

# Cystic fibrosis transmembrane conductance regulator modulators for cystic fibrosis: a new dawn?

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## ABSTRACT

Cystic fibrosis (CF) is the most common life-limiting inherited condition in Caucasians. It is a multisystem autosomal recessive disorder caused by variants in the gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cell-surface localised chloride channel that regulates absorption and secretion of salt and water across epithelia. Until recently, the treatment for CF was predicated on ameliorating and preventing the downstream symptoms of CFTR dysfunction, primarily recurrent respiratory infections and pancreatic exocrine failure. But a new class of therapy—the CFTR modulators, which treat the basic defect and decrease the complications of CF, leads to significantly improved pulmonary function, decreased respiratory infections and improved nutrition. The newest agent, a combination of elexacaftor, tezacaftor and ivacaftor, will be suitable for approximately 90% of all people with CF and is likely to decrease the morbidity and significantly increase the life expectancy for most people with CF. The major barrier to their widespread introduction has been their cost, with many countries unwilling or unable to fund them. Nevertheless, such is their therapeutic efficacy and their likely potent effect on life expectancy that their advent has wider societal implications for the care of children and adults with CF.

## BACKGROUND

Cystic fibrosis (CF) is the most common life-limiting inherited condition in Caucasians, affecting approximately 80 000 people worldwide including >10 000 in the UK. It is a multisystem autosomal recessive disorder caused by variants in the gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cell-surface localised chloride channel that regulates absorption and secretion of salt and water across epithelia.<sup>1</sup> In the lungs, CFTR dysfunction results in the accumulation of thick, tenacious secretions leading to repeated respiratory infections and ultimately death due to respiratory failure. Pancreatic exocrine failure, usually from birth, results in intestinal maldigestion and malabsorption causing growth failure, while later in life the loss of pancreatic endocrine function results in CF-related diabetes. CF is also associated with bowel problems, liver disease, reproductive dysfunction, sinus disease, bone disease and elevated sweat chloride concentrations.<sup>2</sup>

Until recently, the treatment for CF was predicated on ameliorating and preventing the downstream symptoms of CFTR dysfunction, primarily recurrent respiratory infections and pancreatic exocrine failure.<sup>2</sup> The respiratory management

aims to prevent lung damage through judicious use of oral, inhaled and parenteral antibiotics; through airway clearance techniques and inhaled mucocactive drugs such as hypertonic saline or dornase alpha and with onset of respiratory failure consideration of lung transplant. Pancreatic failure is managed through pancreatic enzyme replacement therapy (PERT) and an energy dense, high salt diet, with supplemental calories and fat-soluble vitamins. With increasing age, there is increased prevalence of complications in other organ systems and a progressively increasing burden of care.

When first described in 1938, most CF cases died in infancy. With improved management, life expectancy has progressively increased—median survival for infants born in the UK in 1970 was approximately 20 years,<sup>3</sup> while the median predicted life expectancy is now nearly 50 years<sup>4</sup> (even before modulators). Management has evolved slowly, with small revolutionary improvements with high calorie diets, PERT, nebulised dornase alpha, specialist CF centres and CF newborn screening.

