New drugs in cystic fibrosis: what has changed in the last decade?

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Abstract: Cystic fibrosis (CF), a life-limiting chronic disease caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene, affects more than 90,000 people worldwide. Until recently, the only available treatments were directed to symptom control, but they failed to change the course of the disease. New drugs developed in the last decade have the potential to change the expression, function, and stability of CFTR protein, targeting the basic molecular defect. The authors seek to provide an update on the new drugs, with a special focus on the most promising clinical trials that have been carried out to date. These newly approved drugs that target specific CFTR mutations are mainly divided into two main groups of CFTR modulators: potentiators and correctors. New therapies have opened the door for potentially disease-modifying, personalized treatments for patients with CF.

Keywords: Cystic fibrosis transmembrane conductance regulator, CFTR modulators, correctors, potentiator

Introduction

Cystic fibrosis (CF) is an autosomal recessive monogenic disease that affects more than 90,000 people worldwide. It constitutes the most common life-limiting genetic disease in the Caucasian population.1-3 The clinical manifestations of CF are caused by a defect in the cystic fibrosis transmembrane regulator (CFTR) protein, a chloride channel that is widely distributed on epithelial surfaces.4 CFTR plays a central role in the coordination of electrolyte and fluid transport in a variety of epithelial tissues, including airways, gastrointestinal tract, reproductive tract, and secretory glands, maintaining the volume and liquidity of the luminal compartment and its contents.5,6 Its dysfunction leads to disruption in airway clearance of mucins and increases in bacterial colonization, pancreatic insufficiency, and intestinal obstruction.6

There are many mutations in CF with diverse molecular effects, contributing to the variable phenotype of the disease. Additional contributing effects are due to epigenetic factors, environmental influences, modifier genes, and complex CFTR alleles.7 Although the disease affects multiple systems in the body, the effects in the respiratory system by far contribute the most to the morbidity and low life expectancy characteristic of the disease.8

Until recently, the only available treatments for CF were symptomatic and included the use of mucolytic agents, inhaled mannitol and hypertonic saline, inhaled and systemic antibiotics, and anti-inflammatory drugs.8 In the last decade, enormous progress has been made, and new drugs have been developed with the potential to change the expression, function, and stability of CFTR defective proteins, the so-called CFTR modulators.3,8 Along with newborn screening (available in Portugal since 2013) and early and intensive symptomatic therapy, these new drugs with possible disease-modifying effects are expected to contribute to an increase in the life expectancy and quality of life of patients with CF.9 Improvements in these approaches and new corrective strategies are currently under clinical investigation.3,8,10

In this review, we will provide an overview of the new drugs that are currently approved to restore
CFTR function, covering the molecular bases of their mechanism of action, and focusing on the most promising clinical trials that have been carried out to date.

**Molecular basis of CFTR protein modulators**

A classification system that distributes CFTR mutations into seven classes has been developed and constitutes a useful tool for the development of pharmacotherapy, since similar defects may respond to similar strategies. Despite the existence of a classification system, more than 2000 mutations have been described, many of which have not been characterized, and several of them present pleiotropic defects. The Clinical Function and Translation of CFTR (CFTR 2) is a worldwide database of CFTR variants that includes more than 89,000 patients and targets to provide up-to-date summaries of genotype-phenotype information. To date, 442 mutations are included in the CFTR 2 database, 360 of which are known to be CF-causing, and 48 of which have varying clinical consequences (https://cftr2.org/).

