations observed. Severe CF lung disease patients show differences in the respiratory microbiome compared to milder CF phenotypes, these differences are associated with antibiotic resistance.[16] If persistent infections hinder clinical improvement, this might have implications on the treatment effect. Consequently, our results indicate the need for focusing on early detection of bacterial infections and a precision medicine approach to optimize treatment for individual patients. A larger cohort study could further investigate interindividual differences and predictors of response to ETI treatment to aid a personalized medicine approach.

This study was conducted in CF expertise centers as established by The Netherlands Federation of University Medical Centres. The study was performed and funded independently from the ETI manufacturer. All data were collected as part of routine clinical surveillance (e.g., spirometry, weight and BMI, and laboratory results). Another strength of this study was the follow-up period for 12 months. However, this study was limited by the COVID-19 pandemic, resulting in missing data since some outpatient clinic visits were replaced with video consultations during the patient follow-up. For some patients, home monitoring of lung function was possible to reduce missing values; however, this may have led to underestimation of $ppFEV_1$ due to the lack of support from the lung function technician.[17] Moreover, the COVID-19 pandemic potentially affected the exacerbation rate of the patients, but a drop in exacerbation rate has previously been shown before the COVID-19 pandemic.[18] This study also lacks data on medical adherence to assess the effect on lung function; patients were only interviewed about their use of ETI treatment. Another limitation to this study is the lack of control group; this was not feasible due to ethical considerations. Finally, this study is limited by its sample size due to the small cohort of patients that meet the compassionate use criteria. Nonetheless, due to the large effect size we were able to reproduce the results of the large clinical trials in our dataset.

In summary, this real-life study on CF patients with severe lung disease showed that treatment with ETI leads to a significant increase in lung function ($ppFEV_1$) and weight gain (BMI). Additionally, ETI treatment was well tolerated with mild side effects and led to an increased quality of life as reported by the patients and a reduced number of exacerbations and subsequent hospitalizations. The effects were maintained for 12 months, but long-term studies are necessary to investigate any drop-off in treatment effect. Nonetheless, this study supports the notion that ETI treatment will also benefit CF patients with severe lung disease.

## AUTHOR CONTRIBUTIONS

RK, AHN, PB, SEMV, CJM, LDB, EGH, and AHM contributed to the conception and design of the work. Data acquisition and analysis were carried out by RK, AHN, RL, JR, MHR, SWJT, JA, and CJM. RK, AHN, PB, DWF, EGH, and AHM interpreted the data. All authors drafted and revised the work critically for important intellectual content and finally approved the version to be published and agreement to be accountable.

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## DISCLOSURE

PB has received research grants outside the submitted work from the Amsterdam UMC, Stichting Astma Bestrijding (SAB), Boehringer Íngelheim, and Vertex. JR has received a personal fee outside of the submitted work from the Vertex pharmaceuticals for giving a lecture/webinar. AHM has received research grants outside the submitted work from GSK, Boehringer Íngelheim, and Vertex, she is the PI of a P4O2 (Precision Medicine for more Oxygen) public–private partnership sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (Boehringer Ingelheim, Breathomix, Fluidda, Ortec Logiqcare, Philips, Quantib-U, Roche, Smartfish, SODAQ, Thirona, TopMD, and Novartis), and she has served in advisory boards for AstraZeneca, GSK, and Boehringer Ingelheim with money paid to her institution.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author and are not publicly available due to privacy or ethical restrictions.

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## REFERENCES

1. Cheng SH, Gregory RJ, Marshall J, et al. Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. *Cell*. 1990;63:827-834. https://linkinghub.elsevier.com/retrieve/pii/0092867490901488
2. Cystic Fibrosis Foundation Patient Registry 2019 Annual Data Report, Bethesda, Maryland, Maryland. 2020. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf
3. Nederlandse CF Registratie 2020. Baarn. 2020.
4. HGM H, EF MK, DGD D, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet*. 2019;394:1940-1948. https://linkinghub.elsevier.com/retrieve/pii/S0140673619325978
5. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381:1809-1819. doi:10.1056/NEJMoa1908639
6. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the cystic fibrosis questionnaire-revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest*. 2009;135:1610-1618. https://linkinghub.elsevier.com/retrieve/pii/S0012369209603676
7. Burgel P-R, Munck A, Durieu I, et al. Real-life safety and effectiveness of lumacaftor–ivacaftor in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2020;201:188-197. doi:10.1164/rccm.201906-1227OC
8. Hubert D, Chiron R, Camara B, et al. Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. *J Cyst Fibros*. 2017;16:388-391. https://linkinghub.elsevier.com/retrieve/pii/S1569199317300863
9. Murer C, Huber LC, Kurowski T, et al. First experience in Switzerland in Phe508del homozygous cystic fibrosis patients with end-stage pulmonary disease enrolled in a lumacaftor-ivacaftor therapy trial – preliminary results. *Swiss Med Wkly*. 2018;148. http://doi.emh.ch/smw.2018.14593
10. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med*. 2015;373:220-231. doi:10.1056/NEJMoa1409547
11. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med*. 2017;377:2013-2023. doi:10.1056/NEJMoa1709846
12. Nichols DP, Paynter AC, Heltshe SL, et al. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: a clinical trial. *Am J Respir Crit Care Med*. 2022;205:529-539. doi:10.1164/rccm.202108-1986OC
13. Carnovale V, Iacotucci P, Terlizzi V, et al. Elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for the F508del mutation and advanced lung disease: a 48-week observational study. *J Clin Med*. 2022;11:1021. https://www.mdpi.com/2077-0383/11/4/1021
14. Rink S, Janić M, Lunder M, Šabovič M, Salobir B. *Effect of Elexacaftor-Tezacaftor-Ivacaftor on Pulmonary and Endothelial Function in a Patient With Advanced Cystic Fibrosis*. European Respiratory Society; 2021:104.
15. Loeve M, van Hal PTW, Robinson P, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. *Thorax*. 2009;64:876-882.
16. Bacci G, Mengoni A, Fiscarelli E, et al. A different microbiome gene repertoire in the airways of cystic fibrosis patients with severe lung disease. *Int J Mol Sci*. 2017;18:1654.
17. Richter K, Kanniess F, Mark B, Jörres RA, Magnussen H. Assessment of accuracy and applicability of a new electronic peak flow meter and asthma monitor. *Eur Respir J*. 1998;12:457-462.
18. Flume PA, Saiman L, Marshall B. The impact of COVID-19 in cystic fibrosis. *Arch Bronconeumol*. 2022;58:466-468. https://linkinghub.elsevier.com/retrieve/pii/S0300289621003975

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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