



HAL
open science

The expanded French compassionate programme for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study

Pierre-Régis Burgel, Isabelle Sermet-Gaudelus, Emmanuelle Girodon, Isabelle Durieu, Véronique Houdouin, Camille Audousset, Julie Macey, Dominique Grenet, Michele Porzio, Marlène Murriss-Espin, et al.

► To cite this version:

Pierre-Régis Burgel, Isabelle Sermet-Gaudelus, Emmanuelle Girodon, Isabelle Durieu, Véronique Houdouin, et al.. The expanded French compassionate programme for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. *The Lancet Respiratory Medicine*, 2024, 10.1016/S2213-2600(24)00208-X . hal-04672254

HAL Id: hal-04672254

<https://hal.science/hal-04672254v1>

Submitted on 31 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

The expanded French compassionate programme for elexacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study

Pierre-Régis Burgel¹, Isabelle Sermet-Gaudelus², Emmanuelle Girodon³, Isabelle Durieu⁴, Véronique Houdouin⁵, Camille Audousset⁶, Julie Macey⁷, Dominique Grenet⁸, Michele Porzio⁹, Marlène Murriss-Espin¹⁰, Philippe Reix¹¹, Mélisande Baravalle¹², Chantal Belleguic¹³, Laurent Mely¹⁴, Juliette Verhille¹⁵, Laurence Weiss¹⁶, Martine Reynaud-Gaubert¹⁷, Marie Mittaine¹⁸, Rebecca Hamidfar¹⁹, Sophie Ramel²⁰, Laure Cosson²¹, Benoit Douvry²², Isabelle Danner-Boucher²³, Pierre Foucaud²⁴, Charlotte Roy²⁵, Espérie Burnet²⁶, Caroline Raynal²⁷, Marie-Pierre Audrezet²⁸, Jennifer Da Silva²⁶, Clémence Martin²⁹; French Cystic Fibrosis Reference Network study group Collaborators, Affiliations

Collaborators

- **French Cystic Fibrosis Reference Network study group:**

Reem Kanaan, Nicolas Carlier, Isabelle Honoré, Frédérique Chedevergne, Elise Dreano, Aurélie Hatton, Alexandre Hinzpeter, Iwona Pranke, Laurence Le Clainche-Viala, Sophie Mayer, Harriet Corvol, Guillaume Thouvenin, Sandra de Miranda, Natascha Remus, Benoit Douvry, Louise Duthoit, Thierry Perez, Olivier Le Rouzic, Nathalie Wizla, Claire Bon, Stéphanie Bui, Nora Poey, Nathalie Stremler, Bérengère Coltey, Nadine Dufeu, Jean Lebihan, Asma Gabsi, Delphine Pouradier, Claire Andrejak, Cinthia Rames, Magali Dupuy-Grasset, Jeanne Languépin, Christophe Marguet, Stéphanie Pramil, Baptiste Arnouat, Annlyse Fanton, Michel Abely, Bruno Ravoninjatovo, Aurore Blondé, Anne Guillaumot, Sebastien Kieffer, Aurélie Tatopoulos, Raphaële Nove-Josserand, Camille Ohlmann, Thomas Perrin, Quitterie Reynaud, Catherine Llerena, Sébastien Quétant, Sophie Valois, Marie-Laure Dalphin, Bénédicte Richaud-Thiriez, Eric Deneuille, Raphael Chiron, Floriane Socchi, Tiphaine Bihouée, Julie Mankikian, Thomas Flament, Nathalie Coolen-Allou, Elsa Gachelin, Caroline Périsson, Constance Vuillard, Marion Dupuis, Wael Alkoussa, Sarah Marchal, Sylvie Leroy, Manuela Scalbert, Karine Campbell, Muriel Laurans, Guillaume Labbé, Sylvie Montcouquiol, Pascaline Priou, Paola de Carli, Lydie Lemonnier, Clémence Dehillotte, Thierry Nouvel

¹ Université Paris-Cité, Institut Cochin, CNRS, INSERM, Paris, France; Respiratory Medicine and Cystic Fibrosis National Reference Center, Hôpital Cochin, AP-HP, Paris, France; ERN-Lung CF network, Frankfurt, Germany. Electronic address: pierre-regis.burgel@aphp.fr.

² ERN-Lung CF network, Frankfurt, Germany; Centre de Référence Maladies Rares, Mucoviscidose et Affections Liées à CFTR, Pneumologie Pédiatrique et Allergologie, Hôpital Necker Enfants Malades, AP-HP, Paris, France; Université Paris-Cité, Institut Necker Enfants Malades, INSERM U1151, Paris, France.

³ Centre-Université Paris-Cité, Service de Médecine Génomique des Maladies de Système et d'Organe, Hôpital Cochin, AP-HP, Paris, France.

⁴ ERN-Lung CF network, Frankfurt, Germany; Centre de Référence Adulte de la Mucoviscidose, Service de Médecine Interne, Hospices Civils de Lyon, Pierre Bénite, France; Université de Lyon, Research on Healthcare Performance, INSERM U1290, Lyon, France.

⁵ Centre de Ressources et de Compétence pour la Mucoviscidose, Centre Hospitalier Universitaire Robert Debré, AP-HP, Paris, France.

- ⁶ Centre de Ressources et de Compétences Calmette, Centre Hospitalier Universitaire de Lille, Université de Lille, Lille, France; University of Lille, CHU Lille, INSERM, CNRS, Institut Pasteur de Lille, U1019, UMR 9017, Center for Infection and Immunity of Lille, Lille, France.
- ⁷ Respiratory Medicine and Cystic Fibrosis Center, CHU de Bordeaux, Bordeaux, France.
- ⁸ Centre de Transplantation Pulmonaire. Service de Pneumologie, Hôpital Foch, Suresnes, France.
- ⁹ Department of Respiratory Medicine and Cystic Fibrosis Center, Federation of Translational Medicine of Strasbourg, University Hospitals, Strasbourg, France.
- ¹⁰ Cystic Fibrosis Center Service de Pneumologie Pôle des Voies Respiratoires, Hôpital Larrey CHU de Toulouse, Toulouse, France.
- ¹¹ Centre de Ressources et de Compétence de la Mucoviscidose Pédiatrique, Hospices Civils de Lyon, Bron, France.
- ¹² Centre de Ressources et de Compétence de la Mucoviscidose, Hôpital de la Timone, Marseille, France.
- ¹³ Université de Rennes, CHU Rennes, Department of Respiratory Medicine, Rennes, France.
- ¹⁴ Hôpital Renée Sabran, Cystic Fibrosis Center, Giens, France.
- ¹⁵ Centre Hospitalier Universitaire Félix Guyon, Saint Denis, La Réunion, France.
- ¹⁶ Centre de Ressources et de Compétence de la Mucoviscidose Pédiatrique, CHU, Strasbourg, France.
- ¹⁷ Department of Respiratory Medicine and Lung Transplantation, Aix Marseille Université, AP-HM, Hôpital Nord, Marseille, France.
- ¹⁸ Hôpitaux de Toulouse, Toulouse, France.
- ¹⁹ Service Hospitalo-Universitaire de Pneumologie et Physiologie, Pôle Thorax et Vaisseaux, Centre hospitalier universitaire de Grenoble-Alpes, La Tronche, France.
- ²⁰ Centre de Ressources et de Compétences de la Mucoviscidose, Fondation Ildys, Roscoff, France.
- ²¹ Centre de Mucoviscidose, Service de Pneumologie et Immuno-Allergologie, Hôpital de la Mucoviscidose Pédiatrique, CHU, Tours, France.
- ²² Service de Pneumologie, Centre Hospitalier Intercommunal, FHU SENEK, Créteil, France.
- ²³ Service de Pneumologie, L'Institut Du Thorax, CHU Nantes, Nantes, France.
- ²⁴ Association Vaincre la Mucoviscidose, Paris, France.
- ²⁵ Centre de Référence Maladies Rares, Mucoviscidose et Affections Liées à CFTR, Pneumologie Pédiatrique et Allergologie, Hôpital Necker Enfants Malades, AP-HP, Paris, France.
- ²⁶ Respiratory Medicine and Cystic Fibrosis National Reference Center, Hôpital Cochin, AP-HP, Paris, France; ERN-Lung CF network, Frankfurt, Germany.

²⁷ Génétique Moléculaire, CHU Montpellier, Montpellier, France; PhyMedExp, INSERM, CNRS UMR, Montpellier, France.

²⁸ Service de Génétique Moléculaire, CHRU Brest, Brest, France; Université de Brest, INSERM, UMR 1078, GGB, Brest, France.

²⁹ Université Paris-Cité, Institut Cochin, CNRS, INSERM, Paris, France; Respiratory Medicine and Cystic Fibrosis National Reference Center, Hôpital Cochin, AP-HP, Paris, France; ERN-Lung CF network, Frankfurt, Germany.

Abstract

Background:

Elexacaftor-tezacaftor-ivacaftor has been approved in Europe for people with cystic fibrosis with at least one F508del CFTR variant. Additionally, it is approved by the US Food and Drug Administration (FDA) for people with cystic fibrosis with at least one of 177 rare variants. The aims of this study were to describe the clinical response to elexacaftor-tezacaftor-ivacaftor for people with cystic fibrosis without a F508del CFTR variant in France and to determine CFTR variant responsiveness to elexacaftor-tezacaftor-ivacaftor based on the observed clinical response.

Methods:

The French compassionate programme expanded access to elexacaftor-tezacaftor-ivacaftor to people with cystic fibrosis, aged 6 years and older, without a F508del variant, excluding those with two variants previously characterised as non-responsive. Participants at France's 47 cystic fibrosis centres were given a 4-6 week trial of elexacaftor-tezacaftor-ivacaftor and response was determined by a centralised committee based on evolution of clinical data, lung function, and sweat chloride concentration. Responsiveness of individual CFTR variants was derived from observed clinical responses.

