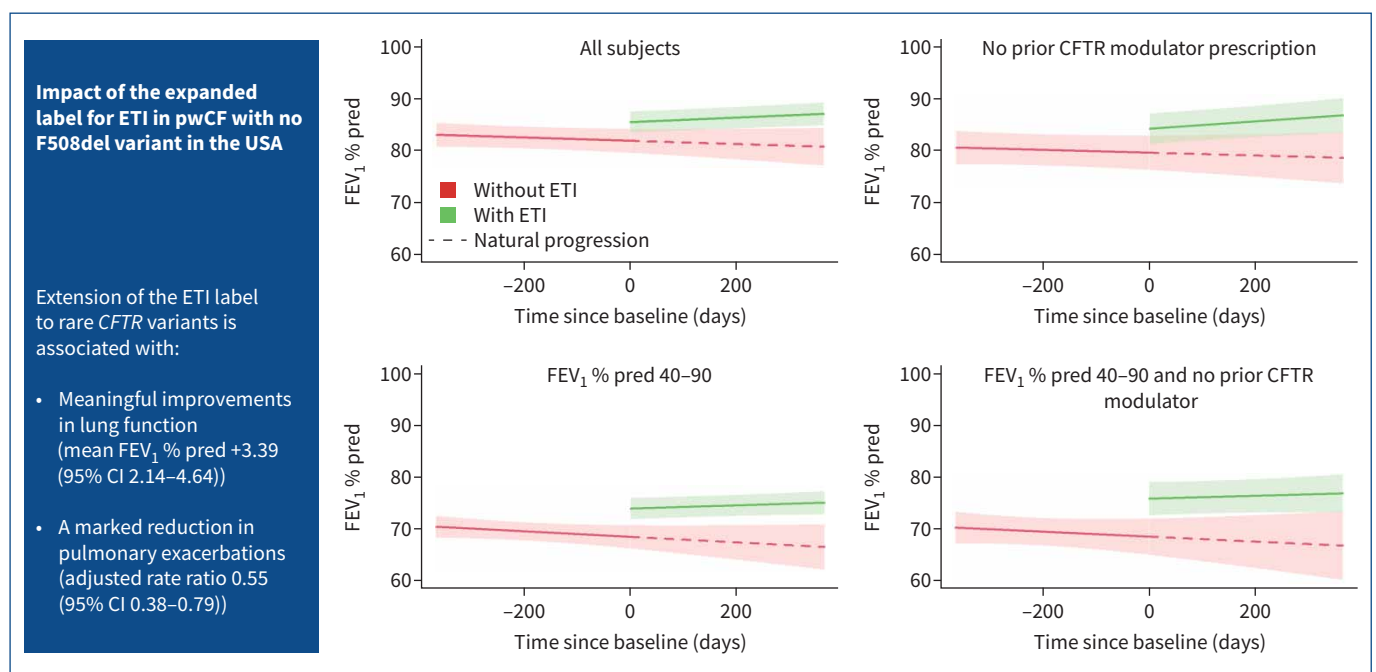




# Impact of the expanded label for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with no F508del variant in the USA

Elizabeth A. Cromwell, Josh S. Ostrenga, Don B. Sanders, Wayne Morgan, Carlo Castellani, Rhonda Szczesniak and Pierre-Regis Burgel 



**GRAPHICAL ABSTRACT** Summary of the effect of elexacaftor/tezacaftor/ivacaftor (ETI) on forced expiratory volume in 1 s (FEV<sub>1</sub>) percentage predicted and pulmonary exacerbations for people with cystic fibrosis (pwCF) with no F508del *CFTR* (cystic fibrosis transmembrane conductance regulator) variant eligible under the US Food and Drug Administration label extension in December 2020. The model-based estimates of the ETI FEV<sub>1</sub> % pred effect and 95% confidence intervals are visualised for all subgroups: all study subjects, those with no history of a CFTR modulator, individuals with a pre-ETI FEV<sub>1</sub> % pred 40–90, and individuals with both pre-ETI FEV<sub>1</sub> % pred 40–90 and no history of a CFTR modulator. The dashed line extrapolates the pre-ETI trend for comparison with the post-ETI period.



# Impact of the expanded label for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with no F508del variant in the USA

Elizabeth A. Cromwell<sup>1</sup>, Josh S. Ostrenga<sup>1</sup>, Don B. Sanders<sup>2</sup>, Wayne Morgan<sup>3</sup>, Carlo Castellani<sup>4</sup>, Rhonda Szczesniak<sup>5</sup> and Pierre-Regis Burgel <sup>6,7</sup>

<sup>1</sup>Cystic Fibrosis Foundation, Bethesda, MD, USA. <sup>2</sup>Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, USA. <sup>3</sup>Department of Pediatrics, University of Arizona College of Medicine, Tucson, AZ, USA. <sup>4</sup>Cystic Fibrosis Center, IRCCS Istituto Giannina Gaslini, Genoa, Italy. <sup>5</sup>Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH, USA. <sup>6</sup>Respiratory Medicine and French National Reference CF Center, Hôpital Cochin, AP-HP, Paris, France. <sup>7</sup>Institut Cochin, Inserm U1016, Université Paris Cité, Paris, France.

Corresponding author: Elizabeth A. Cromwell ([ecromwell@cff.org](mailto:ecromwell@cff.org))



Shareable abstract (@ERSpublications)

Data from patients who received elexacaftor/tezacaftor/ivacaftor (ETI) in the USA for non-F508del indications show that ETI was associated with a clinically relevant increase in FEV<sub>1</sub> percentage predicted and a decrease in pulmonary exacerbations <https://bit.ly/3ThhFoh>

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## Abstract

**Background** Elexacaftor/tezacaftor/ivacaftor (ETI), which is approved for people with cystic fibrosis (pwCF) with a F508del variant, was further approved based on *in vitro* data in the USA for those carrying at least one of 177 rare *CFTR* (cystic fibrosis transmembrane conductance regulator) variants.

**Methods** PwCF, aged ≥6 years, carrying no F508del variant but with at least one of these 177 rare variants, were identified within the US Cystic Fibrosis Foundation Patient Registry (CFPR) between 2020 and 2022. The evolution of forced expiratory volume in 1 s (FEV<sub>1</sub>) percentage predicted and rates of pulmonary exacerbations were analysed over the first year following ETI initiation, using a linear regression with generalised estimating equations and a negative binomial model, respectively.