## HOW DIFFERENT VARIANTS IN THE CF GENE RESULT IN CFTR DYSFUNCTION

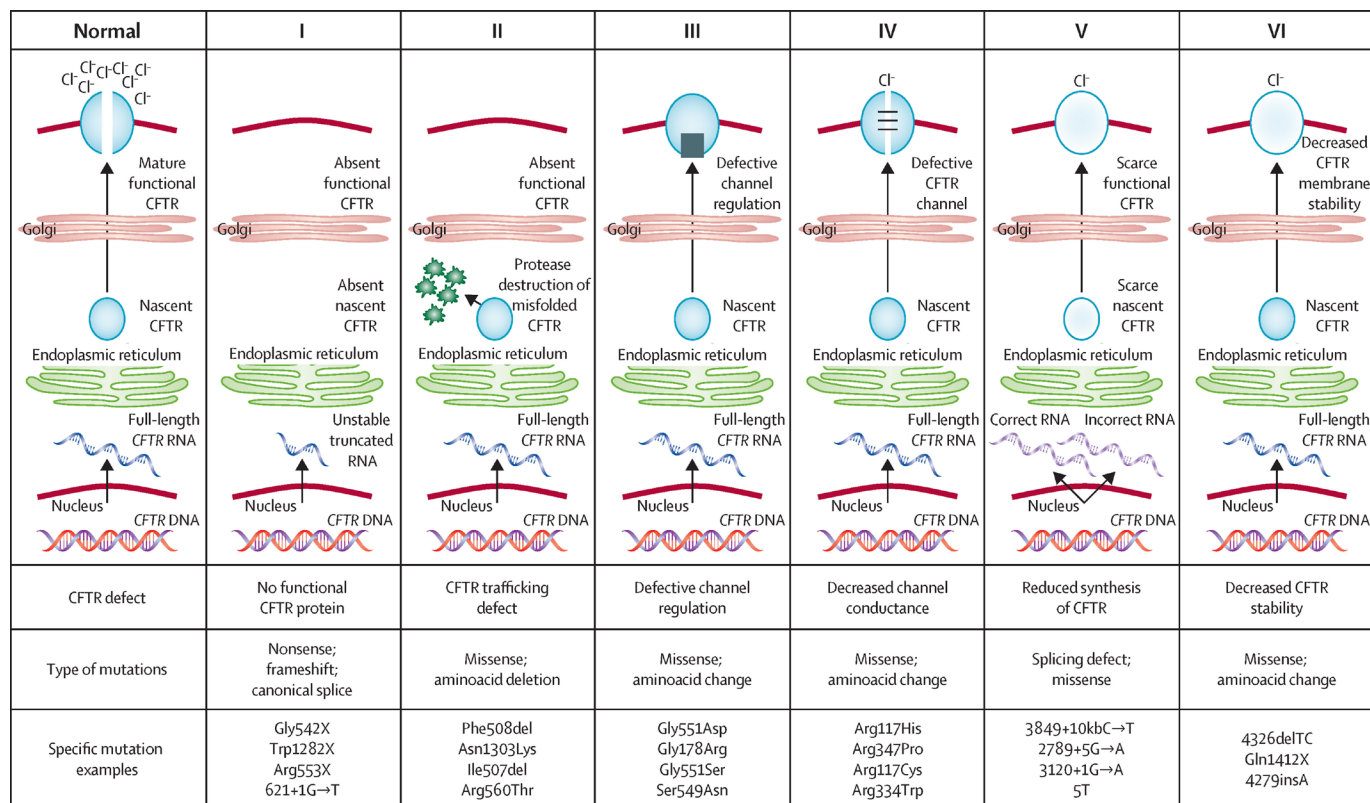
The identification of the gene for CF in 1989 facilitated the characterisation of CFTR function, and over 2000 CFTR gene variants have since been identified (<https://cftr2.org/>). Based on an understanding of the pathophysiological consequences of individual variants, they have been divided into six broad functional classes ([figure 1](#)) based on the molecular fate of CFTR.<sup>5</sup> Class I variants are frameshift, splicing or nonsense variants that interrupt CFTR synthesis resulting in severely reduced or absent CFTR expression. Class II variants, including the most common variant Phe508del, result in abnormal protein folding and premature degradation severely reducing CFTR expression. Class III variants, such as G551D, result in CFTR that reaches the apical membrane but fails to open due to impaired regulation. Class IV variants result in normal protein processing but reduced ion conduction. Class V and VI variants usually produce normal CFTR, but there is a decreased number on the cell membrane either due to decreased production or increased turnover.

There is a hierarchy of severity of CFTR function and clinical phenotype, with class I–III variants resulting in minimal or no CFTR function and a more severe disease, while class IV–VI variants may have some residual CFTR function and milder phenotype.<sup>6,7</sup> In truth the paradigm is more complex, as for example in Phe508del the small



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**Figure 1** Cystic fibrosis transmembrane conductance regulator (CFTR) variant classes.

amount of CFTR that does migrate to the cell membrane also displays defective channel gating.