Findings:

The first compassionate programme was launched on May 19, 2022; by March 8, 2024, 516 people with cystic fibrosis had been identified for inclusion in this real-world study: 37 were not included due to the presence of two variants previously characterised as non-responsive to elexacaftor-tezacaftor-ivacaftor, and 479 (229 females [48%] and 250 males [52%]) received elexacaftor-tezacaftor-ivacaftor for 4-6 weeks. Among 443 participants who received no CFTR modulator before elexacaftor-tezacaftor-ivacaftor, 83 had at least one FDA-approved variant, of whom 81 (98%) were responders and continued elexacaftor-tezacaftor-ivacaftor; in responders, mean absolute change in sweat chloride was -44.5 mmol/L (95% CI -39.1 to -49.8) and percentage of predicted FEV₁ (ppFEV₁) was 11.1 percentage points (95% CI 8.4 to 13.7; both comparisons $p < 0.0001$). Among 360 participants with no FDA-approved variant and no previous CFTR modulator, 177 (49%) were responders; in responders, mean absolute change in sweat chloride was -20.5 mmol/L (-17.2 to -23.8) and ppFEV₁ was 13.2 percentage points (11.4 to 15.0; both comparisons $p < 0.0001$). Among 36 participants who were receiving ivacaftor before elexacaftor-tezacaftor-ivacaftor, 32 (89%) continued elexacaftor-tezacaftor-ivacaftor. Of 251 individual CFTR variants, 64 (28 FDA-approved) were classified as responsive or possibly responsive to elexacaftor-tezacaftor-ivacaftor, and 123 (two FDA-approved) as non-responsive or possibly non-responsive to elexacaftor-tezacaftor-ivacaftor.

Interpretation:

In France, over half of the population with cystic fibrosis without a F508del variant responded to elexacaftor-tezacaftor-ivacaftor, with most responders having no FDA-approved variant. The treatment period was relatively short and further research is warranted to describe the long-term safety and effectiveness of elexacaftor-tezacaftor-ivacaftor in this population.

Introduction

Elexacaftor–tezacaftor–ivacaftor is a combination of cystic fibrosis transmembrane conductance regulator (CFTR) modulators approved in several countries for the treatment of people with cystic fibrosis with at least one copy of the F508del CFTR variant, who constitute approximately 82% of people with cystic fibrosis worldwide.¹ Findings from large phase 3 randomised clinical trials,^{2–5} real-world data,^{6,7} and registry studies^{8,9} have established that treatment with elexacaftor–tezacaftor–ivacaftor results in improved respiratory symptoms and quality of life, increased percentage of predicted FEV1 (ppFEV1) and BMI, and decreased frequency of pulmonary exacerbations. Several studies have also reported a marked reduction in the requirement for lung transplantation.^{8,10,11} Elexacaftor–tezacaftor–ivacaftor is now largely recognised as a life-changing treatment for people with cystic fibrosis with at least one F508del CFTR variant. Because the F508del variant is less prevalent in non-White individuals, eligibility for CFTR modulators, including elexacaftor–tezacaftor–ivacaftor, is lower in non-White populations worldwide,¹² and in non-White minorities in the USA in particular, than in White individuals.¹³

Tezacaftor and elexacaftor were discovered thanks to high-throughput screening in cells expressing the F508del-CFTR protein,¹⁴ and mechanistic studies have shown that elexacaftor–tezacaftor–ivacaftor restores ion transport by binding of its individual molecules to specific sites in the mutated F508del-CFTR protein.¹⁵ Although the structure of the mutated CFTR protein is affected by the underlying CFTR variant, research has shown that elexacaftor–tezacaftor–ivacaftor can also restore CFTR function in some non-F508del CFTR variants in vitro,¹⁶ suggesting that elexacaftor–tezacaftor–ivacaftor could be effective in selected people with cystic fibrosis with no F508del variant. In December, 2020, the US Food and Drug Administration (FDA) approved elexacaftor–tezacaftor–ivacaftor for an additional 177 rare CFTR variants.¹⁷ Because including rare CFTR variant carriers in clinical trials is challenging due to the small number of potential participants, FDA approval has been based on in vitro studies in Fisher Rat Thyroid (FRT) cells using stable transfection with CFTR variants.^{17,18} Importantly, data are scarce for a direct correlation between results obtained in FRT cells and clinical outcomes in humans.^{19–21}

The French compassionate programme for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del CFTR who had advanced lung disease and were aged 12 years or older was launched on May 19, 2022, to provide access to elexacaftor–tezacaftor–ivacaftor for patients with rare CFTR variants, including FDA-approved and non-FDA approved variants. Initial data from this programme were obtained from 84 patients and revealed that those with selected FDA-approved and non-FDA-approved rare CFTR variants respond to elexacaftor–tezacaftor–ivacaftor.^{20,22} Based on these data, the French compassionate programme was expanded on June 1, 2023, to all people with cystic fibrosis, aged 6 years and older, without a F508del variant, regardless of disease severity. In this Article, we report data from 516 participants who enrolled in the programme since its inception. Our aims are to describe the clinical response to elexacaftor–tezacaftor–ivacaftor for people with cystic fibrosis without a F508del CFTR variant in France and to determine CFTR variant responsiveness to elexacaftor–tezacaftor–ivacaftor based on the observed clinical response.

Methods

Study design and participants

The French compassionate programme was launched on May 19, 2022, by the French drug agency (Agence nationale de sécurité du médicament et des produits de santé) for people with cystic fibrosis without a F508del variant, aged 12 years and older, with advanced lung disease (characterised by the Global Lung Function Initiative²³ ppFEV₁ ≤40 or consideration for lung transplantation, or both).²⁰

All patients received written information on the study's goals and design, and were informed of the use of their medical data for research purposes. Although they could decline to participate, written informed consent was not required according to French law. The study was approved by the institutional review board of the French Society for Respiratory Medicine (#2020–003).

Procedures

People with cystic fibrosis who agreed to participate in this programme were given elexacaftor–tezacaftor–ivacaftor for 4–6 weeks. Response to treatment was then determined by a centralised adjudication committee composed of three medical doctors specialised in adult or paediatric cystic fibrosis (PRB, IS, CM), a geneticist (EG), and a research manager (JDS), based on medical files addressed to the committee by physicians from France's 47 cystic fibrosis centres. Participants who were identified as responders were able to continue treatment thereafter, and non-responders stopped elexacaftor–tezacaftor–ivacaftor after the 4–6 week trial. When effectiveness, or lack thereof, could not be firmly established, the elexacaftor–tezacaftor–ivacaftor trial was extended for 2 additional months and response re-evaluated. The programme was expanded on June 1, 2023, to allow inclusion of all people with cystic fibrosis without a F508del variant, aged 6 years and older, regardless of disease severity.²⁴ Participants with two variants expected to produce no CFTR protein and for which at least three participants in the programme showed no response to elexacaftor–tezacaftor–ivacaftor after 4–6 weeks were considered ineligible to elexacaftor–tezacaftor–ivacaftor.²⁴ Consequently, the refusal to grant access to elexacaftor–tezacaftor–ivacaftor evolved over the course of the programme as the list of non-responsive variants was compiled.

The initial results for the first 84 participants treated with elexacaftor–tezacaftor–ivacaftor through the French compassionate programme have been published.²⁰ Because the programme uses all available data from people with cystic fibrosis without a F508del variant who are exposed to elexacaftor–tezacaftor–ivacaftor to derive

conclusions on the responsiveness of selected CFTR variants, the present Article includes all participants included in the programme since inception (including the previously published cases).

Participants were informed that treatment could be interrupted after the 4–6 week trial, or after the 2 month extension when warranted, if clinical improvement was insufficient to confirm treatment effectiveness. All patients, regardless of their response to treatment, received background clinical care from the multidisciplinary team before, during, and after receiving elexacaftor–tezacaftor–ivacaftor.

Outcomes

The centralised adjudication committee determined responder status based on a combination of outcomes (including clinical symptoms, weight, concomitant treatments, sweat chloride concentration, ppFEV1, and CT findings). As described previously,²⁰ the assessment considered all clinical evidence without specific criteria or cutoff values. Post-hoc analyses were conducted on aggregated data from responders and non-responders to determine the proportion of participants that had a decrease in sweat chloride concentration of at least 20 mmol/L or an increase in ppFEV1 of 5 or more percentage points or 10 or more percentage points. The adjudication committee also took into consideration all adverse effects reported by local physicians.

The potential responsiveness of each variant was predicted based on the variant's nature and classification using published evidence,²⁵ as well as available functional data, either from the literature^{16,22,26–33} or from the CFTR2 database³⁴ or the CFTR-France database.³⁵ Variants were classified as predicted responsive or predicted non-responsive. Several variants were classified as unknown predicted responsiveness due to insufficient data. The observed responsiveness of each variant was then determined based on observed outcomes in participants who received treatment with elexacaftor–tezacaftor–ivacaftor. Because cystic fibrosis is a recessive disease, deriving information on the responsiveness of a given CFTR variant based on responder or non-responder status of participants exposed to elexacaftor–tezacaftor–ivacaftor requires knowledge or determination of the other variant's responsiveness. Clinical response in the elexacaftor–tezacaftor–ivacaftor recipient (responder) implies that at least one of their variants is responsive to the treatment. In responders, information on the responsiveness of a variant can therefore be derived only when the carrier has two copies of that variant (homozygous genotype) or when the variant is in trans with a non-responsive variant. When non-responder status is confirmed, both variants are considered non-responsive in that participant. For the purposes of determining a list of responsive variants, a variant was defined as responsive when at least three participants that were homozygous for that variant or heterozygous in trans with a non-responsive variant were categorised as responders. A variant was defined as possibly responsive when only one or two participants met these criteria. Similarly, a variant was defined as non-responsive when at least three participants were characterised as non-responders and as possibly non-responsive when only one or two participants did not respond to elexacaftor–tezacaftor–ivacaftor. Variants that were present only in responders and were in trans with a responsive variant or with a variant of unknown responsiveness were classified as inconclusive. Complex alleles were counted as single variants.

Statistical analysis

Data are presented as n (%), median (IQR), or mean (95% CI), as appropriate. Comparisons of sweat chloride concentrations, ppFEV1, and bodyweight before initiation of elexacaftor–tezacaftor–ivacaftor and with elexacaftor–tezacaftor–ivacaftor were conducted using the non-parametric Wilcoxon’s matched-pairs signed rank test, which tested for evidence against the null hypothesis that the distribution of paired changes before to after exposure to elexacaftor–tezacaftor–ivacaftor was symmetrical about zero. All analyses were conducted using Prism 10.03 (GraphPad).