**Results** A total of 1791 individuals aged ≥6 years with rare *CFTR* variants were eligible for ETI, corresponding to 5.2% of CFPR participants. 815 individuals (45.5%), of which 57.9% were already treated with another *CFTR* modulator, initiated ETI within the first 2 years following approval. Individuals with more severe respiratory disease were more likely to initiate ETI, whereas those previously treated with another *CFTR* modulator or those with no private insurance coverage had less ETI initiation. ETI initiation was associated with an increase in mean FEV<sub>1</sub> % pred by +3.39 (95% CI 2.14–4.64) and a decrease in the rates of pulmonary exacerbations (adjusted rate ratio 0.55, 95% CI 0.38–0.79). These effects were greater in individuals naïve of previous *CFTR* modulators.

**Conclusions** Extension of the ETI label to rare *CFTR* variants is associated with meaningful improvements in lung function and a marked reduction in pulmonary exacerbations.

## Introduction

Cystic fibrosis (CF) is a genetic disease caused by variations in the gene encoding for the CF transmembrane conductance regulator (*CFTR*) protein, which is an ion channel for chloride and bicarbonate in epithelia [1]. Over 2000 variants in the *CFTR* gene have been identified but a single variant, F508del (c.1521\_1523delCTT), is present in 85% of individuals with CF in the USA [2]. The *CFTR* defect leads to a multisystemic disease dominated by gastrointestinal and pulmonary manifestations. Pancreatic insufficiency occurs in ~80% of people with CF (pwCF) [2], often leading to abdominal pain, diarrhoea and malnutrition. The pulmonary disease is characterised by excessive production of a viscous mucous, airway bacterial infection and inflammation, leading to structural damage and accelerated loss of



lung function. The evolution is characterised by the occurrence of pulmonary exacerbations that promote loss of lung function, and recurrent exacerbations are further associated with reduced survival or the need for lung transplantation [3]. For many years, CF treatment has consisted of managing the consequences of the CFTR dysfunction, using nutritional intervention and pancreatic enzyme replacement, inhaled and systemic antibiotics, and pharmacological and non-pharmacological airway clearance therapies [1].

Over the past 15 years, small molecules, called CFTR modulators, directly targeting the defective CFTR protein [4] with the aim of restoring ion transport, have been identified. Ivacaftor (IVA) is a CFTR modulator that increases the open probability of the chloride channel [5]. Because IVA alone has limited effects on F508del-CFTR, novel molecules that target ion transport in F508del-CFTR were searched and identified by high-throughput screening in NIH/3T3 mouse fibroblasts transfected with F508del-CFTR [6]. Among these molecules, tezacaftor (TEZ) and elxacaftor (ELX) were selected based on *in vitro* and animal studies. Following a classic process of clinical development involving large-scale clinical trials [7–10], treatment with the triple combination of ELX/TEV/IVA (ETI) was shown to result in a reduction in respiratory symptoms, increased forced expiratory volume in 1 s (FEV<sub>1</sub>) percentage predicted, an increase in body weight and body mass index (BMI), and a decrease in the rate of pulmonary exacerbations. These studies led to the approval of ETI for pwCF with at least one F508del variant in 2019 in the USA and in multiple other countries [11]. Importantly, the initial ETI approval in the USA excluded individuals with no F508del variant, for which no clinical trial data were available.

In 2017, the US Food and Drug administration (FDA) recognised the difficulty of performing clinical trials on CFTR modulators in individuals with CF carrying rare *CFTR* variants and proposed an approach based on the use of a cell-based *in vitro* system to support efficacy in individuals with CF with rare variants [4]. In December 2020, this approach led the FDA to expand the approval of ETI for individuals with no F508del variant but carrying at least one of 177 rare *CFTR* variants for which the ETI ability to partially restore ion transport was shown in Fisher rat thyroid cells. In the phase 3 and extension trials [12], the safety profile of ETI appeared favourable and durable for most patients, which likely contributed to the FDA decision. The FDA decision was rather unique and worldwide most regulatory agencies did not follow a similar approach, questioning the clinical relevance of the *in vitro* data [13]. As there was no clinical trial performed in this population, the only available evidence regarding the effectiveness of ETI in individuals with these 177 rare *CFTR* variants comes from small case series [14–16]. We reasoned that using large-scale clinical data to describe the effects of ETI in individuals with no F508del and one of the 177 rare *CFTR* variants would promote the acceptance of *in vitro* data for expanding labels by other regulatory agencies.

In the present study, our aim was to evaluate the impact of the expansion of the ETI label to the 177 rare *CFTR* variants on the US population of pwCF. We analysed Cystic Fibrosis Foundation Patient Registry (CFFPR) data to determine the uptake of ETI in individuals eligible for the expanded ETI label over the first 2 years following the FDA approval. We further described the evolution of FEV<sub>1</sub> % pred, BMI and the rate of pulmonary exacerbations within the year following the initiation of ETI.

## Methods

### Data source and study population

The CFFPR maintains data on pwCF who consent (or parents and guardians who consent on behalf of children aged <18 years) to participate at CFF-accredited care centres in the USA [17]. The CFFPR reports demographic, diagnostic and encounter-based clinical data on pwCF, representing ~80% of the US CF population [18]. Individuals with a reported CF diagnosis were included if they had at least one *CFTR* variant approved for ETI under the December 2020 FDA label extension and were aged ≥6 years as of 31 December 2022 (individuals with at least one F508del variant were excluded). We classified all individuals by ETI prescription status as reported at the date of CF care team encounters of any type (routine visit, acute care, *etc.*): never-prescribed and prescribed with no change (all encounters with medication data reported after the first prescription include an ETI prescription). Individuals for whom ETI prescription status changed multiple times (ETI not reported for all encounters following first prescription) were classified as intermittently prescribed.