Class I mutations include premature stop codons resulting in unstable, truncated, or absent proteins. Class II mutations cause defects in protein processing or trafficking, which result in reduced amounts of CFTR at the cell surface due to premature degradation by the proteasome. In class III, CFTR fails to transport chloride and bicarbonate ions since the activation or regulation of the protein by nucleotides is impaired. In class IV mutations, CFTR has decreased conductance. Mutations in class V are located within the promoter or splice sites of the CFTR gene and are responsible for reduced biosynthesis of CFTR. In class VI, the reduced stability of CFTR at the cell surface leads to increased turnover. Class VII mutations comprise frameshift, indels, or large deletions that result in total absence of mRNA and, consequently, no protein. Treatment approaches to these abnormal processes must address these mutation-specific issues. The therapeutic goal in class I mutations is to rescue protein synthesis, whereas in class II, it is to correct protein folding. In both classes III and IV, the goal is to restore channel function, while in class V, the goal is to correct the missplicing or to induce maturation of CFTR. The objective in class VI mutations is to promote protein stability. CFTR modulators are small molecules that aim to enhance or even restore the function of defective CFTR proteins by different approaches. There are five categories of modulators: potentiators, correctors, stabilizers, read-through agents, and amplifiers. Potentiators (e.g. ivacaftor) act on CFTR channels that have reached the cell surface and increase the open probability (gating) and conductance of ions. Correctors (e.g. lumacaftor, tezacaftor, and elexacaftor) act on misfolded CFTR and permit delivery to the cell surface, thereby improving the channel density at the plasma membrane. Since the most prevalent mutation in individuals with CF is F508del, a class II mutation linked to a trafficking CFTR defect, the importance of this type of modulator is even greater. Stabilizers (e.g. cavosonstat) decrease the endocytosis rate of CFTR proteins that are present at the plasma membrane. Amplifiers (e.g. PTI-801) are expected to increase the mRNA expression of CFTR and increase protein biosynthesis, which are potentially important for all mutation classes. Read-through agents (e.g. ataluren) are intended to promote the ribosomal read-through of premature termination codons in CFTR mRNA. Information regarding the different classes of CFTR mutations and their prevalence, including some examples of mutations of each class and directed therapeutic approaches, are shown in Table 1 and Figure 1.

To date, four different modulators have reached clinical practice – potentiator ivacaftor (Kalydeco®), combination therapy with a potentiator and a corrector: lumacaftor + ivacaftor (Orkambi®), tezacaftor + ivacaftor (Symkevi®) and triple therapy combining two correctors and a potentiator: elexacaftor + tezacaftor + ivacaftor (Kaftrio®).

**Clinical trials of CFTR modulators**

**Potentiator ivacaftor**

Preclinical trials identified ivacaftor (formerly VX-770) as a promising substance to increase the activity of defective CFTR protein. It acts as a potentiator with the greatest effect in cells with a substitution of glycine for aspartic acid at amino acid 551 in the CFTR protein (G551D-CFTR mutation), with a favorable pharmacokinetic profile. Many clinical trials with notable results have subsequently been conducted, and ivacaftor (Kalydeco®) was approved by the Food and
Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2012. Ivacaftor was the first medicine to treat the underlying cause of CF, constituting a major breakthrough.3,15

Initial clinical trials showed that ivacaftor was effective in improving lung function by a greater than 10.6% change from baseline through week 24 in predicted FEV1 in the ivacaftor group compared with placebo (p < 0.001). Other outcomes were an improvement in quality of life, as well as a reduction in the number of exacerbations. Ivacaftor also proved to be effective in weight gain both for patients with mild lung

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**Table 1.** CFTR mutation classes regarding their main defect, their prevalence, some examples, and directed therapeutic approaches.

| Defect | Class I  | Class II | Class III | Class IV | Class V | Class VI |
|--------|----------|----------|-----------|----------|---------|---------|
|        | More severe phenotype | Milder phenotype |          |          |         |         |
| Prevalence | 10%     | 70% (at least one allele) | 4–5%     | 3%       | 3%      | –       |
| Examples  | G542X, W1282X, R553X | F508del, I507del, G85E, N1303K | G551D, S549R, V520F | R117H, R334W, S1235R | A455E, 1680–886A > G | r.F508del, Q1412X |
| Therapeutic approach | Read-through agents + Stabilizers | Correctors + Potentiators + Stabilizers | Potentiators + Stabilizers | Correctors + Potentiators | Stabilizers + Amplifiers | Stabilizers + Amplifiers |

CFTR, cystic fibrosis transmembrane regulator.