Role of the funding source

Funding sources had no role in data interpretation or analysis, nor in the writing or the decision to submit this manuscript.

	All (n=479)	At least one FDA-approved variant (n=114)	None of the FDA-approved variants (n=365)
Sex assigned at birth			
Female	229 (48%)	58 (51%)	171 (47%)
Male	250 (52%)	56 (49%)	194 (53%)
Age, years	23 (13–33)	32 (20–42)	21 (12–31)
Children			
<18 years	180 (38%)	26 (23%)	154 (42%)
12–17 years	87 (18%)	14 (12%)	73 (20%)
<12 years	93 (19%)	12 (11%)	81 (22%)
Adults (≥18 years)	299 (62%)	88 (77%)	211 (58%)
Pancreatic insufficiency	340 (71%)	55 (48%)	285 (78%)
Sweat chloride concentration, mmol/L	97 (79–107)	67 (38–95)	100 (89–108)
FEV ₁ , L	1.81 (1.26–2.59)	1.96 (1.26–2.86)	1.77 (1.27–2.46)
Percentage of predicted FEV ₁	64 (42–86)	63 (38–91)	65 (43–85)
Diabetes	107 (22%)	14 (12%)	93 (25%)
Liver cirrhosis	14 (3%)	2 (2%)	12 (3%)
Ivacaftor at initiation	36 (8%)	31 (27%)	5 (1%)

Data are n (%) or median (IQR). CFTR=cystic fibrosis transmembrane conductance regulator. FDA=US Food and Drug Administration. Race and ethnicity were not collected as this is prohibited by French laws.

Table 1: Main characteristics before treatment initiation of 479 people with cystic fibrosis who received elexacaftor–tezacaftor–ivacaftor in the French compassionate programme

Results

The screening began on May 19, 2022, and by March 8, 2024, a total of 516 people with cystic fibrosis without a F508del CFTR variant had been screened for inclusion in the French compassionate programme for a 4–6 week elexacaftor–tezacaftor–ivacaftor trial. 37 participants carried two CFTR variants already known to be non-responsive to elexacaftor–tezacaftor–ivacaftor and were considered not eligible to receive treatment. The CFTR genotypes that were excluded from the programme are presented in the appendix (p 4).

479 participants (229 females and 250 males) were given elexacaftor–tezacaftor–ivacaftor for an initial period of 4–6 weeks; 114 (24%) had at least one of the 177 FDA- approved variants, the other 365 (76%) did not. Participants' characteristics are presented in table 1. At the time of treatment initiation, 443 (92%) participants were CFTR modulator-naïve and 36 (8%; including 31 with an FDA-approved variant) were receiving ivacaftor.

Elexacaftor–tezacaftor–ivacaftor was initiated in all participants at recommended doses for age and bodyweight. Clinical outcomes were evaluated by the centralised evaluation committee, as described previously.²⁰ A flow chart describing the number of responders and non-responders among enrolled participants, categorised into FDA-approved variant carriers and ivacaftor treatment at elexacaftor–tezacaftor– ivacaftor initiation, is presented in figure 1.

The centralised adjudication committee reached a final decision on responder status after the initial 4–6 week treatment period in 424 (89%) of the 479 participants who received elexacaftor–tezacaftor– ivacaftor. For 55 (11%) participants, effectiveness could not be firmly determined after 4–6 weeks, and an extension was granted for an additional 2 months of elexacaftor–tezacaftor–ivacaftor treatment.

Overall, study treatment was confirmed effective in 290 participants (responders), who thereafter gained ongoing free access to elexacaftor–tezacaftor–ivacaftor, the cost of which is fully covered by national health insurance. The proportion of responders in our sample of participants without a F508del variant was 61% (290 of 479) among those who benefited from the 4–6 week elexacaftor–tezacaftor–ivacaftor trial and 56% (290 of 516) among all participants who were considered for treatment eligibility through the compassionate programme. Among the 290 responders, 181 (62%) had no FDA-approved variant and 109 (38%) had at least one FDA-approved variant. 189 (39%) of 479 participants who were determined to be non- responders stopped elexacaftor–tezacaftor–ivacaftor at the end of the evaluation process. The changes in sweat chloride concentrations, ppFEV1, and bodyweight after study treatment initiation are shown in table 2 and figure 2. These changes were large, with clinical and statistical significance in responders. Significant differences were also observed for sweat chloride concentrations and ppFEV1 after elexacaftor–tezacaftor– ivacaftor initiation in the 183 non-responders with no FDA-approved variants. However, these differences were minimal (mean -1.8 mmol/L [95% CI -3.0 to 0.3] for sweat chloride concentration and 1.6 percentage points [0.5 to 2.8] for ppFEV1) and not deemed to be clinically significant. The differences were probably attributable to variability in measurement and for ppFEV1 to the potential effect of other treatments (eg, antibiotics). The change in sweat chloride concentration and ppFEV1 by age group (6–11 years, 12–17 years, and ≥ 18 years) as well as additional data stratified by age group are presented in the appendix (pp 2–3, 31–33).

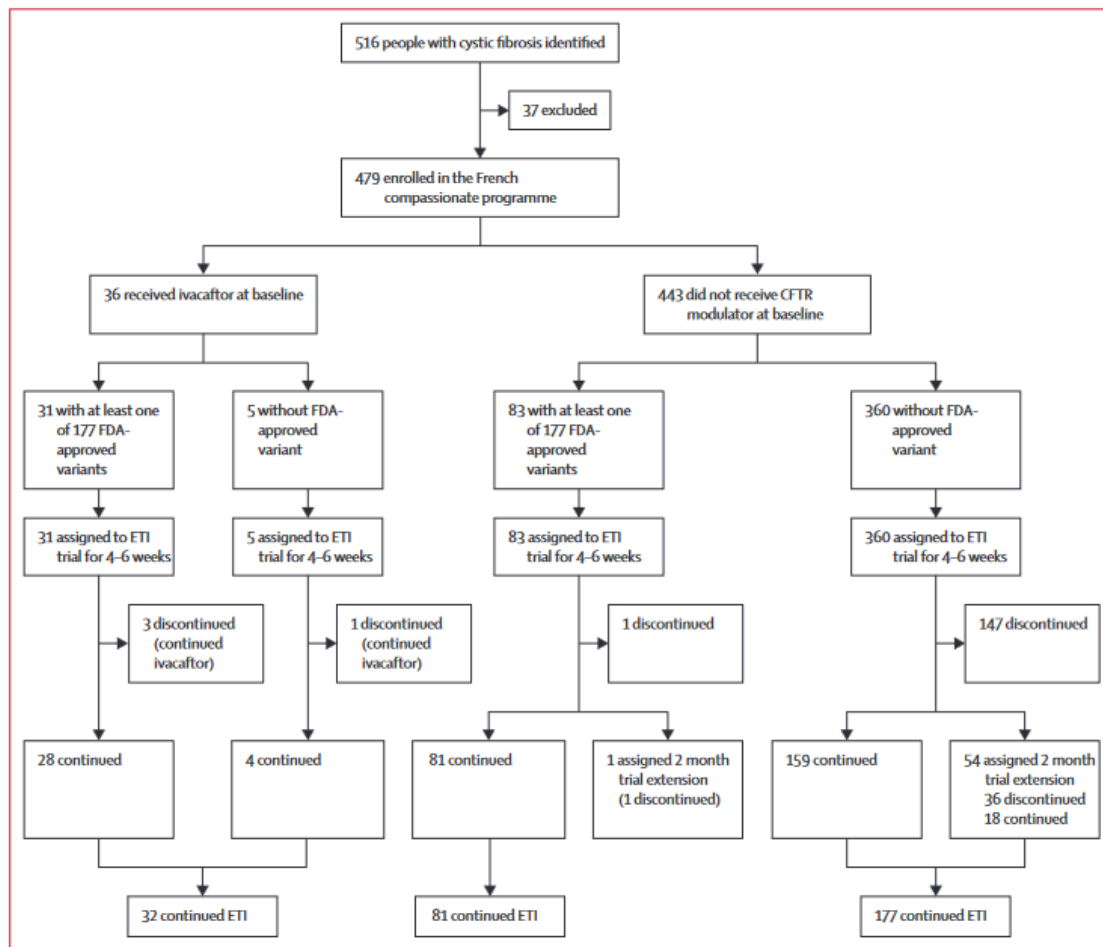


Figure 1: Study profile

Flow-chart depicting the clinical response outcomes to ETI in 516 people with cystic fibrosis evaluated by the French compassionate programme centralised adjudication committee, grouped by *CFTR* genotypes and treatment with ivacaftor at baseline. Participants were excluded from the programme if they carried two *CFTR* variants previously classified as non-responsive to ETI. Subpopulations included people with cystic fibrosis receiving no modulator versus those receiving ivacaftor at the time of study treatment initiation, and people with cystic fibrosis carrying at least one of the 177 FDA-approved variants for ETI versus none of the 177 FDA-approved variants. Outcomes are described after 4–6 weeks of ETI, and after 2 additional months of ETI if consensus could not be reached after the evaluation at 4–6 weeks. Discontinuations were due to absence of observed treatment response; no discontinuations were based on experiences of adverse events. ETI=elexacaftor-tezacaftor-ivacaftor. FDA=US Food and Drug Administration.

The safety profile corresponded to that expected for elexacaftor–tezacaftor–ivacaftor. The most prevalent adverse effects were cutaneous rash in 30 (6%) of 479 participants and headache or mild mental health symptoms (mild anxiety, difficulties falling asleep, and irritability) in 12 (3%) of 479 participants. No elevation of liver enzymes above three times the upper limit of normal was observed in any of the participants and no patient discontinued treatment due to adverse effects.