### Statistical analyses

We summarised the pre-ETI characteristics of study subjects by prescription status (excluding those with intermittent report). Descriptive statistics were calculated from annualised data reported in 2019 to avoid bias due to less frequent CF care utilisation during the coronavirus disease 2019 (COVID-19) pandemic from 2020 to 2021 [2]. We also compared the demographic and clinical characteristics of individuals with an ETI prescription by history of prior CFTR modulator therapy summarised at first ETI prescription. In

the CFFPR, modulator prescription dates are reported on an encounter-level basis (any type of visit to a CF care team), and all prior prescription history was reviewed. Categorical variables were summarised as proportion and continuous variables as median with interquartile range or mean with standard deviation. To characterise the uptake of ETI and identify factors associated with a prescription, we used a Cox proportional hazards model adjusting for covariates based on previously identified factors associated with an increased odds of lumacaftor/IVA prescription [19]. In the Cox model, individuals were censored at the date of their last encounter or at the date of first lung transplant.

To quantify the effect of ETI among those prescribed we utilised a pre/post design for individuals who had outcome data in the 365 days preceding and the 365 days following the first prescription (intermittently prescribed individuals and individuals with a history of lung transplant prior to the label extension were excluded). We analysed four outcomes: FEV<sub>1</sub> % pred based on Global Lung Function Initiative 2012 reference equations [20], BMI percentile (<20 years of age), BMI value (≥20 years of age; all ages) and rate of intravenous (IV) antibiotics-treated pulmonary exacerbations. Additional inclusion criteria were applied specific to each outcome. For FEV<sub>1</sub> % pred and nutrition (weight and BMI), individuals were required to have at least three measures reported, with ≥6 months between the first and last measurements, excluding measures reported during a hospitalisation or home IV treatment. Individuals were censored upon lung transplant or prescription of any other CFTR modulator reported after ETI prescription, and women with any report of pregnancy were excluded due to the impact of pregnancy on weight and lung function. Individuals who died were censored at their date of death and those who received a lung transplant were censored at the date of transplant. For IV-treated pulmonary exacerbations, we calculated person-time at risk from 2019 to 2022 classified as pre- versus post-ETI based on the date of the first ETI prescription. Total IV-treated pulmonary exacerbation events were calculated per person for care episodes with reason of either pulmonary exacerbation or other acute respiratory complications.

To estimate the effect of ETI on FEV<sub>1</sub> % pred and nutrition, we used linear regression with generalised estimating equations with an exchangeable correlation structure including covariates for time since ETI prescription (time 0 equals the date of the first ETI prescription), ETI prescription (yes/no) and an interaction between time and ETI. Individuals with intermittent prescription were excluded. With this design, the primary parameter of interest is the ETI covariate, which can be interpreted as the short-term change in the outcome (*i.e.* a shift in the intercept). To estimate the effect of ETI on rate of IV-treated pulmonary exacerbations, we employed a negative binomial model (also accounting for within-subject correlation) with ETI prescription as a covariate with the log of person-time at risk as the offset and adjusting for calendar time (supplementary material) [19]. For all analyses, we *a priori* chose to estimate subgroup effects by restricting to unique populations under the hypothesis that the following characteristics might modify an ETI treatment effect: any prescription of IVA or TEZ/IVA in the 12 months preceding an ETI prescription, pancreatic insufficiency as defined by any enzyme prescription within the study period and individuals whose FEV<sub>1</sub> at the encounter immediately preceding the ETI prescription was 40–90% predicted.

Statistical analysis was performed in SAS version 9.4 (SAS Institute, Cary, NC, USA). The study was classified exempt by the Advarra Institutional Review Board ([www.advarra.com](http://www.advarra.com); #00076219).

