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Abstract

Structural biology and functional studies are a powerful combination to elucidate fundamental knowledge about the cystic fibrosis transmembrane conductance regulator (CFTR). Here, we discuss the latest findings, including how clinically-approved drugs restore function to mutant CFTR, leading to better clinical outcomes for people with cystic fibrosis (CF). Despite the prospect of regulatory approval of a CFTR-targeting therapy for most CF mutations, strenuous efforts are still needed to fully comprehend CFTR structure-and-function for the development of better drugs to enable people with CF to live full and active lives.

Background

Mutations in the Cystic Fibrosis (CF) gene alter the structure and function of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) channel, impairing the flow of chloride and bicarbonate ions across epithelia in many organs of the body [1]. CFTR shares an overall architecture that is conserved within ATP-binding cassette (ABC) transporters and consists of two transmembrane domains (TMD1 and TMD2), two nucleotide-binding domains (NBD1 and NBD2), and a unique regulatory (R)-region (Fig. 1A) [2]. The correct assembly of these individual domains into a stable, yet flexible structure facilitates conformational changes, driven by phosphorylation of the R-region and ATP-binding and hydrolysis at the NBDs, which gate the channel pore formed by the TMDs [3,4].

Combined efforts from structural biology and electrophysiology provides a comprehensive view of CFTR's structure-function relationships [3,4]. This fundamental principle of protein science is key to understanding how disease-causing mutations and clinically-approved drugs impact the local structure of CFTR, leading to long range (allosteric) conformational changes, which alter channel function. This knowledge is of interest not just to scientists, clinicians and healthcare professionals, but also to people with CF. Through patient education, therapy adherence might be increased, leading to greater clinical benefit.

Four excellent speakers (John F. Hunt [JFH], Isabelle Callebaut [IC], Tzyh-Chang Hwang [T-CH] and Isabelle Sermet-Gaudelus [IS-G]) were invited to the Pre-Conference Meeting (PCM) of the 16th ECFS Basic Science Conference (Dubrovnik, Croatia, 27-30 March 2019) to share their views on CFTR structure-and-function in health and disease, the mechanism of action of clinically-approved therapeutics targeting CFTR, their clinical benefit and future prospects. Here, we summarise the highlights from the speakers' presentations and the plenary discussions, facilitated by e-voting to engage the expertise of the audience.

Recent highlights from the CFTR structure: the resolution revolution

Pioneering work which solved the first high-resolution crystal structures of an ABC transporter [5] and the first nucleotide-binding domain of CFTR [6] paved the way for the first three-dimensional molecular models of CFTR [7,8], which were improved using molecular dynamics simulations (Fig. 1B&C right) [9]. Recently, in less than three years, Jue Chen and colleagues have made a huge impact by solving cryo-EM structures of human CFTR in dephosphorylated [10], phosphorylated [11], and even drug-bound conformations [12] (Fig. 1B&C left and centre and Fig. 1D).

Comparison of the in silico 3D-models and the cryo-EM structures highlights a remarkable degree of similarity [9,13], which are conserved in ABC exporters, such as CFTR [14]. These include (i) the dimerization and the partial or full dissociation of the NBDs; (ii) the binding of the NBDs to two intracellular loops (ICLs), one each from TMD1 and TMD2 (Fig. 1B) and (iii) the 'mixing' or 'domain-swapping' of two transmembrane segments from one TMD with four segments from the other TMD to form two structural units, which move to gate the pore. The 3D models of CFTR have stood the test of

time very well, arguing that cryo-EM and molecular dynamics simulations (together with electrophysiology) should be combined to explore CFTR's conformational landscapes to understand its structure-and-function (Fig. 1B&C, **IC, PCM**).

New insights into CFTR structure-and-function emerged from the cryo-EM structures (Fig. 1B-D). These include (i) the unique conformation of CFTR's N-terminus (lasso motif, dark blue, Fig. 1), which wraps around TM2 and TM6 of TMD1 and TM10 and TM11 of TMD2 [10]; (ii) the R-region that 'wedges' between the NBDs to prevent their interaction, but which moves away when phosphorylated to allow NBD dimerization and hence, channel opening [11,15]; (iii) a locally unstructured region in TM8 (TMD2), located close to the transmembrane segments that gate the channel pore [11] (**IC & JFH, PCM**) and (iv) a binding site for small molecule potentiators (Ivacaftor and GLPG1837), which enhance channel gating, sandwiched between the TMDs; both compounds contact the unstructured region of TM8 when bound at this site [12,16] (**T-CH, PCM**). As summarised below, these latter two points were the subject of much discussion at the PCM.