Among the 443 participants who were not being treated with a *CFTR* modulator at the time of elexacaftor–tezacaftor–ivacaftor initiation, 83 had at least one FDA-approved variant, of whom 81 (98%) were considered responders. One I175V carrier (in trans with *CFTR*dele2) and one M152V carrier (in trans with 3120+1G>A) were considered non-responders and stopped elexacaftor–tezacaftor–ivacaftor. Individual-level clinical outcomes in this group of FDA-variant carriers are presented in the appendix (pp 5–8). In the group that did not have an FDA-approved variant and were *CFTR* modulator-naïve (n=360), 177 (49%) were determined to respond to elexacaftor–tezacaftor–ivacaftor. Individual data for these 177 responders and for the 183 non-responders with no FDA-approved variant are presented in the appendix (pp 9–26). Aggregated data obtained in

responders with the most prevalent (ie, present in at least five patients) non-FDA- approved variants (including N1303K, 2789+5G>A, R334W, 3272-26G>A, R1066C, c.870-1113_870-1110del, and 3849+10kbC>T) and FDA-approved variants (G85E, R347P, and D1152H) are presented in table 3. Sweat chloride concentration decrease was minimal in responders with N1303K, 2789+5G>A, and R334W variants, with values often remaining greater than 60 mmol/L. These three variants were present in 97 (55%) of 177 responders with no FDA-approved variant, which could explain the smaller decrease in sweat chloride concentration observed in responders with no FDA-approved variants compared with those with FDA-approved variants (mean -20.5 mmol/L [95% CI -17.2 to -23.8] vs -44.5 mmol/L [-39.1 to -49.8]; $p<0.0001$; table 2).

36 participants (31 with at least one of the 177 FDA- approved variants and five carrying at least a 2789+5G>A or a 3849+10kbC>T, which are approved by the FDA for ivacaftor, but not for elexacaftor–tezacaftor–ivacaftor), were treated with ivacaftor at the time of elexacaftor–tezacaftor– ivacaftor initiation. No other modulator (lumacaftor– ivacaftor or tezacaftor–ivacaftor) was prescribed before elexacaftor–tezacaftor–ivacaftor, as these modulator combinations are not approved for use in people with cystic fibrosis without a F508del CFTR variant in France. Among participants treated with ivacaftor, 32 (89%) of 36 were considered responders and four (11%) interrupted elexacaftor–tezacaftor–ivacaftor and continued ivacaftor as there was no evidence of incremental clinical improvement with elexacaftor–tezacaftor–ivacaftor. Their characteristics are presented in the appendix (pp 27–28). Aggregated data obtained in 17 participants with at least one G551D variant and treated with ivacaftor before elexacaftor–tezacaftor–ivacaftor initiation are shown in table 3.

Overall, among the 516 participants presented for inclusion in the French compassionate programme, 251 individual CFTR variants were identified, including 42 variants approved by the FDA for elexacaftor–tezacaftor–ivacaftor. An initial prediction of variant responsiveness to elexacaftor–tezacaftor–ivacaftor was determined based on published literature and CFTR databases;^{34,35} the rules applied in this prediction are described in the appendix (p 34). All 42 FDA-approved variants found in our patient sample were predicted responsive to elexacaftor–tezacaftor–ivacaftor since efficacy has been shown in FRT cells, although documented splicing defects could have resulted in some variants being predicted non-responsive.³⁶ For non-FDA-approved variants, 35 were predicted to be responsive and 146 to be non-responsive to elexacaftor–tezacaftor– ivacaftor; the predicted response in the remaining 28 variants was uncertain due to insufficient data.

	Non-responders with no FDA-approved CFTR variants (n=183)	Responders with at least one FDA-approved CFTR variant (n=81*)	Responders with no FDA-approved CFTR variants (n=177)	People treated with ivacaftor at initiation of elexacaftor-tezacaftor-ivacaftor (n=36)
Sweat chloride concentration, mmol/L				
Before elexacaftor-tezacaftor-ivacaftor	103 (94 to 110)	81 (61 to 101)	96 (81 to 106)	30 (21 to 42)
With elexacaftor-tezacaftor-ivacaftor	101 (94 to 108)	30 (20 to 46)	80 (50 to 94)	18 (11 to 28)
Mean absolute change	-1.8 (-3.9 to 0.3)	-44.5 (-39.1 to -49.8)	-20.5 (-17.2 to -23.8)	-11.2 (-15.0 to -7.5)
Sweat chloride concentration with elexacaftor-tezacaftor-ivacaftor				
≥60 mmol/L	179 (98%)	13 (16%)	123 (69%)	3 (8%)
30-59 mmol/L	0	28 (35%)	28 (16%)	5 (14%)
<30 mmol/L	0	40 (49%)	25 (14%)	28 (78%)
Missing values	4	0	1	0
Decrease in sweat chloride concentration by ≥20 mmol/L with elexacaftor-tezacaftor-ivacaftor				
n (%)	11 (6%)	68 (84%)	74 (42%)	10 (28%)
Missing values	5	0	1	0
ppFEV₁				
Before elexacaftor-tezacaftor-ivacaftor	65 (42 to 82)	72 (43 to 95)	65 (45 to 86)	53 (33 to 78)
With elexacaftor-tezacaftor-ivacaftor	67 (46 to 84)	89 (56 to 105)	80 (57 to 101)	63 (39 to 86)
Mean absolute change	1.6 (0.5 to 2.8)	11.1 (8.4 to 13.7)	13.2 (11.4 to 15.0)	4.9 (2.0 to 7.7)
Absolute increase in ppFEV₁				
≥5% percentage points	47 (26%)	56 (69%)	138 (78%)	11 (31%)
≥10% percentage points	23 (13%)	40 (49%)	96 (54%)	5 (14%)
Missing values	9	0	5	2
Weight, kg				
Before elexacaftor-tezacaftor-ivacaftor	46 (35 to 56)	58 (48 to 69)	54 (43 to 67)	63 (56 to 75)
With elexacaftor-tezacaftor-ivacaftor	47 (36 to 56)	60 (49 to 71)	55 (44 to 69)	62 (56 to 75)
Mean absolute change	0.5 (0.3 to 0.7)	1.6 (1.2 to 2.1)	1.4 (1.1 to 1.6)	0.1 (-0.4 to 0.7)
Data are n (%), median (IQR), or mean (95% CI). CFTR=cystic fibrosis transmembrane conductance regulator. ppFEV ₁ =percentage of predicted FEV ₁ . FDA=US Food and Drug Administration. * There were 83 people with cystic fibrosis with at least one FDA-approved variant; the two non-responders with FDA-approved variants were excluded from this table.				
Table 2: Changes from elexacaftor-tezacaftor-ivacaftor treatment initiation in sweat chloride concentration, ppFEV₁, and bodyweight in 479 people with cystic fibrosis				

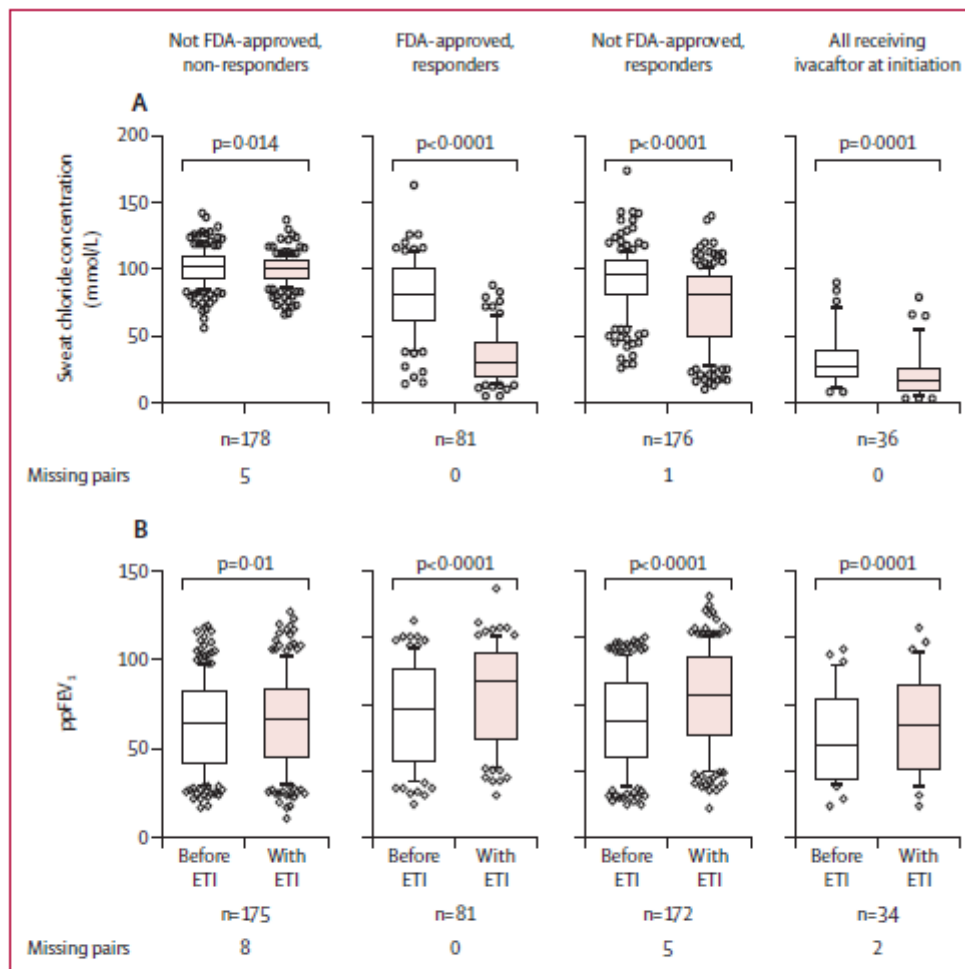


Figure 2: Comparison of (A) sweat chloride concentration and (B) ppFEV₁ before ETI initiation and with ETI treatment

Data are grouped according to responder and non-responder status, as determined by the centralised adjudication committee, in people with cystic fibrosis with no modulator at ETI initiation. Responders are shown separately according to the presence or absence of at least one FDA-approved variant. Data obtained in participants treated with ivacaftor before initiation of study treatment are shown separately. Data were analysed using the Wilcoxon matched-pairs signed rank test. Data are presented as median, IQR, and 10–90th percentiles with outliers.

ETI=elexacaftor-tezacaftor-ivacaftor. FDA=US Food and Drug Administration. ppFEV₁=percentage of predicted FEV₁.