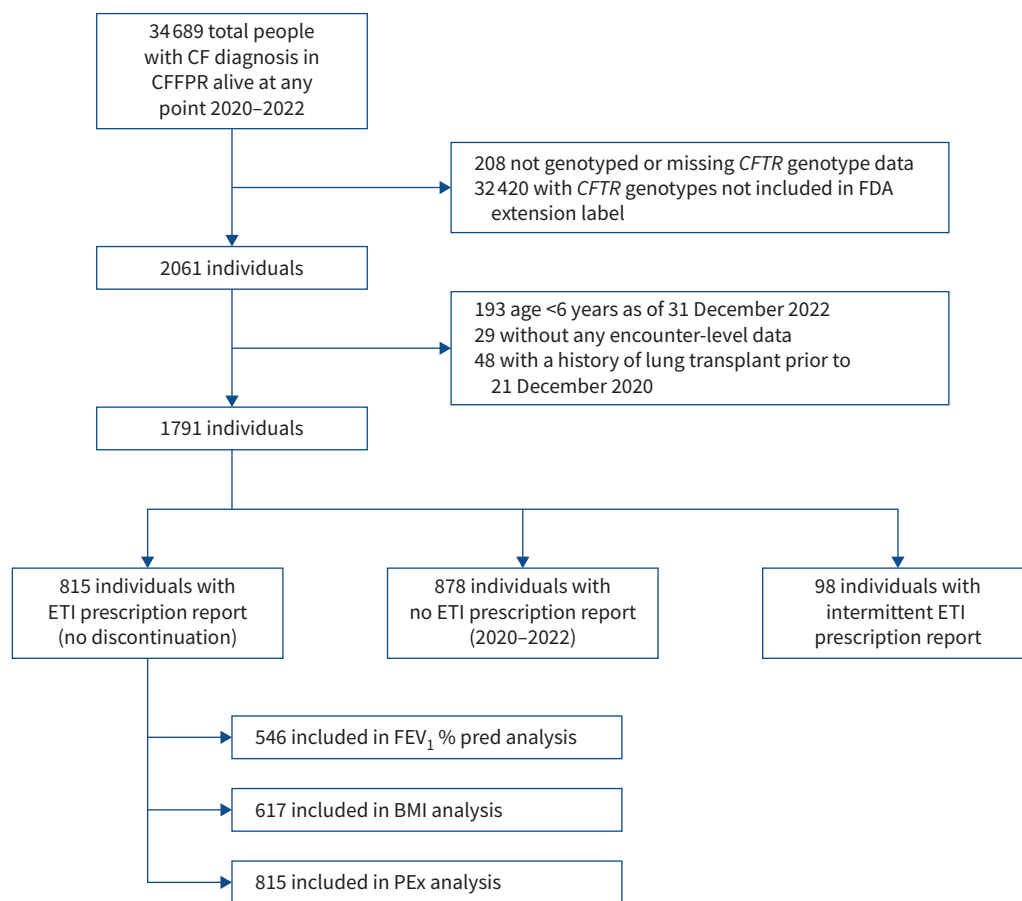
## Results

### Study population

A total of 2061 pwCF with no F508del variant and at least one of the 177 variants included under the FDA label extension contributed data to the CFFPR in 2020–2022. We further excluded 193 individuals <6 years of age as of 31 December 2022, 48 individuals with a history of lung transplant prior to 21 December 2020 and 29 individuals who contributed no encounter-level data. A total of 98 individuals were prescribed ETI intermittently, suggesting possible interruption or discontinuation of CFTR modulator therapy, and were only included in time to first prescription analyses. Among the 815 individuals with stable ETI prescription report, 546 individuals had sufficient FEV<sub>1</sub> % pred data for analysis of the ETI effect on lung function, 617 individuals were included in the BMI analyses and all 815 individuals contributed to the estimate of ETI on rate of IV antibiotics-treated pulmonary exacerbations. As illustrated in figure 1, 815 individuals (with 92 individual CFTR variants on the extended FDA list; see supplementary table S1) had an ETI prescription with no evidence of discontinuation and 878 individuals had no ETI prescription reported. There was a total of 30 deaths (less than five deaths among the ETI-prescribed population) and six individuals received a first lung transplant during the follow-up period.

### Comparison of individuals treated versus not treated with ETI

Table 1 summarises characteristics as reported in 2019 for individuals by ETI prescription status. The prescribed population was more likely to be female (55.6% versus 49.1%) and more likely to be >18 years



**FIGURE 1** Flowchart depicting the selection of the study population. CF: cystic fibrosis; CFFPR: Cystic Fibrosis Foundation Patient Registry; *CFTR*: cystic fibrosis transmembrane conductance regulator; FDA: Food and Drug Administration; ETI: elexacaftor/tezacaftor/ivacaftor; FEV<sub>1</sub>: forced expiratory volume in 1 s; BMI: body mass index; PEx: pulmonary exacerbation.

of age (50.2% versus 43.4%) compared to those with no ETI prescription. The ETI-prescribed population had a higher proportion of individuals with lung lower lung function: 22.3% of the prescribed population had an annualised FEV<sub>1</sub> % pred 40–70 compared to 10.1% of the never-prescribed population. Another 47.5% of the ETI-prescribed population had FEV<sub>1</sub> % pred >90 compared to 64.0% of the never-prescribed group. Nutrition indicators were consistently lower among the ETI-prescribed group compared to the never-prescribed group. During the baseline year, the ETI-prescribed population had a higher prevalence of other medications, including a higher prevalence of pancreatic insufficiency (61.1% versus 42.4%) as well as a higher average number of IV-treated pulmonary exacerbations (mean±SD: 0.4±1.1 versus 0.2±0.6). A total of 467 individuals (57.3%) had a history of IVA or TEZ/IVA prescription; details on prior history of *CFTR* modulator therapy are presented in supplementary table S2.

The median time to prescription among those eligible for ETI under the label extension was 540 (95% CI 497–584) days and median time to prescription was similar regardless of prior modulator prescription (log-rank  $p=0.48$ ). Of the 1791 individuals eligible for an ETI prescription, 1405 had sufficient covariate data for the Cox model (table 2). Lower FEV<sub>1</sub> % pred, female sex, pancreatic insufficiency, inhaled tobramycin prescription and history of IV-treated pulmonary exacerbations were associated with a higher hazard of prescription (*i.e.* earlier prescription). Prior history of IVA or TEZ/IVA prescription (HR 0.84, 95% CI 0.72–0.98) and age ≥18 years (HR 0.74, 95% CI 0.62–0.89) were associated with a lower hazard of prescription (*i.e.* later prescription). Details on time to first prescription are included in the supplementary material.

#### Effects of ETI in the treated population

All estimates of ETI effect along with a summary of data availability by group are presented in table 3. Overall, we found ETI increased FEV<sub>1</sub> % pred by an average of 3.4 (95% CI 2.1–4.6) among the entire

**TABLE 1** Characteristics of 1693 people with cystic fibrosis (CF) with no F508del and at least one US Food and Drug administration (FDA)-approved *CFTR* (CF transmembrane conductance regulator) variant according to elxacaftor/tezacaftor/ivacaftor (ETI) prescription in 2019 (before FDA label extension)