TM8 leads the dance to open the channel

Comparison of the phosphorylated [11] and dephosphorylated cryo-EM structures [10] of human CFTR suggest that rigid-body rotation of the TMDs and local conformational changes at the extracellular end of TM8 and TM12 'toggle' the CFTR pore between open and closed conformations. However, in the published phosphorylated structure the CFTR pore is slightly smaller than the diameter of a chloride ion, raising the possibility that this conformation does not correspond to the open channel state observed in electrophysiological experiments (Fig. 1B&C) [11]. Thus, the fully open state might be an alternative conformation not observed in the published structures nor the new cryo-EM structures of human CFTR (JFH, PCM).

To gain more insight in the molecular motions of the TMDs, particularly TM8, IC and co-workers performed molecular dynamics simulations. These simulations suggest that when TM8 'swings out' to open the channel, there are coordinated movements of TM6, TM7 and TM12 (Fig. 1B&C) (**IC, PCM**). Of note, both TM8 and TM6 are in a balancing act between stability and flexibility (i.e. structure and function). These transmembrane segments contain charged residues essential for CFTR function at the expense of their overall hydrophobicity and stability in the bilayer, which explains why they need more assistance during CFTR synthesis to increase their stability in the bilayer [17,18]. Moreover, the CF mutation R347P in TM6, which perturbs conductance [19] requires correction by the small molecule Lumacaftor to deliver it to the plasma membrane [20]; the same is likely true for the CF mutation L927P in TM8 [21].

Interestingly, in chicken CFTR TM8 adopts a conformation much more similar to the 3D models of human CFTR than the cryo-EM structures (Fig. 1B&C) [15]. This result emphasizes the importance of the conformational dynamics of TM8. It also highlights the need for more cryo-EM structures and the value of other techniques, such as solid-state NMR [22] or single-molecule DEER (double electron-electron resonance) analysis [23] combined with conformation-specific nanobodies to stabilize a

particular structure, in case cryo-EM fails to complete the picture of CFTR's dynamic landscape at atomic resolution.

TM8: A 'sweet spot' for a small pebble to hit the giant!

This analogy from David and Goliath was used to describe how a small molecule precisely modulates CFTR function (T-CH, PCM). The small pebbles in this story are CFTR potentiators, such as Ivacaftor [24], which has high affinity (nM range), but low efficacy and GLPG1837 [25], which has lower affinity (µM range), but higher efficacy (**T-CH, PCM**). Despite their structural differences, both potentiators modulate CFTR gating in a competitive manner [25], a finding consistent with the latest cryo-EM structures, which demonstrate that they share the same binding site [12,16].

Molecular modelling and cryo-EM in combination with structure-guided biochemical and electrophysiological experiments found a 'sweet spot' made mostly of hydrophobic residues involved in potentiator (Ivacaftor and GLPG1837) binding in the phosphorylated and dephosphorylated states of CFTR. Consistent with earlier data (reviewed by Wang et al [26]), this site is sandwiched in the membrane embedded regions of the TMDs (Fig. 1D) [12,16]. Of note, the unstructured region of TM8 is part of this potentiator-binding pocket [12,16]. Given the role of TM8 in gating the CFTR pore, this observation strongly links the site-of-binding and site-of-action of these small molecules [12,16].

CFTR is highly dynamic, spontaneously opening and closing in the presence of ATP once it is phosphorylated by PKA [27]. Based on its properties, a simple kinetic model of allosteric modulation to explain how potentiators bind to CFTR in a state-dependent manner. This model predicts that potentiators have higher affinity for the open state and lower affinity for the closed state consistent with their action on gating kinetics ([25], **T-CH, PCM**). Because the potentiator-binding site was also found in the closed channel conformation [25], further investigation is required to elucidate how potentiator binding initiates allosteric modulation of conformational changes during CFTR channel gating. Some clues are provided by structural analyses using limited proteolysis [20] and hydrogen/deuterium exchange [28], which suggest that the N-terminus of TMD1 and ICL1, ICL2 and ICL4 may be involved.