Variant responsiveness, as ascertained after elexacaftor–tezacaftor–ivacaftor treatment through the French compassionate programme, is presented in table 4. 17 variants were unequivocally responsive (always responsive in at least three responders homozygous or in trans with non-responsive variants), including nine FDA-approved variants (D1152H, G1249R, G551D, G85E, L206W, R347P, S549N, S945L, and S977F) and, importantly, eight non-FDA-approved variants (N1303K, R334W, R1066C, 2789+5G>A, 3272-26A>G, 3849+10kbC>T, c.3874-4522A>G, and c.870-1113_870-1110del). In addition, 47 variants (19 FDA-approved and 28 non-FDA-approved) were probably responsive (always responsive in one or two responders homozygous or in trans with non-responsive variants).

37 variants were unequivocally non-responsive (always non-responsive in at least three non-responders), including I507del, L227R, E1104X, E585X, G542X, Q220X, R1162X, R553X, S466X, W1098X, W1282X, W846X, Y122X, 1078delT, 1677delTA, 2183AA>G, 3659delC, 394delTT, 1717-1G>A, 2622+1G>A, 3120+1G>A, 621+1G>T, 711+1G>T, CFTRdele17a-18, CFTRdele2-3, 1811+1.6kbA>G, and c.3469-1304C>G. In addition, 96 variants (two FDA-approved [I175V and M152V] and 94 non-FDA-approved) were probably non-responsive (always non-responsive in one or two non-responders).

Another 64 variants were present only in trans of known responsive variants and could therefore not be categorised.

Discussion

The short-term clinical outcomes of elexacaftor–tezacaftor–ivacaftor in people with cystic fibrosis without a F508del *CFTR* who received treatment through the French compassionate programme show that more than half of the participants demonstrated rapid improvement in clinical symptoms, sweat chloride concentration, or ppFEV₁, or all of these outcomes. Overall, 290 of 479 participants responded to treatment and were able to continue elexacaftor–tezacaftor–ivacaftor in the long term. Treatment effectiveness was determined by a centralised adjudication committee and allowed the categorisation of 64 *CFTR* variants as responsive or possibly responsive to elexacaftor–tezacaftor–ivacaftor, among which several variants are not currently approved for this treatment anywhere in the world. Another 123 variants were considered non-responsive or possibly non-responsive. These data contribute to our knowledge of responsiveness to elexacaftor–tezacaftor–ivacaftor in people with cystic fibrosis without F508del *CFTR* variants.

	N1303K (n=60)	T7895G>A (n=23)	R334W (n=14)	S273-26G>A (n=11)	R1066C (n=8)	c.870- 1113_870- 1110del (n=10)	384910kbC>T (n=9)	G85E* (n=11)	R347P* (n=9)	D1152H* (n=7)	G551D* treated with ivacaftor at initiation (n=17)
Sweat chloride concentration, mmol/L											
Before elexacaftor-tezacaftor-ivacaftor	103 (94 to 109)	99 (90 to 107)	103 (91 to 105)	87 (81 to 100)	102 (96 to 107)	55 (47 to 82)	52 (38 to 63)	102 (82 to 109)	102 (95 to 113)	38 (23 to 46)	30 (26 to 41)
With elexacaftor-tezacaftor-ivacaftor	92 (85 to 100)	76 (61 to 86)	85 (66 to 91)	72 (55 to 84)	60 (48 to 80)	42 (27 to 48)	28 (17 to 33)	56 (20 to 66)	65 (38 to 81)	17 (10 to 30)	17 (11 to 28)
Mean absolute change	-12.0 (-16.9 to -7.1)	-12.8 (-19.1 to -6.4)	-17.3 (-23.4 to -11.3)	-19.6 (-29.9 to -9.1)	-41.2 (-60.1 to -22.3)	-23.5 (-35.9 to -11.1)	-25.1 (-34.8 to -15.4)	-44.2 (-61.1 to -27.3)	-43.3 (-62.7 to -24.0)	-18.0 (-27.2 to -8.7)	-12.8 (-18.7 to -7.0)
Missing values	1	0	1	0	0	0	0	0	0	0	0
Decrease in sweat chloride ≥ 20 mmol/L with elexacaftor-tezacaftor-ivacaftor											
n (%)	14 (23%)	6 (26%)	5 (38%)	4 (36%)	7 (88%)	5 (50%)	7 (78%)	9 (82%)	8 (89%)	3 (43%)	4 (24%)
Missing values	1	0	0	0	0	0	0	0	0	0	0
Sweat chloride concentration with elexacaftor-tezacaftor-ivacaftor											
≥60 mmol/L	56 (93%)	23 (100%)	12 (92%)	8 (73%)	4 (50%)	0	0	5 (46%)	5 (56%)	0	0
30-59 mmol/L	1 (2%)	0	0	3 (27%)	3 (38%)	7 (70%)	4 (44%)	3 (27%)	3 (33%)	2 (29%)	3 (18%)
<30 mmol/L	2 (3%)	0	1 (8%)	0	1 (12%)	3 (30%)	5 (56%)	3 (27%)	1 (11%)	5 (71%)	14 (82%)
Missing values	1	0	0	0	0	0	0	0	0	0	0
ppFEV₁											
Before elexacaftor-tezacaftor-ivacaftor	63 (47 to 86)	67 (46 to 91)	67 (42 to 102)	64 (56 to 100)	63 (27 to 90)	53 (41 to 89)	69 (29 to 83)	55 (36 to 92)	60 (27 to 93)	87 (86 to 102)	60 (37 to 91)
With elexacaftor-tezacaftor-ivacaftor	82 (61 to 100)	84 (59 to 102)	83 (56 to 101)	77 (64 to 106)	75 (42 to 124)	79 (48 to 104)	80 (40 to 113)	86 (52 to 108)	60 (39 to 105)	94 (70 to 111)	66 (45 to 96)
Mean absolute change	15.1 (11.3 to 18.9)	11.0 (6.5 to 15.5)	11.4 (4.1 to 18.6)	9.0 (3.5 to 14.5)	21.4 (10.1 to 32.7)	13.0 (1.1 to 24.9)	11.3 (3.5 to 19.1)	16.5 (9.5 to 23.5)	10.9 (2.9 to 18.9)	7.3 (-4.7 to 19.2)	6.5 (1.1 to 11.9)
Missing values	1	2	0	0	0	0	2	0	0	0	0
Absolute increase in ppFEV₁											
≥5% percentage points	48 (80%)	17 (74%)	12 (86%)	7 (64%)	7 (88%)	8 (70%)	5 (56%)	10 (91%)	6 (67%)	6 (86%)	9 (53%)
≥10% percentage points	34 (57%)	9 (39%)	5 (38%)	4 (36%)	7 (88%)	5 (50%)	3 (33%)	9 (82%)	5 (56%)	2 (29%)	3 (18%)
Missing values	1	2	0	0	0	0	2	0	0	0	0
Weight, kg											
Before elexacaftor-tezacaftor-ivacaftor	47 (31 to 56)	63 (50 to 73)	64 (49 to 74)	57 (50 to 71)	38 (21 to 52)	67 (52 to 77)	50 (25 to 60)	64 (54 to 67)	55 (41 to 67)	70 (66 to 73)	58 (56 to 73)
With elexacaftor-tezacaftor-ivacaftor	48 (33 to 58)	64 (51 to 74)	68 (52 to 73)	58 (50 to 72)	41 (22 to 53)	67 (55 to 80)	52 (25 to 62)	66 (57 to 68)	55 (44 to 66)	71 (67 to 74)	58 (56 to 73)
Mean absolute change	1.8 (1.4 to 2.3)	0.6 (-0.4 to 1.6)	1.4 (-0.2 to 2.9)	0.9 (-0.1 to 1.8)	2.2 (0.7 to 3.6)	1.6 (0.4 to 2.9)	1.3 (0.3 to 2.4)	2.6 (1.5 to 3.6)	1.8 (-0.1 to 3.7)	1.1 (-0.5 to 2.7)	0.6 (-0.2 to 1.3)
Data are n (%), median (IQR), or mean (95% CI). FDA=US Food and Drug Administration. ppFEV ₁ =percentage of predicted FEV ₁ . Data in this table are limited to variants with data available from at least five responders. * G85E, R347P, D1152H, and G551D are FDA-approved variants; all other variants are non-FDA-approved. For non-FDA-approved variants, results include data from all people with cystic fibrosis with the variant of interest, excluding those in trans with an FDA-approved variant. A variant was defined as responsive when at least three people with cystic fibrosis that were homozygous for that variant or heterozygous in trans with a non-responsive variant were categorised as responders.											

Table 3: Changes from elexacaftor-tezacaftor-ivacaftor treatment initiation in sweat chloride concentration, ppFEV₁, and weight