Characteristic (2019 annualised data)	Total <sup>#</sup>	ETI prescription	No ETI prescription
<b>Individuals</b>	1693	815	878
<b>Female</b>	884 (52.22)	453 (55.58)	431 (49.09)
<b>Homozygous <i>CFTR</i> genotypes</b>	111 (6.56)	63 (7.73)	48 (5.47)
<b>Two <i>CFTR</i> variants<sup>#</sup> on extended label list</b>	365 (21.42)	177 (21.7)	188 (21.4)
<b>Age (years)</b>			
<18	903 (53.34)	406 (49.82)	497 (56.61)
≥18	790 (46.66)	409 (50.18)	381 (43.39)
<b>Age at diagnosis (years)</b>	4.8 (0.2–21.8)	4.9 (0.2–19.3)	4.7 (0.2–25.0)
<b>Highest sweat chloride (mmol·L<sup>-1</sup>)</b>	78.0 (56.0–99.0)	86.0 (63.0–102.0)	71.0 (52.0–94.0)
<b>Race and Hispanic ethnicity<sup>+</sup></b>			
White	1468 (86.71)	706 (86.63)	762 (86.79)
Black	110 (6.50)	51 (6.26)	59 (6.72)
Native American/Hawaiian/Pacific Islander	9 (0.53)	<5	<5
Asian or Other	106 (6.26)	51 (6.26)	55 (6.26)
Any Hispanic ethnicity	270 (15.95)	118 (14.48)	152 (17.31)
<b>Insurance<sup>+</sup></b>			
Private	835 (49.32)	414 (50.80)	421 (47.95)
Medicare/Medicaid/State	553 (32.66)	266 (32.64)	287 (32.69)
Tricare/Military/Indian Health	43 (2.54)	23 (2.82)	20 (2.28)
No insurance	16 (0.95)	6 (0.74)	10 (1.14)
Missing	246 (14.53)	106 (13.01)	140 (15.95)
<b>Clinic visits per year</b>	3.5±2.0	4.0±2.3	3.1±1.7
<b>Lung function FEV<sub>1</sub> % pred</b>	89.9 (71.4–101.9)	85.0 (63.4–98.8)	93.5 (80.0–104.5)
<40	69 (4.08)	40 (5.6)	29 (4.9)
40–70	235 (15.7)	160 (22.3)	75 (10.1)
70–90	340 (23.2)	176 (24.6)	164 (22.0)
>90	817 (55.9)	340 (47.5)	477 (64.0)
Missing	232	99	133
<b>Nutrition</b>			
Height percentile age <20 years (0–100)	48.2 (23.0–74.5)	43.5 (21.2–70.5)	53.5 (24.8–77.4)
Weight percentile age <20 years (0–100)	64.9 (39.2–86.6)	57.1 (35.0–81.7)	69.7 (43.5–90.1)
BMI percentile age <20 years (0–100)	69.9 (45.2–89.1)	67.5 (39.6–85.5)	71.9 (48.4–91.2)
BMI value age ≥20 years (kg·m <sup>-2</sup> )	24.4 (21.5–28.6)	23.9 (21.0–27.6)	24.9 (22.4–29.3)
<b>Hospitalisations</b>			
Intravenous-treated PEx	0.3±0.9	0.4±1.1	0.2±0.6
Total hospitalisations	0.4±1.0	0.5±1.1	0.2±0.8
Nights hospitalised for PEx	14.2±20.1	15.5±21.0	11.8±18.3
<b>Infection status</b>			
Bacterial culture tested	1404	698	706
<i>Pseudomonas aeruginosa</i> -positive	387 (27.56)	249 (35.67)	138 (19.55)
MRSA	207 (14.74)	123 (17.62)	84 (11.90)
MSSA	740 (52.71)	355 (50.86)	385 (54.53)
Any <i>Burkholderia</i> species	20 (1.42)	15 (2.15)	5 (0.71)
<i>Burkholderia cepacia</i> ever reported	63 (3.72)	47 (5.77)	16 (1.82)
<i>Aspergillus</i>	105 (7.48)	74 (10.60)	31 (4.39)
<b>Medications/therapies</b>			
Any pancreatic enzymes	735 (51.08)	424 (60.06)	311 (42.43)
Dornase alfa	1039 (72.20)	582 (82.44)	457 (62.35)
Hypertonic saline	828 (57.54)	464 (65.72)	364 (49.66)
Any inhaled antibiotic	427 (29.6%)	288 (40.7%)	139 (18.9%)
Inhaled tobramycin	339 (23.56)	233 (33.00)	106 (14.46)
Any other inhaled antibiotic <sup>§</sup>	212 (14.7)	149 (21.1)	63 (8.6)
Any chronic oral antibiotic	416 (28.91)	259 (36.69)	157 (21.42)
Missing medications data	254	109	145
<b>Ever IVA prescription</b>	900 (53.16)	425 (52.15)	475 (54.10)
<b>Ever TEZ/IVA prescription</b>	169 (9.98)	112 (13.74)	57 (6.49)

Continued

TABLE 1 Continued

Characteristic (2019 annualised data)	Total <sup>#</sup>	ETI prescription	No ETI prescription
<b>Complications</b>			
Any diabetes (CFRD, Type 1, Type 2)	139 (8.21)	848 (10.31)	55 (6.26)
Complications data available	1435	705	730
Liver disease, non-cirrhosis	24 (1.67)	16 (2.27)	8 (1.10)
ABPA	82 (5.71)	51 (7.23)	31 (4.25)
Asthma	438 (30.52)	243 (34.47)	195 (26.71)

Data are presented as n, n (%), median (interquartile range) or mean $\pm$ sd. FEV<sub>1</sub>: forced expiratory volume in 1 s; BMI: body mass index; PEx: pulmonary exacerbation; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *S. aureus*; IVA: ivacaftor; TEZ: tezacaftor; CFRD: CF-related diabetes; ABPA: allergic bronchopulmonary aspergillosis. <sup>#</sup>: 98 individuals with inconsistent CFTR modulator prescription status were excluded (figure 1); <sup>¶</sup>: includes individuals homozygous for the same *CFTR* variant; <sup>†</sup>: race categories are not mutually exclusive and health insurance categories are not mutually exclusive; <sup>‡</sup>: colistin, aztreonam and other inhaled antibiotics.

extended label population. While there is not sufficient sample size to test an interaction effect between ETI and possible modifiers of lung function, in a restricted analysis we estimated that ETI increased FEV<sub>1</sub> % pred by 4.6 (95% CI 2.8–6.4) for those with no IVA or TEZ/IVA prescription in the 12 months preceding ETI, and increased FEV<sub>1</sub> % pred by 7.3 (95% CI 4.3–10.3) for those with no IVA or TEZ/IVA and pre-ETI FEV<sub>1</sub> % pred 40–90. Figure 2 visualises the estimates of ETI effect on FEV<sub>1</sub> % pred. While the proportion of individuals who were classified as underweight decreased after report of ETI (7.3% in the encounter preceding ETI prescription versus 4.8% as of the last encounter), we did not detect an effect of ETI on BMI percentile (<20 years of age) or BMI (either among  $\geq$ 20 years of age or all subjects).

In 2019, 16.5% of the ETI-exposed population had one IV-treated pulmonary exacerbation and 9.5% reported two or more IV-treated pulmonary exacerbations compared to 6.9% and 4.2% in 2022, respectively. We estimated a crude rate ratio of 0.39 (95% CI 0.29–0.53) of ETI on IV-treated pulmonary exacerbations from 2019 to 2022. Inclusion of calendar time as a covariate to account for the impact of the

TABLE 2 Association between patient characteristics and hazard of elexacaftor/tezacaftor/ivacaftor (ETI) prescription