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**Figure 1.** Site and mechanism of action of different CFTR modulator drugs. Source: Reused with permission from De Boeck.17
disease and normal spirometry as well as those with severe lung disease [forced expiratory volume in the first second (FEV1) <40%]. The drug was well tolerated in all clinical trials and raised no major concerns regarding safety.\textsuperscript{19–23} Initially, the studies encompassed children older than 6 years of age and with the G551D-CFTR mutation only; however, new clinical trials have expanded these indications.

Subsequent studies assessing the efficacy and safety of ivacaftor in patients with CF and a non-F508del mutation (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D) also proved that ivacaftor was effective in monotherapy at improving lung function without raising major safety concerns for other class III mutations; therefore, its use was extended.\textsuperscript{24} For R117H, a residual function mutant, ivacaftor also improved FEV1 in individuals older than 18 years and with a polythymidine tract variant, but all individuals showed clinical benefits, increasing ivacaftor usage indications.\textsuperscript{25} Currently, ivacaftor is approved for a total of 38 CF-causing mutations, comprising splicing mutations and other rarer mutations (Table 3).\textsuperscript{15} Several studies have demonstrated the lack of clinical effects of ivacaftor in monotherapy for patients homozygous for the F508del mutation, demonstrating the pleiotropic defects of this mutation and the need for a combination of drugs with different mechanisms of action to obtain more efficient rescue of this mutated protein.\textsuperscript{26}

The KIWI clinical trial expanded the use of ivacaftor to children older than 6 months (in the United States), showing that ivacaftor was generally safe and was associated with rapid and sustained reduction in sweat chloride concentrations (Tables 2 and 3).\textsuperscript{27–29}

**Corrector lumacaftor**

Lumacaftor (formerly VX809) is a CFTR corrector discovered through high-throughput screening. The safety, tolerability, and pharmacokinetics of lumacaftor were evaluated in a phase II, randomized, multicenter, placebo-controlled clinical trial in adults homozygous for the F508del mutation.\textsuperscript{30} This study demonstrated that modulation of CFTR function with lumacaftor in monotherapy was safe in F508del homozygous patients but insufficient to match clinically relevant results.\textsuperscript{30} In the PROGRESS extension clinical trial\textsuperscript{38} in which TRAFFIC and TRANSPORT patients participated, it was found that both the long-term safety and benefits of the lumacaftor + ivacaftor combination were maintained. Subsequently, a clinical trial was carried out to evaluate the safety and efficacy of the combination of lumacaftor + ivacaftor in children aged 6–11 years who were homozygous for the F508del mutation only; however, new clinical trials have expanded these indications.

**Combination therapy lumacaftor (corrector) + ivacaftor (potentiator)**

A phase II, randomized, multicenter, multidose and placebo-controlled clinical trial was performed in patients aged 18 years or older who were homozygous and heterozygous for the F508del mutation.\textsuperscript{36} The results revealed that the dose of lumacaftor 600 mg (id) + ivacaftor 250 mg (2id) in homozygous patients for F508del was the only dose that demonstrated a significant effect on FEV1, and this therapy did not have a clinically significant effect in patients heterozygous for F508del.\textsuperscript{36}

Based on the previous results, two phase III randomized, double-blind, placebo-controlled clinical trials were conducted to assess the effects of the combination of lumacaftor + ivacaftor in patients aged 12 years and older who were homozygous for the F508del mutation.\textsuperscript{31} In these clinical trials, called TRAFFIC and TRANSPORT, patients were randomly assigned to one of the following groups: lumacaftor 600 mg (id) + ivacaftor 250 mg every 12 h, lumacaftor 400 mg every 12 h + ivacaftor 250 mg every 12h or placebo in the same regimen for 24 weeks.\textsuperscript{31} The primary outcome was to assess the absolute change from the baseline value of FEV1. For the results, there was an average absolute increase in FEV1 in relation to placebo from 2.6% to 4% (p<0.001) in TRAFFIC and 2.6% to 3% (p<0.001) in TRANSPORT. This effect occurred within 15 days from the start of treatment and remained consistent for 24 weeks. The rate of pulmonary exacerbations also decreased significantly compared with placebo, and there was an improvement in body mass index (BMI) z score (0.24–0.28, p<0.001 in the dataset).\textsuperscript{31} Based on data from this study, the combination of lumacaftor + ivacaftor was approved by the FDA in July 2015 and by the EMA in November 2015 for the treatment of patients with CF homozygous for the F508del mutation older than 12 years of age.\textsuperscript{35}
Table 2. Summary and simplified presentation of the absolute changes in relation to placebo of the most relevant clinical trials.