	Responsive (n≥3 responders)	Probably responsive (1-2 responders)	Probably non-responsive (1-2 non-responders)	Non-responsive (n≥3 non-responders)	Inconclusive
FDA-approved variants					
All	Missense: D1152H, G1249R, G551D, G85E, L206W, R347P, S549N, S945L, S977F	Missense: A455E (n=2), D110H (n=1), E92K (n=1), F311L (n=1), G178R (n=1), G576A, R668C* (n=1), H1054D (n=1), I601F (n=1), P205S (n=1), R1066H (n=1), R117H (n=2), R347H (n=1), R74W, V201M*, D1270N* (n=1), R933G (n=1), S13F (n=1), S364P (n=2), S549R (n=1), V1153E (n=2), V232D (n=2)	Missense or splicing: I175V (n=1), M152V (n=1)	--	Missense: A46D, E60K, G628R, G1061R, H1085R, P5L, L165S, L997F, M1101K, S1251N, S492F, R117C
Non-FDA-approved variants					
Predicted responsive†	Missense: N1303K, R334W, R1066C Splicing: 2789+5G>A, 3272-26A>G Deep intronic, splicing: 3849+10kbC>T, c.3874-4522A>G, c.870-1113_870-1110del	Missense: A559V (n=1), A1067D (n=1), D513G (n=1), D985Y (n=1), E1044G (n=1), E1104V (n=2), F1078S (n=1), G149R (n=1), I618N (n=2), L1065R (n=1), Q552P (n=1), R31C (n=1), R851L (n=1), T1057R (n=1) Nonsense or splicing: E831X (n=1) Leading to nonsense in last exon: 4374+1G>A (n=1)	Missense: G85V (n=1)	--	Missense: D1445N, E292K, F575V, R600S, S1235R, TG12T5*, T1086I, V1020E Nonsense in last exon: Q1476X Frameshift in last exon: 4382delA Deep intronic: c.2989-313A>T
Predicted non-responsive†	--	Missense: A561E (n=1)	Missense: A559T (n=1), H199R (n=2), I601T (n=1), L558S (n=2) Nonsense: C1410X (n=1), K52X (n=1), K710X (n=1), Q493X (n=2), Q525X (n=1), R1158X (n=1), R709X (n=2), R75X (n=1), R792X (n=2), R851X (n=1), S1196X (n=1), S424X (n=2), S776X (n=2), W1063X (n=1), W1089X (n=1), W1204X (n=1), Y275X (n=2) Frameshift: 1134delG (n=1), 1213delT (n=1), 1259insA (n=1), 1380insT (n=1), 1448dupC (n=1), 1609delCA (n=1), 1874insT (n=1), 2026_2027delGA (n=1), 2143delT (n=1), 2184delA (n=1), 2184insA (n=1), 2347delG (n=2), 241delAT (n=1), 2567delT (n=1), 2582delG (n=1), 2634delT (n=1), 2711delT (n=1), 2869insG (n=1), 2896insAG (n=1), 3007delG (n=1), 306delTAGA (n=1), 3129delAAATT (n=1), 3143delC (n=1), 3154delG (n=1), 3213_3214insT (n=1), 3270delA (n=1), 3312delA (n=1), 3586_3587delCA (n=1), 359insT (n=1), 3730_3731AA>G (n=1), 3730delAinsTCT (n=1), 3791delC (n=1), 3905insT (n=2), 4016insT (n=2), 4040delA (n=1), 4271delC (n=1), 440delG (n=1), 489delC (n=1), 503delG (n=1), 733delG (n=1), 905delG (n=1), 907delCins11pb (n=1), 991delS (n=1) Canonical splicing: 1525-1G>A (n=2), 1811+1G>C (n=1), 185+1G>T (n=2), 3040+1G>A (n=1), 3600+1G>T (n=1), 406-2A>G (n=1), 621+2T>G (n=1) Translation start: M1T (n=2) Exon deletions: CFTRdele2 (n=1), CFTRdele14b-15 (n=1), CFTRdele14b-17b (n=2), CFTRdele16-17b (n=1), CFTRdele17a-17b (n=1), CFTRdele17b (n=1), CFTRdele19 (n=1), IVS1-5811-IVS2+2186del8108ins182 (n=1), CFTRdele2-4 (n=1), CFTRdele3-10,14b-16, V754M* (n=2), CFTRdele4 (n=1), CFTRdele7-9, M498I* (n=2)	In-frame deletion: I507del Missense: L227R Nonsense: E1104X, E585X, G542X, Q220X, R1162X, R553X, S466X, W1098X, W1282X, W846X, Y122X Frameshift: 1078delT, 1677delTA, 2183AA>G, 3659delC, 394delTT Canonical splicing: 1717-1G>A, 2622+1G>A, 3120+1G>A, 621+1G>T, 711+1G>T Exon deletions: CFTRdele17a-18, CFTRdele2-3	In-frame deletion: 3199del6 Missense: I506T Nonsense: E60X, K951X, Q270X, Q290X, S489X, S1206X, W79X, W401X, Y1092X Frameshift: 1221delCT, 181_182dup, 2640delT, 2875_2877delGTGinsA, 2828delG, 2937_2942delinsTCAGA, 2942insT, 3396delC, 354_355delGinsA, 3629delT, 3667ins4, 3737delA, 3747delC, 4172delGC, 4326delTC, 852del22 Canonical splicing: 1248+1G>A, 2790-1G>C, 3121-1G>A, 712-1G>T, 875+1G>A*, S1235R* Translation start: M1V Exon deletions: CFTRdele4-7,12-18, CFTRdele22-24 Exon duplication: CFTRdup4-10
Unknown predicted responsiveness†	--	In-frame deletion: 232delI8 (n=1), D192del (n=1) Missense: L101S (n=1), V938L, A969A* (n=1) Splicing: 1341G>A (n=2), 1898+3A>G (n=1), 3041-15T>G (n=2), 3272-11A>G (n=1), 4096-3C>G (n=1), 622-3T>G (n=1), G970V (n=1)	Splicing: 3600G>A (n=1), G970R (n=1), 1717-8G>A (n=1), 3850-1G>A (n=2), K464N (n=1), 4005+1G>A (n=2), 4374+1G>T (n=1), 4375-2A>C (n=1), R560K (n=2)	Deep intronic, splicing: 1811+1.6kbA>G, c.3469-1304C>G	Missense: K598E Splicing: 1898+3A>C, 1898+5G>A, 3120G>A, 4006-1G>A, 711+5G>A
Data are grouped according to FDA-approved status and predicted responsiveness based on data from the literature. For variants found to be probably responsive or probably non-responsive in the present study, the number of participants with the variant is given in brackets. FDA=US Food and Drug Administration. *Complex alleles. †Prediction based on previously available data from the literature and CFTR databases.					
Table 4: Variant responsiveness to elxacaftor–tezacaftor–ivacaftor, as determined from observed response in people with cystic fibrosis in the French compassionate programme					

The proportion of CFTR modulator-naïve participants who had at least one FDA-approved variant and responded to elxacaftor–tezacaftor–ivacaftor was very high (98%). This finding suggests that responsiveness in FRT cells is highly predictive of clinical response, and extends the findings of published studies with smaller patient and variant samples.^{19,20} Two patients with two different FDA-approved variants (I175V and M152V) were nevertheless determined to be non-responders. These observations are in keeping with previous studies, which clearly showed their marked effect on mRNA splicing, resulting in non-responsive CFTR proteins deleted in 12 and 19 residues, respectively.^{30,31} Our findings further confirm the near absence of a normal residual transcript and protein that could respond to elxacaftor–tezacaftor–ivacaftor in vivo. Such a discrepancy between the correction of mutant CFTR M152V and I175V proteins in FRT cells and the absence of clinical response to elxacaftor–tezacaftor–ivacaftor illustrate the importance of considering the potential of variants

to alter splicing, which can inform treatment, as suggested by Raraigh and colleagues.³⁶ Among the participants in the French compassionate programme who responded to elexacaftor–tezacaftor–ivacaftor, the proportion of those who did not carry an FDA-approved variant exceeded those with FDA-approved variants, confirming our initial reports.^{20,22} This finding, supported by previous data from this programme^{20,22,37} and other reports,^{38,39} shows that the list of FDA-approved variants is not comprehensive. Elexacaftor–tezacaftor–ivacaftor might therefore be effective in many people with cystic fibrosis with non- FDA-approved variants.

The French compassionate programme helped to identify 17 variants that were consistently responsive to elexacaftor–tezacaftor–ivacaftor, eight of which are, at the time of writing, not approved anywhere in the world for this drug combination. These variants are: three missense variants (N1303K, R334W, and R1066C), two splicing variants in the border of exons (2789+5G>A and 3272-26A>G), and three deep intronic or splicing variants (3849+10kbC>T, c.3874-4522A>G, and c.870-1113_870-1110del). These eight variants were present in 130 of the 177 (73%) responders with no FDA-approved variants. Of note, three of the splicing variants identified here as responsive to elexacaftor–tezacaftor–ivacaftor (2789+5G>A, 3272-26A>G, and 3849+10kbC>T) were also included in a recently completed clinical trial by Vertex Pharmaceuticals.⁴⁰ The present study further suggests that elexacaftor–tezacaftor–ivacaftor might amplify residual CFTR protein function in people with cystic fibrosis carrying non-canonical splicing variants.

A number of people with cystic fibrosis who participated in the French compassionate programme were treated with ivacaftor at the time of initiation of treatment with elexacaftor–tezacaftor–ivacaftor, which allowed us to assess the effect of this combined treatment compared with ivacaftor alone in ivacaftor-eligible participants. Adding the correctors tezacaftor and elexacaftor to ivacaftor increased ppFEV1 and decreased sweat chloride concentration, especially in G551D carriers. This finding would suggest either that G551D and other gating variants can induce more than a gating defect or that tezacaftor and elexacaftor, in combination or individually, increase the potentiation induced by ivacaftor.

The French compassionate programme was implemented thanks to a collaboration between the French Cystic Fibrosis Reference Centre Network and the French patient association Vaincre la Mucoviscidose. All 47 French cystic fibrosis centres participated in the programme and all clinical outcomes were evaluated by a centralised adjudication committee, which ensured consistency in evaluating clinical outcomes and enabled the iterative integration of variant responsiveness status. The programme included participants across a wide range of age and disease severity profiles, and showed the feasibility of such an approach. The committee’s evaluation of each patient’s response was centralised and did not rely on decisions made by local investigators; although there could be some subjectivity in the determination of clinical effectiveness, the committee’s decisions were confirmed by the results of the post-hoc analyses of aggregated data, which showed marked differences in the evolution of ppFEV1 and sweat chloride concentrations between responders and non-responders. Although most decisions on responder and non-responder status were easy to achieve after the initial 4–6 week elexacaftor–tezacaftor–ivacaftor treatment, it was uncertain in 55 of the 479 (11%) participants, who received a 2 month treatment extension at the end of which 37 (67%) of 55 participants were classified as non-responders. The combined drug treatment period was relatively short and further research is warranted to describe the long-term safety and effectiveness of elexacaftor–tezacaftor–ivacaftor. Some of the participants that were characterised as non-responders to elexacaftor–tezacaftor–ivacaftor had a decrease in cough and sputum production, which could be ascribed to a placebo effect. We cannot exclude that a longer observation period might have resulted in different outcomes, although this is highly unlikely because the onset of action of elexacaftor–tezacaftor–ivacaftor usually occurs within days or weeks. *CFTR* variants present in this study are representative of the genetic diversity in France, a multiethnic country. These data are likely generalisable to other countries where these variants are found, although rates of response to elexacaftor–tezacaftor–ivacaftor within a geographical area could differ due to worldwide variability in genetic diversity.