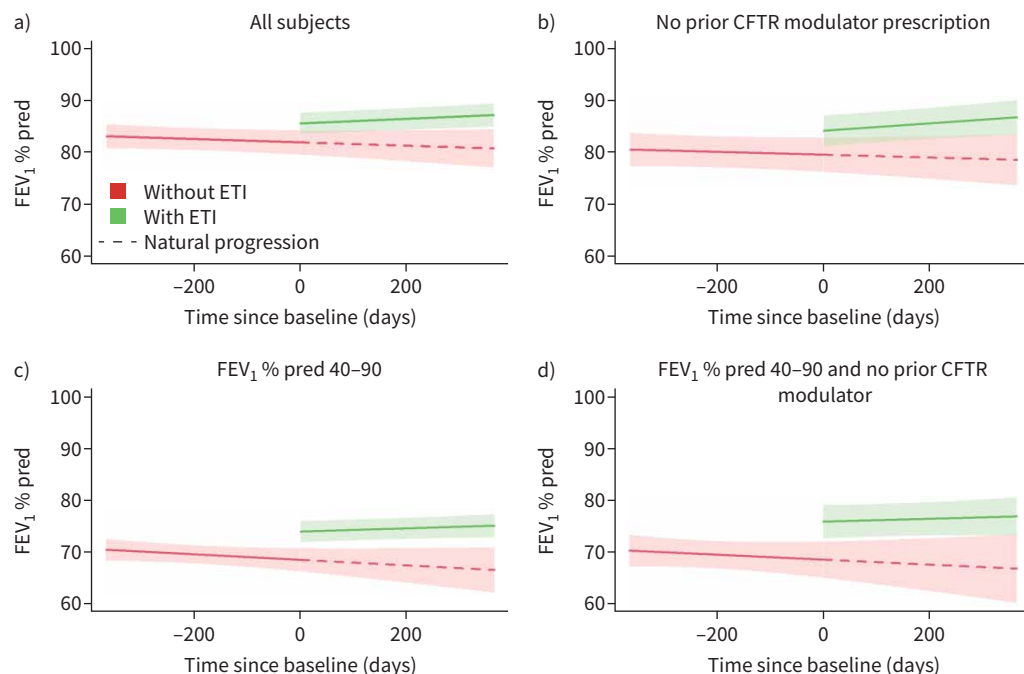
Characteristics <sup>#</sup>	Hazard ratio (95% CI)
Female sex versus male	1.17 (1.01–1.36)
White versus all other race categories	0.96 (0.77–1.21)
Hispanic ethnicity versus none	0.99 (0.81–1.23)
Age $\geq$ 18 versus <18 years	0.74 (0.62–0.89)
<b>Insurance</b>	
Medicare/Medicaid/State versus Private	0.84 (0.71–0.99)
No insurance versus Private	0.78 (0.34–1.77)
Tricare/Military/Indian Health versus Private	1.52 (1.04–2.21)
<b>Lung function FEV<sub>1</sub> % pred</b>	
<40 versus >90	1.37 (0.95–1.98)
40–70 versus >90	1.36 (1.08–1.71)
70–90 versus >90	1.16 (0.96–1.40)
<b>Intravenous-treated pulmonary exacerbations</b>	
1 versus 0	1.28 (1.04–1.58)
$\geq$ 2 versus 0	1.68 (1.26–2.23)
<b>Diabetes (CFRD, Type 1, Type 2) versus none</b>	
Any IVA or TEZ/IVA ever reported	1.08 (0.85–1.37)
Any IVA or TEZ/IVA ever reported	0.84 (0.72–0.98)
<b>Pancreatic insufficient versus sufficient</b>	
<i>Pseudomonas aeruginosa</i> -positive culture	1.54 (1.32–1.81)
<i>Pseudomonas aeruginosa</i> -positive culture	1.14 (0.94–1.38)
MRSA-positive culture	1.14 (0.93–1.38)
Any inhaled antibiotic prescription	1.43 (1.19–1.74)

FEV<sub>1</sub>: forced expiratory volume in 1 s; CFRD: CF-related diabetes; IVA: ivacaftor; TEZ: tezacaftor; MRSA: methicillin-resistant *Staphylococcus aureus*. <sup>#</sup>: all covariates extracted from 2019 reported data. A hazard ratio >1 implies earlier ETI prescription.

TABLE 3 Summary of data availability and the effect of elexacaftor/tezacaftor/ivacaftor (ETI) by outcome

	Subjects (n)	Total measures or PEx events (n)		Median (IQR) or person-time (years)		ETI effect (95% CI) <sup>#</sup>	Rate ratio estimate (95% CI) <sup>¶</sup>	
		Pre-ETI	Post-ETI	Pre-ETI	Post-ETI		Crude	Adjusted
<b>FEV<sub>1</sub> % pred analysis</b>								
All subjects	546	1394	1880	85.60 (61.8–98.98)	89.68 (68.22–101.5)	3.39 (2.14–4.64)		
Pancreatic insufficient	349	914	1232	83.11 (60.05–97.93)	88.79 (67.19–101.2)	4.70 (3.16–6.24)		
Prior IVA or TEZ/IVA <sup>†</sup>	315	800	1101	86.82 (63.38–101.0)	90.50 (69.1–103.0)	2.39 (0.68–4.09)		
No IVA or TEZ/IVA	231	594	779	84.05 (59.84–97.32)	88.78 (66.9–99.97)	4.57 (2.77–6.38)		
FEV <sub>1</sub> % pred 40–90	228	560	789	68.50 (54.21–78.92)	74.01 (60.99–84.94)	5.49 (3.45–7.54)		
FEV <sub>1</sub> % pred 40–90 and no CFTRm <sup>†</sup>	103	241	357	69.74 (55.18–79.58)	77.39 (62.81–88.79)	7.33 (4.34–10.32)		
<b>BMI value (≥20 years)</b>								
All subjects	310	744	1004	23.43 (20.78–27.31)	24.12 (21.77–28.71)	0.22 (–0.03–0.47)		
Pancreatic insufficient	196	483	645	23.10 (20.54–26.2)	23.76 (21.75–27.28)	0.32 (–0.01–0.64)		
Prior IVA or TEZ/IVA <sup>†</sup>	169	395	554	24.00 (22.01–28.02)	24.11 (21.98–28.4)	0.31 (–0.02–0.64)		
No IVA or TEZ/IVA	141	349	450	22.48 (19.74–26.68)	24.19 (21.25–28.96)	0.11 (–0.26–0.48)		
FEV <sub>1</sub> % pred 40–90	183	451	607	23.24 (20.58–27.14)	23.89 (21.53–28.92)	0.32 (0.00–0.64)		
FEV <sub>1</sub> % pred 40–90 and no CFTRm <sup>†</sup>	85	209	273	22.29 (19.68–26.31)	24.14 (20.48–29.0)	0.14 (–0.32–0.61)		
<b>BMI percentile (&lt;20 years)</b>								
All subjects	307	925	1111	69.49 (41.29–87.89)	70.19 (41.68–88.49)	0.81 (–0.95–2.57)		
Pancreatic Insufficient	196	624	736	65.36 (36.69–86.21)	65.17 (35.56–85.99)	0.61 (–1.78–2.99)		
Prior IVA or TEZ/IVA <sup>†</sup>	183	564	689	68.79 (41.49–89.16)	68.79 (39.74–89.06)	–0.02 (–2.24–2.19)		
No IVA or TEZ/IVA	124	361	422	70.88 (40.9–86.65)	72.74 (42.07–87.89)	2.10 (–0.81–5.01)		
FEV <sub>1</sub> % pred 40–90	109	307	373	67.00 (40.9–85.08)	70.88 (42.07–87.89)	0.25 (–3.31–3.81)		
FEV <sub>1</sub> % pred 40–90 and no CFTRm <sup>†</sup>	48	132	166	65.36 (31.75–83.27)	74.20 (40.90–88.87)	1.77 (–3.90–7.44)		
<b>Intravenous-treated PEx</b>								
All subjects	815	653	170	2168.5	1035.2		0.39 (0.29–0.53)	0.55 (0.38–0.79)
Pancreatic insufficient	424	460	118	1092.5	566.3		0.35 (0.23–0.51)	0.54 (0.34–0.87)
Prior IVA or TEZ/IVA <sup>†</sup>	420	334	82	1097.9	554.4		0.42 (0.31–0.57)	0.70 (0.43–1.14)
No IVA or TEZ/IVA	395	319	88	1070.6	480.7		0.36 (0.21–0.62)	0.43 (0.25–0.72)
FEV <sub>1</sub> % pred 40–90	228	238	58	578.5	314.4		0.33 (0.22–0.48)	0.41 (0.25–0.66)
FEV <sub>1</sub> % pred 40–90 and no CFTRm <sup>†</sup>	103	99	33	265.2	138.7		0.37 (0.21–0.67)	0.36 (0.19–0.67)