| Drug | Age | Mutation | Sweat chloride (mmol/L) | FEV1 improvement | Other significant data |
|------|-----|----------|-------------------------|------------------|-----------------------|
| Ivacaftor [KALYDECO®] | | | | | |
| Phase III STRIVE²⁰ | ⩾12 years | G551D | −48.1 | 10.5% | 55% reduction in pulmonary exacerbations; average weight gain 2.7 kg |
| Phase III ENVISION²¹ | ⩾6 years | G551D | −53.5 | 10.0% | Average weight gain 2.8 kg |
| Phase III KONNECTION²⁴ | ⩾6 years | Class III mutations non-G551D [G178R; S549N; S549R; G551S; G1244E; S1251N; S1255P; or G1349D] | −49.2 | 10.7% | Average BMI increase 0.7 kg/m² |
| Phase III KIWI²⁹ | ⩾2 years and ⩽5 years | At least one allele with class III mutation | −46.9 | NA | Liver enzymes increase in 15% |
| Phase II DISCOVER²⁶ | ⩾12 years | F508del Homozygous | −2.9 | NSS | Primary and secondary outcomes not achieved |
| Lumacaftor | | | | | |
| Phase II³⁰ | ⩾18 years | F508del Homozygous | −8.21 | NSS | |
| Lumacaftor + Ivacaftor [ORKAMBI®] | | | | | |
| Phase III TRAFFIC³¹ | ⩾12 years | F508del Homozygous | NA | 2.6% | 34% pulmonary exacerbations reduction |
| Phase III TRANSPORT³¹ | ⩾12 years | F508del Homozygous | NA | 3.0% | 43% pulmonary exacerbation reduction; BMI increase 0.36 kg/m² |
| Phase III³² | ⩾6 and ⩽11 years | F508del Homozygous | −20.8 | 2.4% | |
| Phase III³² | ⩾6 and ⩽11 years | F508del Homozygous | −24.8 | ENS | BMI increase + 0.15 kg/m²; QoL; LCI (−0.88) |
| Tezacaftor + Ivacaftor [SYMKEVI® or SYMDEKO®] | | | | | |
| Phase III EVOLVE³³ | ⩾12 years | F508del Homozygous | −10.1 | 4.0% | 35% pulmonary exacerbations reduction |
| Phase III EXPAND³⁴ | ⩾12 years | F508del + residual function mutation | −9.5 | 6.8% | |
| Elexacaftor + tezacaftor + ivacaftor [KAFRTIO® or TRIKAFTA®] | | | | | |
| Phase III³⁵ | ⩾12 years | At least one allele with F508del | −41.8 | 14.3% | |

BMI, body mass index; FEV1, forced expiratory volume in the first second; LCI, lung clearance index; NA, not applicable/not evaluated; NSS, not statistically significant; QoL, quality of life score.
FEV1 did not improve significantly until week 24 (+2.5% over the baseline level, \(p = 0.0671\)), but there were improvements over the initial baseline level in sweat chloride concentration (−24.8 mmol/L, \(p < 0.0001\)), BMI \(z\) score (−0.15, \(p < 0.0001\)), quality of life, and lung clearance index (LCI) (−0.88, \(p < 0.0018\)).