### MEASURING OUTCOMES IN CF

The evaluation of CF therapies has historically measured changes in downstream disease markers, particularly respiratory outcomes, given that respiratory failure is the leading cause of death. The most common outcome measure is forced expiratory volume in 1 s (FEV<sub>1</sub>), either as a percentage predicted (% predicted) adjusted for age, sex and height or as a percentage annual decrease. FEV<sub>1</sub> is relatively accurate and reproducible, and as it is cheap and easy to measure from early childhood, it offers a longitudinal measurement of airflow obstruction from childhood through to adulthood. FEV<sub>1</sub> reflects the complex respiratory pathophysiology of CF, and crucially FEV<sub>1</sub> % predicted<sup>8</sup> and rate of decline of FEV<sub>1</sub> % predicted<sup>9</sup> are important predictors of morbidity and life expectancy in CF. The life expectancy of an individual aged 16 years with CF and an FEV<sub>1</sub> % predicted of 50% is likely to be considerably shorter than someone of the same age with an FEV<sub>1</sub> % predicted of 90%, although both will have fairly predictable annual declines in FEV<sub>1</sub> % predicted until respiratory failure and death. The magnitude of improvement in FEV<sub>1</sub> with commonly used CF therapies are of the order of 3.2% for nebulised hypertonic saline<sup>10</sup> and 5.8% for nebulised dornase alpha.<sup>11</sup>

Other outcome measures include the rate of pulmonary exacerbations; body mass index (BMI) and quality of life assessments such as the Cystic Fibrosis Questionnaire—Revised (CFQ-R). Rarely do improvements in pulmonary physiology such as FEV<sub>1</sub> translate into meaningful improvements in quality of life. Although the diagnosis of CF is based on the evaluation of CFTR function with a sweat chloride concentration of >60 mmol/L,

until recently sweat chloride measurement was not considered a realistic outcome measure.

### CFTR MODULATORS

Based on this understanding of the functional effect of CFTR variants, two classes of modulators have been developed—‘correctors’ that facilitate processing and trafficking of the protein to the cell surface, and ‘potentiators’ that increase the opening ability of the channel once at the apical membrane.<sup>12</sup> For class III or IV variants, a potentiator alone might be enough to significantly improve ion channel function. But for class II variants such as Phe508del, a combination is required of a corrector, to facilitate trafficking of the misfolded and prematurely degraded protein to the cell membrane, and also a potentiator to rectify the defective ion channel function when it reaches the cell membrane.

The first agent was the potentiator ivacaftor (Kalydeco) that increases the time the activated CFTR channel remains open at the cell surface and was tested in patients heterozygous for the G551D variant, the most common class III variant. The findings were striking; an 8.7% improvement in FEV<sub>1</sub> % predicted, but for the first time ever a CF treatment that significantly decreased the sweat chloride. The decrease in sweat chloride to 59.5 mmol/L was such that many of the participants would not fit the diagnostic criteria for CF on sweat test. The benefits to lung function persisted, with a significant increase in FEV<sub>1</sub> % predicted of 9.2% compared with placebo after 48 weeks treatment, with clinically meaningful improvements in BMI, CFQ-R and decreased respiratory exacerbations.<sup>13</sup>

These benefits have been replicated in real-world population-based studies where national registry data have reported that those treated with ivacaftor had significantly lower hospital admission rates, lower rates of respiratory *Pseudomonas* and

*Aspergillus* infection compared with controls,<sup>14</sup> while the annualised rate of decline in FEV<sub>1</sub> % predicted was halved.<sup>15</sup> In a comparison of US and UK patients receiving ivacaftor and matched controls, after 5 years those receiving ivacaftor had an FEV<sub>1</sub> % predicted approximately 9% greater than controls in both countries, and the FEV<sub>1</sub> % predicted was still higher than baseline for those receiving ivacaftor suggesting at least 5 years survival benefit.<sup>16</sup>

The lower age for initiation of ivacaftor has progressively decreased to 4 months without significant adverse effects but similar therapeutic benefit, and its use has extended from just G551D to all the class III variants. Intriguingly in younger children initiation of ivacaftor was associated with increased faecal elastase levels suggesting improved pancreatic exocrine function. The effect was greatest in children <12 months of age where over 75% had normal faecal elastase concentrations after commencing ivacaftor,<sup>17</sup> suggesting that early pancreatic exocrine failure is not inevitable. There are similar reports of discontinuation of insulin therapy for CF-related diabetes in older patients commencing ivacaftor.<sup>18</sup> However, ivacaftor cannot reverse all late complications of CF, and although some patients clear chronic *Pseudomonas aeruginosa* respiratory infection, it is not universal.<sup>14</sup>

### COMBINATION THERAPIES

G551D and the class III variants are relatively infrequent and Phe508del is by far the most common CF-causing variant, with approximately 50% of people with CF homozygous for Phe508del and another 40% heterozygous for Phe508del. But Phe508del was a challenging variant to treat and required a combination of correctors and potentiators.