PEx: pulmonary exacerbations; IQR: interquartile range; FEV<sub>1</sub>: forced expiratory volume in 1 s; IVA: ivacaftor; TEZ: tezacaftor; CFTRm: cystic fibrosis transmembrane conductance regulator modulator; BMI: body mass index. <sup>#</sup>: ETI parameter estimate from linear regression for FEV<sub>1</sub> % pred, BMI value and BMI percentile; <sup>¶</sup>: rate ratios for IV-treated PEx are estimated from a negative binomial model (adjusted rate ratio includes calendar time in the model); <sup>†</sup>: 12 months prior to the first ETI prescription.



**FIGURE 2** Mean effect and 95% confidence interval for the effect of elexacaftor/tezacaftor/ivacaftor (ETI) on forced expiratory volume in 1 s ( $FEV_1$ ) percentage predicted for subgroups: **a)** all study subjects, **b)** those with no history of a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, **c)** individuals with a pre-ETI  $FEV_1$  % pred 40–90, and **d)** individuals with both pre-ETI  $FEV_1$  % pred 40–90 and no history of a CFTR modulator. Days from baseline indicate the period pre-ETI (negative days) and post-ETI (positive days). The dashed line extrapolates pre-ETI lung function over time.

COVID-19 pandemic on transmission of respiratory illnesses led to an estimated ETI effect (rate ratio) of 0.55 (95% CI 0.38–0.79). Among individuals classified as pancreatic insufficient, the adjusted rate ratio for ETI was 0.54 (95% CI 0.34–0.87). For individuals with no IVA or TEZ/IVA prescription history in the 12 months preceding ETI and a pre-ETI  $FEV_1$  % pred 40–90, the adjusted rate ratio was 0.36 (95% CI 0.18–0.67). Model parameter estimates are presented in supplementary tables S3–S6.

## Discussion

As the USA was the first country in the world to expand the ETI label to selected rare *CFTR* variants based on *in vitro* data, the present study represents the first comprehensive analysis of the impact of this decision in a large CF population. It provided the opportunity to study data at the population level in a country setting that included individuals with 92 rare *CFTR* variants, corresponding to more than half of the 177 FDA-approved rare variants. Individuals were more likely to initiate ETI when they exhibited markers associated with more severe disease, including lower lung function, higher rates of pulmonary exacerbations, pancreatic insufficiency or female sex, whereas ETI was less likely to be initiated in those already treated with previous CFTR modulators (IVA or TEZ/IVA) or with Medicaid, Medicare or State health insurance compared to privately insured individuals. In those individuals who initiated ETI, improvement in  $FEV_1$  % pred and reduction in rates of pulmonary exacerbations occurred, consistent with expected effects of ETI.

Expanding the label to individuals aged  $\geq 6$  years with no F508del and at least one FDA-approved variant resulted in 5.2% of all pwCF followed in the CFFPR from 2020 to 2022 becoming newly eligible for ETI. Of these, the rate of ETI uptake appeared relatively low, as approximately half of the eligible patients initiated ETI within the first 2 years following label extension. In contrast, ETI uptake among individuals with the F508del variant indicates that 75% of pwCF eligible for CFTR modulators were prescribed ETI in the 2 years following the initial approval [2]. These findings suggest that the uptake in individuals with non-F508del variants was lower and occurred at a slower rate than in the F508del population. The reasons for not starting ETI could have included less severe pulmonary disease and reduced access to treatment due to out-of-pocket expense. We cannot exclude the possibility that other factors also contributed to the

lower uptake in this population, such as limited awareness of the expansion label by patients and/or physicians and, at least in some patients, a phenotype with fewer clinical manifestations. Of note, individuals with a previous CFTR modulator (IVA or TEZ/IVA) were less likely to initiate ETI, which may be related to a better health status in these individuals and to the absence of previously available data on incremental benefit associated with ETI compared to previous modulators. Individuals identified as minority race represented ~15% of pwCF eligible for ETI under the expanded label to 177 rare variants, confirming previous reports that showed that minoritised individuals in the USA and the UK are more likely to have no F508del variant [21, 22], and a recent report further found that non-White minorities may be less likely to be prescribed ETI in the USA [23].