During the implementation of the programme, five participants who were initially classified as non-responders were reclassified as responders. Three of them carried the 2789+5G>A variant, one was 4096-3C>G homozygous, and one was a c.2989-313A>T/2942insT carrier. Status was reclassified to non-responder in one 1717-1G>A/2183AA>G carrier. Altogether, these changes in response classification occurred in 1% of

participants (six of 479; appendix pp 29–30), confirming the robustness of our approach. At the time of writing, the only discrepancy for variant responsiveness was for 1898+3A>C (one homozygous categorised as non-responder and one in trans with the probably non-responsive 1811+1G>C categorised as responder); 1898+3A>C was thus classified as inconclusive and further data will be necessary to reach a definitive conclusion. The present study was designed with no placebo or control group. Although this can be viewed as a limitation, the FDA has acknowledged that a clinical trial-based approach grows increasingly difficult as *CFTR* variants become less common.¹⁸ Of note, the changes described in ppFEV1 and sweat chloride concentration were greater in responders than those expected by random variability. Finally, there were some instances of missing data, which could not be collected for various reasons (eg, difficulties in performing tests for participants hospitalised in critical care units or willingness of participants to complete some tests). However, missing data were minimal and did not affect our evaluations.

We chose not to assign to elexacaftor–tezacaftor–ivacaftor participants who carried two variants previously shown to be non-responsive to this combination of drugs in at least three patients among the programme participants. 37 people with cystic fibrosis were therefore not exposed to the study treatment because they were highly unlikely to be responders. 60 (12%) of the 516 patient files that were submitted to the programme contained genotype mistakes, which were identified by examining genetic laboratory reports, most of which were minor and did not result in substantial changes regarding predicted responsiveness to elexacaftor–tezacaftor–ivacaftor. However, 14 (3%) mistakes were major (eg, E92X instead of E92K, and E1104X instead of E1104V) and could have introduced bias in the interpretation of patient and variant response. In addition, complex alleles containing at least two variants on the same parental allele (in cis) might explain unexpected non-responses to elexacaftor–tezacaftor–ivacaftor for variants previously predicted responsive. In our study, four patients carried the FDA-approved V754M in cis with the non-responsive *CFTR*dele3-10,14b-16,16 and one patient carried the FDA-approved M498I in cis with the non-responsive *CFTR*dele7-9.¹⁶ These cases highlight the importance of verifying a patient’s genotype directly from the genetic laboratory report, especially before denying access to elexacaftor–tezacaftor–ivacaftor.

The responsiveness of *CFTR* variants was determined using data obtained in people with cystic fibrosis exposed to elexacaftor–tezacaftor–ivacaftor in our programme and was compared with the predicted responsiveness reported in published data or *CFTR* databases.^{34,35} The results of studies conducted in FRT cells, on which the list of FDA-approved variants is based, were largely confirmed, with the exception of the M152V and I175V splicing variants. Non-FDA-approved variants that were expected to respond to the study treatment were all confirmed responsive in our sample, except for G85V. They include missense variants, non-canonical splicing variants, and deep intronic variants, which lead to the synthesis of a residual normal transcript, resulting in residual *CFTR* protein function. Variants that were predicted to be non-responsive were largely confirmed as such and include nonsense, frameshift, and canonical splicing variants as well as large deletions. Applying these findings to the list of variants with inconclusive responsiveness based on the sole analysis of responder status (table 4, right column) would lead to classification of an additional 34 loss-of-function variants as non-responsive, which also include the missense L227R and the in-frame deletion I507del *CFTR* variants. This finding is largely consistent with FRT cell results,¹⁶ except for A561E, which was described as non-responsive by Bihler and colleagues¹⁶ and was considered as probably responsive in our study.

The mechanism by which certain missense variants fail to respond to elexacaftor–tezacaftor–ivacaftor remains to be elucidated. In a few instances, predictions were hampered by discrepancies between studies, depending on the cell model, the transfection type, and the failure to consider potential effect on splicing, as for G85E, R334W, R1066C, S364P, or I175V. Furthermore, no prediction could be made based on available data for 28 (11%) of 251 variants, 11 of which were found in at least one responder in trans with a non-responsive variant, which made these variants probably responsive. By contrast, 11 variants found to be non-responsive or probably non-responsive were non-canonical splicing or deep intronic variants. This finding would imply that they have a major effect on splicing and on preventing the synthesis of a residual *CFTR* protein, as for K464N, R560K, or G970R, which are located at the last nucleotide of exons, and 1811+1.6kbA>G.

The reason why most responders carrying N1303K, R334W, or 2789+5G>A in trans of a non-responsive variant did not exhibit a significant decrease in sweat chloride concentrations but did show significant improvements in lung function is intriguing. Hypotheses related to tissue specificity of expression or regulation of CFTR have been proposed, in particular for N1303K.²¹ However, a different mechanism might be at play for the 2789+5G>A splicing defect, as for other rare splicing variants such as 1898+3A>C or 4096-3C>G. Elucidating these mechanisms will contribute to our understanding of how these variants affect CFTR dysfunction, with important implications for precision medicine. Sweat chloride might no longer be appropriate as a universal biomarker for assessing therapeutic response to CFTR modulators, since important improvement in clinical status might occur in people with cystic fibrosis carrying selected *CFTR* variants, including at least N1303K, R334W, and 2789+5G>A.

The French compassionate programme enabled us to build a classification of variant response to elexacaftor–tezacaftor–ivacaftor, which has been considered an important goal to achieve.^{41,42} This list includes 44 variants (17 responsive, 27 non-responsive) for which data is consistent and verified in at least three people with cystic fibrosis and 143 (47 responsive, 96 non-responsive) for which conclusions are compelling but less definitive (verified in 1 or 2 people with cystic fibrosis). The absence of definitive evidence for variants classified as inconclusive (as they were always present in trans of responsive variants) and for variants classified as probably responsive or non-responsive (as there were only one or two individuals available to draw a conclusion) highlights the need for future research in this area. Only 251 variants were included in this study, corresponding to the genetic makeup of the French cystic fibrosis population, which does not represent worldwide genetic diversity, particularly of ultra-rare variants. All individual-level data are presented in the appendix and the list of responsive and non-responsive variants can be updated as data become available. We recommend that future studies reporting real-world evidence on the use of elexacaftor–tezacaftor–ivacaftor in people with cystic fibrosis with rare *CFTR* variants also publish individual-level data, which will facilitate data aggregation and meta-analyses, as previous publications have done.³⁷ We hereby propose creating and developing an international database that assembles all individual-level reports and case series in people with cystic fibrosis with rare *CFTR* variants who received CFTR modulators. Integrating these data with data obtained from in vitro models will help to determine the responsiveness of rare variants to CFTR modulators. This iterative process would contribute to deepening of our understanding of elexacaftor–tezacaftor–ivacaftor responsiveness in a large number of rare *CFTR* variants.

Study group

Reem Kanaan, Nicolas Carlier, Isabelle Honoré (Cochin, Paris); Frédérique Chedevergne, Elise Dreano, Aurélie Hatton, Alexandre Hinzpeter, Iwona Pranke (Necker, Paris); Laurence Le Clainche-Viala, Sophie Mayer (Robert Debré, Paris); Harriet Corvol, Guillaume Thouvenin (Trousseau, Paris); Sandra de Miranda (Suresnes); Natascha Remus, Benoit Douvry (Créteil); Louise Duthoit, Thierry Perez, Olivier Le Rouzic, Nathalie Wizla (Lille); Claire Bon, Stéphanie Bui, Nora Poey (Bordeaux); Nathalie Stremmler, Bérengère Coltey, Nadine Dufeu (Marseille); Jean Lebihan (Roscoff); Asma Gabsi, Delphine Pouradier (Versailles); Claire Andrejak, Cinthia Rames (Amiens); Magali Dupuy-Grasset, Jeanne Languépin (Limoges); Christophe Marguet, Stéphanie Pramil (Rouen); Baptiste Arnouat (Vannes); Annlyse Fanton (Dijon); Michel Abely, Bruno Ravoninjatovo (Reims); Aurore Blondé, Anne Guillaumot, Sebastien Kieffer, Aurélie Tatopoulos (Nancy); Raphaële Nove-Josserand, Camille Ohlmann, Thomas Perrin, Quitterie Reynaud (Lyon); Catherine Llerena, Sébastien Quétant, Sophie Valois (Grenoble); Marie-Laure Dalphin, Bénédicte Richaud-Thiriez (Besançon); Eric Deneuille (Rennes); Raphael Chiron, Floriane Socchi (Montpellier); Tiphaine Bihouée (Nantes); Julie Mankikian, Thomas Flament (Tours); Nathalie Coolen-Allou, Elsa Gachelin, Caroline Périssou, Constance Vuillard (La Réunion); Marion Dupuis (Toulouse); Wael Alkoussa, Sarah Marchal, Sylvie Leroy (Nice); Manuela Scalbert (Dunkerque); Karine Campbell, Muriel Laurans (Caen); Guillaume Labbé, Sylvie Montcouquiol (Clermont-Ferrand); Pascaline Priou (Angers); Paola de Carli, Lydie Lemonnier, Clémence Dehillotte, Thierry Nouvel (Association Vaincre la Mucoviscidose, Paris).

Contributors

P-RB, JDS, EG, IS-G, CM conceptualised and designed the study. P-RB, JDS, and CM verified the data. P-RB, JDS, EG, IS-G, and CM analysed and interpreted the data. P-RB, JDS, and EG drafted the manuscript. P-RB supervised the study and conducted statistical analysis. All authors participated in the acquisition of data and critical revision of the manuscript for important intellectual content. All authors had access to the data and were responsible for the decision to submit the manuscript for publication.

Declaration of interests

P-RB declares consulting fees from AstraZeneca, Chiesi, GSK, Insmmed, MSD, Sanofi, Vertex, Viatriis, and Zambon, outside of the submitted work. IS-G declares grants and consulting fees from Vertex, outside of the submitted work. ID declares support for attending meetings from Mylan and Zambon. CA declares consulting fees from Vertex and Viatriis and support for attending meetings from SOS Oxygène, Viatriis, and Zambon. DG declares support for attending meetings from Zambon. MM-E declares fees for report testimony from Vertex. MM declares consulting fees from Vertex. BD declares fees for participation on a data safety and monitoring board from Vertex. CR reports grants from Vaincre la Mucoviscidose and unpaid participation on the leadership of the French newborn screening programme and the French Rare Diseases Network. CM declares consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, and GSK, and support for attending meetings from Boehringer Ingelheim and Chiesi. All other authors declare no competing interests.