Based on these two clinical trials, in January 2018, the EMA approved the combination of lumacaftor + ivacaftor for the treatment of CF in patients at least 6 years old and homozygous for the \(F508del\) mutation. This indication was extended to those who were 2 years of age in Europe in January 2019 \(^{39}\) (Tables 2 and 3).

### Table 3. Approved CFTR modulators: product names and dosages, approved patient ages, and types of CF mutations.

| Substance | Commercial name | Mutations | Approval age |
|-----------|-----------------|-----------|--------------|
| Ivacaftor | Kalydeco        | E56K, G178R, S549R, K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N, R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H, 3272-26A\(\rightarrow\)G, 711 + 3A\(\rightarrow\)G, E831X, 3849 + 10kbC\(\rightarrow\)T e 2789 + 5G\(\rightarrow\)A | >12 months >6 months (US) |

| Lumacaftor/Ivacaftor | Orkambi (EU) Symkevi (US) Symdeko | F508del homozygotes | >2 years |
|-------------|----------------|---------------------|--------|
| Tezacaftor/Ivacaftor | (EU) Symdeko (US) Symdeko | F508del homozygotes or F508del heterozygotes with E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, 711 + 3A\(\rightarrow\)G, R347H, R352Q, A455E, D579G, E831X, 2789 + 5G\(\rightarrow\)A, S945L, S977F, F1074L, K1060T, A1067T, R1070W, F1074L, 3272-26A\(\rightarrow\)G, D1152H, D1270N, 3849 + 10kbC\(\rightarrow\)T | >12 years |

| Elexacaftor/ Tezacaftor/Ivacaftor | (EU) Kaftrio (US) Trikafta | At least one F508del mutation | >6 years (US) |
|----------------|----------------|----------------|--------|

\(\text{CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; EU, Europe; US, United States of America.}\)

FEV1 did not improve significantly until week 24 (+2.5% over the baseline level, \(p = 0.0671\)), but there were improvements over the initial baseline level in sweat chloride concentration (−24.8 mmol/L, \(p < 0.0001\)), BMI \(z\) score (−0.15, \(p < 0.0001\)), quality of life, and lung clearance index (LCI) (−0.88, \(p < 0.0018\)).

Based on these two clinical trials, in January 2018, the EMA approved the combination of lumacaftor + ivacaftor for the treatment of CF in patients at least 6 years old and homozygous for the \(F508del\) mutation. This indication was extended to those who were 2 years of age in Europe in January 2019 \(^{39}\) (Tables 2 and 3).

**Combination therapy tezacaftor (corrector) + ivacaftor (potentiator)**

Tezacaftor (formerly VX-661) is a CFTR modulator that belongs to the corrector class, similar to lumacaftor. The EVOLVE clinical trial aimed to evaluate the efficacy and safety of the tezacaftor + ivacaftor combination in subjects aged 12 years and over and homozygous for the \(F508del\) mutation. This indication was extended to those who were 2 years of age in Europe in January 2019 \(^{39}\) (Tables 2 and 3).

**Triple therapy: elexacaftor (corrector) + tezacaftor (corrector) + ivacaftor (potentiator)**

Elexacaftor (formerly VX-445) is the latest approved CFTR corrector, which together with tezacaftor and ivacaftor has proven to be the most effective combination in the treatment of CF. A randomized, double-blind, placebo-controlled phase III clinical trial was carried out, including 403 patients aged 12 years and over with at least one \(F508del\) mutation.
one F508del mutation and one mutation with no function. Patients were divided into two groups: one group that received the triple combination for 24 weeks and one placebo group, and the main objective was to assess the change in the absolute value of the FEV1 percentage after 4 weeks. In the triple therapy group, there was a 13.8% increase in the predicted FEV1 at 4 weeks and a 14.3% increase at 24 weeks. The rate of pulmonary exacerbations was 63% lower, and there was an improvement in the quality of life and a 41.8 mmol/L decrease in sweat chloride concentration. Mild to moderate adverse effects and the need to discontinue the medication due to adverse effects occurred in 1%. FDA approved this triple therapy, branded Trikafta®, in October 2019 and allowed the extension of these modulating drugs to all patients who have at least one allele with the F508del mutation (approximately 90% of individuals with CF). EMA approval was obtained in 2020 under the trade name Kaftrio® (Tables 2 and 3).