Initiation of ETI in individuals with non-F508del FDA-approved *CFTR* variants was associated in an increase in lung function and a decrease in pulmonary exacerbations. The improvement in FEV<sub>1</sub> % pred in the overall cohort was +3.39 (95% CI 2.14–4.64) and appeared smaller than the improvement described in individuals with F508del in the PROMISE cohort study of +9.76 (95% CI 8.76–10.76) [24]; this observation was in part due to the finding that 57.7% (315 out of 546) of individuals contributing to the FEV<sub>1</sub> % pred analysis were previously treated with IVA or TEZ/IVA, which are considered highly effective modulators in the population of individuals with residual function. Importantly, exploratory subgroup analyses found that the improvement in FEV<sub>1</sub> % pred was +4.57 (95% CI 2.77–6.38) in individuals naïve of modulators at ETI initiation and was +7.33 (95% CI 4.34–10.32) in the subpopulation of individuals naïve of modulators with FEV<sub>1</sub> % pred 40–90, the usual range of lung function used for recruitment in clinical trials [8, 10]. Although a definitive conclusion regarding the effect size in FEV<sub>1</sub> % pred improvement between individuals with rare non-F508del variants and those with F508del appears impossible, and the present study presents observational data with no control group, the change in FEV<sub>1</sub> % pred described in the present study appears greater than was expected in an untreated population. Importantly, our data also showed a marked decrease in exacerbation rates (–45% in the overall population and –30% in those with IVA or TEZ/IVA at ETI initiation), even when controlling for the effects of the COVID-19 pandemic. Such findings appear comparable to those reported in clinical trials [10] and in registry data [25] in F508del individuals treated with ETI. The incremental benefit of ETI over TEZ/IVA or IVA in individuals with no F508del variant is also consistent with the effects observed in pwCF with F508del–gating and F508del–residual function genotypes in which the increase in FEV<sub>1</sub> % pred was 3.5 (95% CI 2.2–4.7) percentage points [7]. The effects on pulmonary exacerbations, which are reported in our study, could not be addressed in that previous study which examined the effects of ETI over only 8 weeks. Finally, we found no significant change in BMI in adults or BMI z-score in children and adolescents; these findings may be related to the high rates (~50%) of pancreatic-sufficient individuals and previous use of modulators in more than half of the participants, which resulted in BMI >20 kg·m<sup>-2</sup> in >75% of individuals at ETI initiation. Altogether, these data suggest that individuals with rare FDA-approved variants derive clinically significant benefits following initiation of ETI, which appear greater in those naïve of previous modulators, but are also present in those previously treated with IVA or TEZ/IVA.

The study has several limitations. The observational design of this registry study describes evolution under ETI but cannot infer causality. It did not allow obtaining data on the evolution of clinical symptoms (*e.g.* cough and sputum production), health-related quality of life or sweat chloride concentrations, all of which may have helped in determining the effectiveness of ETI. These results apply to the population level, as the goal was to examine the impact of the expanded label on the US CF population, and further studies will be necessary to examine the ETI responsiveness of individual *CFTR* variants. The effect size could have been underestimated, reflecting the uncertainty about continuous exposure to treatment (due to low observance and/or non-recorded treatment interruptions) for an individual categorised as exposed to ETI in the CFFPR. Statistical analyses showing subgroup differences were exploratory but indicate there is consistent benefit in terms of FEV<sub>1</sub> % pred and pulmonary exacerbation rate reduction. A large number of individuals were previously treated with IVA or TEZ/IVA, which is related to the expanded label for IVA in the USA [26] and to off-label use of TEZ/IVA in this patient population. The treatment effect we observed is influenced by the underlying case mix in the USA, which includes only 92 of the approved variants. Our findings are not necessarily directly transportable to other settings, due to variable genetic diversity and treatment among countries, but the subgroup analyses should aid in interpretation of the benefit if a setting has a high proportion of G551D or individuals with a history of CFTR modulator therapy. Given that many non-US settings may not have access to any CFTR modulator for many of the variants described in our study, the benefit may be even larger in populations naïve of CFTR modulators. We also acknowledge there may be unique CF centre-level factors that contributed to ETI uptake in this population that may not be reflected in the time to prescription analysis as we only included patient-level covariates. For the estimate of ETI effect, use of a pre/post design assumes subjects serve as their own controls, but unmeasured confounding may persist in part due to the COVID-19 pandemic and we

acknowledge there is no standard methodology available to control for the impact of the pandemic as reduced viral illness transmission likely modified CF outcomes. Nevertheless, exacerbation rates have not returned to anywhere near their 2019 levels in this study population or the broader CF population in the USA [2]. Comparison of the ETI-prescribed and never-prescribed groups could also be employed to estimate treatment effects, although we showed substantial confounding by indication and differences in the distribution of age, pancreatic insufficiency and prior history of CFTR modulator therapy.

The findings provide evidence of the positive impact of expanding the ETI label to rare *CFTR* variants in the US population of individuals with CF. It reinforces the FDA approach of expanding the access to CFTR modulators based on *in vitro* data [26], and should prompt other regulatory agencies to accept *in vitro* data as a piece of evidence for approval for individuals with rare *CFTR* variants. In this regard, a recent study has performed analyses of the effects of ETI on a large number of rare *CFTR* variants [27], and investigators further reported on the use of patient-derived cells (*e.g.* nasal epithelial cells or rectal organoids) [28, 29]. Complementary data may come from the limited number of rare variants included in clinical trials (*e.g.* 18 rare variants included a recent clinical trial on CFTR modulators; ClinicalTrials.gov: NCT05274269) and from studies reporting real-world cases, especially when these cases are grouped from multiple reports, allowing statistical analyses of the impact on specific variants [30].

In conclusion, the label expansion of ETI to 177 rare *CFTR* variants resulted in a significant increase in the number of pwCF eligible for this life-changing therapy, with clinically important effects [31]. These findings provide evidence that the FDA approach of approving the expanded label for rare *CFTR* variants based on *in vitro* evidence translates into clinical benefits at the population level. We suggest that other regulatory agencies may follow a similar approach, taking into consideration all available evidence (including *in vitro* data and real-world evidence) to expand the label of CFTR modulators to rare *CFTR* variants. Expansion of the ETI label to rare *CFTR* variants for which effectiveness is clinically proven and/or biologically suspected will further help reduce the worldwide discrepancy in geographic eligibility and access to ETI.

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**Ethics statement:** The study was determined exempt by the Advarra Institutional Review Board ([www.advarra.com](http://www.advarra.com); #00076219).

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