Data sharing

Individual-level data are available in the appendix. Additional data can be requested from the corresponding author.

Acknowledgments

We would like to acknowledge and thank all of the people with cystic fibrosis and their families who consented to participate in the programme. We also thank all the team members working in the 47 cystic fibrosis centres in France. Funding for this study was provided by Association Vaincre la Mucoviscidose, Société Française de la Mucoviscidose, and Filière Maladies Rares MUCO-CFTR.

Funding:

Association Vaincre la Mucoviscidose, Société Française de la Mucoviscidose, and Filière Maladies Rares MUCO-CFTR.

Conflict of interest statement

Declaration of interests P-RB declares consulting fees from AstraZeneca, Chiesi, GSK, Insmmed, MSD, Sanofi, Vertex, Viatriis, and Zambon, outside of the submitted work. IS-G declares grants and consulting fees from Vertex, outside of the submitted work. ID declares support for attending meetings from Mylan and Zambon. CA declares consulting fees from Vertex and Viatriis and support for attending meetings from SOS Oxygène, Viatriis,

and Zambon. DG declares support for attending meetings from Zambon. MM-E declares fees for report testimony from Vertex. MM declares consulting fees from Vertex. BD declares fees for participation on a data safety and monitoring board from Vertex. CR reports grants from Vaincre la Mucoviscidose and unpaid participation on the leadership of the French newborn screening programme and the French Rare Diseases Network. CM declares consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, and GSK, and support for attending meetings from Boehringer Ingelheim and Chiesi. All other authors declare no competing interests.

References

- 1 Burgel PR, Orenti A, Cromwell E, Stephenson A, on behalf of the ECFS patient registry committee and the CF Registry Global Collaboration. Worldwide prevalence of F508del and rare *CFTR* variants responsive to elexacaftor-tezacaftor-ivacaftor. *J Cyst Fibros* 2024; **23**: S3 (abstr).
- 2 Heijerman HGM, McKone EF, Downey DG, 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**: 1940–48.
- 3 Middleton PG, Mall MA, Drevinek P, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019; **381**: 1809–19.
- 4 Barry PJ, Mall MA, Álvarez A, et al. Triple therapy for cystic fibrosis *Phe508del*-gating and -residual function genotypes. *N Engl J Med* 2021; **385**: 815–25.
- 5 Mall MA, Brugha R, Gartner S, et al. Efficacy and safety of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis heterozygous for *F508del* and a minimal function mutation: a phase 3b, randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2022; **206**: 1361–69.
- 6 Burgel PR, Durieu I, Chiron R, et al. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med* 2021; **204**: 64–73.
- 7 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**: 529–39.
- 8 Bower JK, Volkova N, Ahluwalia N, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: interim results of a long-term registry-based study. *J Cyst Fibros* 2023; **22**: 730–37.
- 9 Sutharsan S, Dillenhofer S, Welsner M, et al. Impact of elexacaftor/tezacaftor/ivacaftor on lung function, nutritional status, pulmonary exacerbation frequency and sweat chloride in people with cystic fibrosis: real-world evidence from the German CF Registry. *Lancet Reg Health Eur* 2023; **32**: 100690.

- 10 Martin C, Legeai C, Regard L, et al. Major decrease in lung transplantation for patients with cystic fibrosis in France. *Am J Respir Crit Care Med* 2022; **205**: 584–86.
- 11 Ringshausen FC, Sauer-Heilborn A, Büttner T, et al. Lung transplantation for end-stage cystic fibrosis before and after the availability of elexacaftor-tezacaftor-ivacaftor, Germany, 2012–2021. *Eur Respir J* 2023; **61**: 2201402.
- 12 Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. *J Cyst Fibros* 2022; **21**: 456–62.
- 13 McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on *CFTR* genotype. *Pediatr Pulmonol* 2021; **56**: 1496–503.
- 14 Van Goor F, Straley KS, Cao D, et al. Rescue of $\Delta F508$ -CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. *Am J Physiol Lung Cell Mol Physiol* 2006; **290**: L1117–30.
- 15 Fiedorczuk K, Chen J. Molecular structures reveal synergistic rescue of $\Delta 508$ CFTR by Trikafta modulators. *Science* 2022; **378**: 284–90.
- 16 Bihler H, Sivachenko A, Millen L, et al. In vitro modulator responsiveness of 655 *CFTR* variants found in people with cystic fibrosis. *J Cyst Fibros* 2024; published online Feb 21. <https://doi.10.1016/j.jcf.2024.02.006>.
- 17 Food and Drug Administration. Trikafta. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212273s004lbl.pdf (accessed Nov 13, 2022).
- 18 Durmowicz AG, Lim R, Rogers H, Rosebraugh CJ, Chowdhury BA. The US Food and Drug Administration's experience with ivacaftor in cystic fibrosis. Establishing efficacy using in vitro data in lieu of a clinical trial. *Ann Am Thorac Soc* 2017; **15**: 1–2.
- 19 Livnat G, Dagan A, Heching M, et al. Treatment effects of elexacaftor/tezacaftor/ivacaftor in people with CF carrying non- F508del mutations. *J Cyst Fibros* 2023; **22**: 450–55.
- 20 Burgel PR, Sermet-Gaudelus I, Durieu I, et al. The French compassionate program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del *CFTR* variant. *Eur Respir J* 2023; **61**: 2202437.
- 21 Graeber SY, Balázs A, Ziegahn N, et al. Personalized CFTR modulator therapy for G85E and N1303K homozygous patients with cystic fibrosis. *Int J Mol Sci* 2023; **24**: 12365.
- 22 Dreano E, Burgel PR, Hatton A, et al. Theratyping cystic fibrosis patients to guide elexacaftor/tezacaftor/ivacaftor out-of-label prescription. *Eur Respir J* 2023; **62**: 2300110.
- 23 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**: 1324–43.
- 24 Agence Nationale de Sécurité du Médicament. Décision du 01/06/2023—Extension de l'indication du cadre de prescription compassionnelle de Kaftrio (ivacaftor, tezacaftor, elexacaftor) et Kalydeco (ivacaftor). 2023. <https://ansm.sante.fr/actualites/decision-du-01-06-2023-extension-de-lindication-du-cadre-de-prescription-compassionnelle-de-kaftrio-ivacaftor-tezacaftor-elexacaftor-et-kalydeco-ivacaftor> (accessed June 18, 2024).

- 25 Veit G, Avramescu RG, Chiang AN, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Mol Biol Cell* 2016; **27**: 424–33.
- 26 Raynal C, Baux D, Theze C, et al. A classification model relative to splicing for variants of unknown clinical significance: application to the *CFTR* gene. *Hum Mutat* 2013; **34**: 774–84.
- 27 Sharma N, Evans TA, Pellicore MJ, et al. Capitalizing on the heterogeneous effects of CFTR nonsense and frameshift variants to inform therapeutic strategy for cystic fibrosis. *PLoS Genet* 2018; **14**: e1007723.
- 28 Raraigh KS, Han ST, Davis E, et al. Functional assays are essential for interpretation of missense variants associated with variable expressivity. *Am J Hum Genet* 2018; **102**: 1062–77.
- 29 Han ST, Rab A, Pellicore MJ, et al. Residual function of cystic fibrosis mutants predicts response to small molecule CFTR modulators. *JCI Insight* 2018; **3**: e121159.
- 30 Bergougnoux A, Délétang K, Pommier A, et al. Functional characterization and phenotypic spectrum of three recurrent disease-causing deep intronic variants of the *CFTR* gene. *J Cyst Fibros* 2019; **18**: 468–75.
- 31 Joynt AT, Evans TA, Pellicore MJ, et al. Evaluation of both exonic and intronic variants for effects on RNA splicing allows for accurate assessment of the effectiveness of precision therapies. *PLoS Genet* 2020; **16**: e1009100.
- 32 Bergougnoux A, Billet A, Ka C, et al. The multi-faceted nature of 15 *CFTR* exonic variations: impact on their functional classification and perspectives for therapy. *J Cyst Fibros* 2023; **22**: 515–24.
- 33 Oren YS, Avizur-Barchad O, Ozeri-Galai E, et al. Antisense oligonucleotide splicing modulation as a novel Cystic Fibrosis therapeutic approach for the W1282X nonsense mutation. *J Cyst Fibros* 2022; **21**: 630–36.
- 34 Sosnay PR, Siklosi KR, Van Goor F, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet* 2013; **45**: 1160–67.
- 35 Claustres M, Thèze C, des Georges M, et al. CFTR-France, a national relational patient database for sharing genetic and phenotypic data associated with rare *CFTR* variants. *Hum Mutat* 2017; **38**: 1297–315.
- 36 Raraigh KS, Lewis MH, Collaco JM, et al. Caution advised in the use of CFTR modulator treatment for individuals harboring specific *CFTR* variants. *J Cyst Fibros* 2022; **21**: 856–60.
- 37 Burgel PR, Sermet-Gaudelus I, Girodon E, et al. Gathering real-world compassionate data to expand eligibility for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with N1303K or other rare *CFTR* variants: a viewpoint. *Eur Respir J* 2024; **63**: 2301959.
- 38 Sadras I, Kerem E, Livnat G, et al. Clinical and functional efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis carrying the N1303K mutation. *J Cyst Fibros* 2023; **22**: 1062–69.
- 39 Huang Y, Paul G, Lee J, Yarlagadda S, McCoy K, Naren AP. Elexacaftor/tezacaftor/ivacaftor improved clinical outcomes in a patient with N1303K-CFTR based on in vitro experimental evidence. *Am J Respir Crit Care Med* 2021; **204**: 1231–35.

40 Vertex Pharmaceuticals Incorporated. Evaluation of efficacy and safety of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in cystic fibrosis subjects without an F508del mutation. 2022. <https://clinicaltrials.gov/study/NCT05274269> (accessed Aug 13, 2023).

41 Burgel PR. Reply to: Supporting the case for a targeted approach for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with no F508del *CFTR* variant: further analysis for the French compassionate use programme. *Eur Respir J* 2024; **63**: 2400233.

42 Dooney M, Saba T. Supporting the case for a targeted approach for elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis with no F508del *CFTR* variant: further analysis for the French compassionate use programme. *Eur Respir J* 2024; **63**: 2301392.