Discussion
Since the in vitro discovery of the first molecules capable of modulating the CFTR protein, we entered a new era in the treatment of CF, in which the underlying molecular defect could be treated. Although medical advances in recent decades have provided symptomatic treatments that have increased the average life expectancy of these patients, from a median age of death of 25 years in 1985 to 32.4 years in 2017, the quality of life remains compromised, and the average life expectancy is still lower than that of the general population. However, with novel CFTR modulators, the median predicted survival age for patients born from 2013 to 2017 is now 44 years old.

From the first clinical trials with ivacaftor (Kalydeco®), ivacaftor monotherapy in class III and some class IV mutations was found to produce significant improvements in the symptoms of these patients, with minimal adverse drug reactions, making it a safe and effective drug. However, the mutations for which ivacaftor monotherapy is effective correspond to a very small percentage (~5%) of individuals with CF. The most common mutation, F508del, results in a protein with several molecular defects that require a cocktail of modulating drugs, in which each one corrects a portion of the defect with possible synergistic effects on the others.

Two drug sets, lumacaftor + ivacaftor (Orkambi®) and tezacaftor + ivacaftor (Symkevi®), are the first approved CFTR modulator drug combinations to show significant results for the most common mutation – F508del – but only in homozygosity (or, in the case of SYMKEVI®, in heterozygosity with a small number of mutations).
The triple combination of elexacaftor + tezacaftor + ivacaftor (Kaftrio®) is much more promising. It was shown to be highly efficient with consistently good outcomes and the potential to completely change the life expectancy of individuals with CF. Its widespread use in clinical practice is clearly highly anticipated.

Despite their approval by EMA, these drugs are not yet universally available to patients whose indications are clear, either in Portugal or at the European level. Modulator therapies are expensive (approximately 260,000 euros per year of treatment), which may raise the question of whether the cost-effectiveness is sustainable. However, an important fact to take into account when analyzing the cost-effectiveness of these drugs is that, more than improvement in lung function or nutritional status, they have the potential to stabilize the progression of the disease, particularly if administered early in life, before irreversible damage occurs.

This study reflects a comprehensive collection of published data on the molecular basis and clinical trials of new CFTR modulators. However, because it was not a systematic review or a meta-analysis, the authors recognize these as a limitation of this study.

**Conclusion**

If the defect associated with the F508del mutation is fully overcome, all patients who have at least one F508del mutation would be treated effectively, regardless of the mutation on their second allele. Overcoming the F508del defect could thus result in an effective treatment for the great majority (85–90%) of subjects with CF.

Nevertheless, despite the success of these novel drugs, 10–15% of patients still lack any CFTR-targeted treatment options. In addition, only five CF-causing mutations have a CFTR allele prevalence of >1%, which makes all other mutations rare and therefore difficult to find adequate mutation-specific therapies in conventional clinical trials. The alternative lies in the use of models based on patients’ own tissues, such as intestinal organoids and human epithelial nasal cells, to predict responses to CFTR modulator drugs at an individual level.

**Author contributions**

**Juliana Roda:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

**Catarina Pinto-Silva:** Data curation; Formal analysis; Methodology; Writing – original draft.

**Iris A.I. Silva:** Formal analysis; Investigation; Writing – review & editing.

**Carla Maia:** Formal analysis; Methodology; Writing – review & editing.

**Susana Almeida:** Formal analysis; Methodology; Writing – review & editing.

**Guiomar Oliveira:** Conceptualization; Formal analysis; Methodology; Writing – review & editing.

**Ricardo Ferreira:** Formal analysis; Methodology; Writing – review & editing.

**Availability of data and material**

Raw data is available at request.

**Code availability**

Not applicable.

**Ethics approval and consent to participate**

This review did not involve research in humans or animals.

**Consent for publication**

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