The first corrector, lumacaftor, in combination with the potentiator ivacaftor (lum/iva, Orkambi) had a modest effect of a 2.8% increase in FEV<sub>1</sub> % predicted in those homozygous for Phe508del,<sup>19</sup> and a small decrease (10 mmol/L) in the sweat chloride concentration.<sup>20</sup> There were noticeable side effects including transient increased respiratory symptoms after initiating treatment and biochemical liver dysfunction. Furthermore, lum/iva had little effect in those heterozygous for Phe508del.<sup>20</sup> The second corrector, tezacaftor with ivacaftor (tez/iva marketed as Symkevi in Europe or Symdeko in North America), showed a similar increase in FEV<sub>1</sub> % predicted of 4.0% and 10 mmol/L decrease in sweat chloride concentration, although with decreased side effects.<sup>21</sup> Tez/Iva also showed some benefit for those heterozygous for Phe508del and a milder CFTR variant.<sup>22</sup>

However, the most recent corrector, elexacaftor, was shown in vitro to substantially increase the quantity of mature CFTR protein and quality of its function when used in combination with tezacaftor and ivacaftor in Phe508del heterozygotes,<sup>23 24</sup> irrespective of the other CFTR variant. This suggested it was likely to be efficacious in any person with CF and a Phe508del gene. This triple therapy (marketed as Kafrio in Europe and

Tricaftra in North America) has now been studied in two phase III trials.

Middleton *et al*<sup>25</sup> reported a 24-week double-blind, placebo-controlled trial of elex/tez/iva in patients heterozygous for Phe508del with a minimal-function variant. Compared with placebo elex/tez/iva resulted in a significant, sustained improvement in FEV<sub>1</sub> % predicted of 14%, reduced annual pulmonary exacerbation rate by 63%, improved BMI and quality of life scores and reduced sweat chloride values. The medication was well tolerated, and it is again noteworthy that the mean sweat chloride concentration in those treated with elex/tez/iva was 58 mmol/L, less than the accepted diagnostic threshold for CF of 60 mmol/L.

In a study in patients homozygous for Phe508del reported by Heijerman *et al*,<sup>26</sup> rather than comparing with placebo, elex/tez/iva was compared with the best standard of care—tez/iva. Thus, the control group were likely to already have a 4.0% benefit in FEV<sub>1</sub> % predicted compared with placebo. Nevertheless, those who received elex/tez/iva had a significant increase in FEV<sub>1</sub> % predicted of 10.0%, a significant improvement in quality-of-life scores and decrease in a sweat chloride of 45.1 mmol/L compared with tez/iva. The trial was too short to assess changes in the rate of respiratory exacerbations.

Taken together, these studies suggest that the elex/tez/iva combination has the ability to transform outcomes for the vast majority of people with CF. The magnitude of improvement in FEV<sub>1</sub> % predicted, the decrease in pulmonary exacerbations, the nutritional improvement and improved quality of life are unparalleled. Most people with CF receiving modulators are likely to have a sweat chloride concentration below the diagnostic threshold for CF. Although superseded by elex/tez/iva, iva alone lum/iva and tez/iva may still have a role in certain variants (table 1).

### CONCLUSION

There is long-term experience with ivacaftor alone for those heterozygous for the G551D variant which suggests that ivacaftor significantly increases life expectancy. Earlier initiation of therapy might prevent pancreatic exocrine failure,<sup>17</sup> emphasising that timely detection through newborn screening for CF is crucial. Furthermore, in a ferret model of G551D variant CF, in utero administration of ivacaftor reduced the rate of meconium ileus and protected the male reproductive tract,<sup>27</sup> emphasising both the importance of normal CFTR function in utero and implying that earlier modulator administration is optimal. There is limited evidence of the safety of modulators during pregnancy,<sup>28</sup> but if modulators are found to be safe to use in pregnancy, antenatal screening for the Phe508del variant might be warranted. In the past, a significant proportion of parents of a child with CF would consider terminating a future or current pregnancy if it was determined antenatally that their next child

**Table 1** Modulator therapy and classes of CF variants

Trade name	Generic name	Variant class	Common variants
Kalydeco	Ivacaftor	Class III–V	G551D, S549N, G1349D, R117H, 3849+10kbc→T
Orkambi	Lumacaftor-ivacaftor	Class II	Phe508del homozygous
Symkevi/Symdeko	Tezacaftor-ivacaftor	Class II–V	Phe508del homozygous, Phe508del and a residual function variant—L206W, 3272-26A→G, P67L, heterozygous for one of 154 responsive variants
Kafrio (UK)/Trikafta (USA)	Elxacaftor-tezacaftor-ivacaftor	Class II–V	Phe508del homozygous, Phe508del and any other variant, heterozygous for one of 177 responsive variants

would also be affected.<sup>29 30</sup> With the advent of modulators, it must be questioned if this view is still tenable.

Modulators will change the model of CF care. People with CF have been reviewed on a regular basis by a large CF multidisciplinary team, and the natural history was an ever-increasing burden of chronic therapies and hospitalisations. For those with established disease, modulators will not reverse pancreatic exocrine failure or severe bronchiectasis, and thus there will be a cohort of patients who still require conventional care. But with time complications in childhood should diminish. Modulators offer the hope of fewer treatments and potentially the withdrawal of some chronic therapies. There is also likely to be less need for hospitalisations in childhood, for example, in their planning of future paediatric services in London, NHS England modelled a decrease in the requirement for specialist respiratory beds with the advent of modulators.

Modulators have changed the regulatory landscape for rare and orphan diseases. Many CF-causing variants identified are in a very small number of individuals worldwide, and thus large randomised trials for each rare variant is implausible. When the US Federal Drug Administration extended the marketing authorisation for ivacaftor from just the G551D variant to all the class III variants, it did so for the first time on in vitro data only for each of the other variants. It recognised the wider implications at the time that for drugs that target specific variants, in vitro assay data could in future be used in place of clinical trials when seeking to expand to other population subsets. The European Medicines Agency has been less willing to consider in vitro data, and this is reflected in the more limited marketing authorisation for the modulators in Europe compared with North America. Although the broadened availability of modulators to those with rare variants based on in vitro data is welcomed, conversely it offers modulators to individuals with very mild disease where the risk-benefit ratio is not so clear cut.

There are potential adverse outcomes that warrant consideration. There is a significant proportion of individuals that are unable to tolerate modulator therapies, usually due to severe hepatic dysfunction. There also remain 10% of people with CF where there are currently no modulator therapies available, and these are likely over-represented in ethnic minority communities. The disparity of opportunity for these families will be stark, and those intolerant or ineligible for modulator therapies will need extra support. It is likely that administration of modulator therapies will be lifelong, and although short-term and medium-term safety appears acceptable, long-term safety data are needed.

The major block to the introduction of modulators has been the cost, and many countries remain unwilling or unable to fund them. Tricaftra is listed at US\$311 000 per patient per year, but even with the dramatic clinical benefits, health technology assessments suggest the incremental cost-effectiveness ratio is >US\$1 million.<sup>31</sup> In many low-income and middle-income countries (LMIC), there is limited access to conventional CF therapies and modulator therapies are even less likely to be affordable.<sup>1</sup> Furthermore, people with CF in LMICs are less likely to have a Phe50del variant and thus less likely to respond to the current modulators. In the UK, a managed access agreement brokered between NHS England, the National Institute for Health and Care Excellence, the CF Trust and the manufacturer Vertex Pharmaceuticals offers the medication to all eligible patients at a likely reduced but highly confidential price. The agreement ensures access to Kaftrio for the vast majority of patients in the UK for 4 years, and ensures an effective monopoly for Vertex. Even though there are other therapeutic agents in development, it might currently be very difficult to conduct trials in the UK,

especially if they entail discontinuation of established modulator therapy.

It may also stifle the development of more conventional therapies to the detriment of those ineligible or intolerant of Kaftrio. There are however new modulator therapies in development (<https://www.cff.org/Trials/Pipeline>), including combinations of correctors, potentiators and amplifiers, and of modulators for the as yet untreated class I variants. There are also potential agnostic therapies targeting alternative ion channels,<sup>32</sup> gene editing or the potential for delivering truly personalised medicine through intestinal organoids in n=1 trials.<sup>33</sup> Intestinal organoids are grown from rectal biopsies, and display forskolin-induced swelling that reflects the individual's residual CFTR function. When the organoids are exposed to combinations of drugs, they act as an in vitro readout of the likelihood of therapeutic response.

Nevertheless, CFTR modulators are likely to be the most important development in CF care for a generation, and possibly ever. For a disease that used to be universally fatal in childhood, they offer hope to the majority of people with CF and their families, and their advent should be seen as a new dawn.

**Correction notice** This article has been corrected since it was published online. The first author's surname was spelt incorrectly.

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