With a potentiator-binding site determined at atomic resolution, structure-based drug design should permit the development of even better CFTR potentiators, a view shared by many other scientists (Table 1). Developments in cryo-EM move fast. We therefore anticipate that the CF field will soon have structures of the small molecules from the triple-combination therapy (Tezacaftor-Elexacaftor-Ivacaftor [29]) bound to CFTR. Future structural studies should also target the interaction with CFTR of co-potentiators that enhance markedly the action of Ivacaftor [30] (**JFH, PCM**).

Misfolding and dysfunction of the F508del-CFTR

F508del-CFTR is a textbook example of how a mutation, by causing a local folding (structural) defect in one domain (NBD1) [31,32], allosterically influences the assembly of all other CFTR domains [33],

leading to an unstable protein, which is recognized by cellular protein quality control machineries and degraded (reviewed by Farinha et al [34]). Clearly, F508del-CFTR has multiple conformational defects that impair its structure and function, even when the protein is rescued to the cell surface (reviewed by Mijnders et al [35]). Triple-combination therapy rescues F508del-CFTR folding to ≥50% of the wild-type levels [29,36], but other drugs, maybe even NBD1 specific, might be developed to cure all conformational defects [35,36].

Can we understand the allosteric problems caused by the F508del mutation at the structural level? Does this information identify new target(s) to rescue F508del-CFTR? These were key questions addressed from the new cryo-EM structures of human F508del-CFTR (JFH, PCM). Although compensatory mutations were required to stabilise the protein to express and purify it, new insights about its conformational flexibility will emerge from classifying and resolving different structures harbouring F508del and other CF-causing mutations. More investigations are needed to understand why removal of the unstructured and flexible Regulatory Insertion from NBD1 rescues F508del-CFTR [37]. For this work, nanobodies might help to locally stabilize CFTR to uncover new conformational states as was recently demonstrated by elegant binding studies, which suggest that the dissociation of NBD1 from the TMDs is an important dynamic feature of CFTR [38].

There was clear consensus at the PCM that we should understand how other frequent CF mutations impact CFTR structure-and-function (Table 1). This is especially the case for CF mutations unresponsive to current correctors (e.g. N1303K [39]). Mutation-specific high-throughput screens are required to identify new CFTR modulators [30], but at the same time, it is important to identify all the druggable sites in CFTR (Table 1). This raises an important question - is there a limit to how much mutant CFTR can be corrected and stabilised? Increasing the number of suppressor mutations in wild-type CFTR enhanced protein stability, but concomitantly reduced channel activity [40]. These data highlight a tug-of-war between stability and flexibility with important consequences for how much we can correct mutant CFTR.

The clinical benefit of allosteric modulation of CFTR function

With CFTR modulators approved for use in the clinic (for review, see Table 2), we can investigate whether the allosteric correction of CFTR function has clinical benefit for people with CF. This question is best addressed with Ivacaftor (Kalydeco), which has now been administered to individuals with CFTR gating mutations for more than seven years [41]. At this pre-conference meeting it was shown that robust Ivacaftor-induced improvements in ion transport, airway surface liquid height and ciliary beating *in vitro* by cultured human bronchial epithelial cells correlated well with clinical parameters, including reduced sweat chloride concentration, improved lung function (measured by forced expiratory volume in one second; FEV_1), increased mucus clearance and reduced lung inflammation and exacerbations [42] (**IS-G, PCM**). Clearly, targeting the cause of CF relieves clinical manifestations. Yet, a small pilot study of twelve Ivacaftor-treated patients followed for 2 years

showed an unexpected increase in *Pseudomonas aeruginosa* infection after an initial decline [43], which might reflect disease progression despite Ivacaftor treatment [44].

'Real-world' Ivacaftor data provides much greater insight into how clinically-approved drugs actually impact the lives of people with CF [45] (**IS-G, PCM**). This is even more important for Ivacaftor-Lumacaftor combination therapy (Orkambi), which showed positive results *in vitro*, but only modest clinical benefit [46,47]. Meta-analysis of 1700 homozygote F508del patients revealed a small increase in FEV_1 of 2.8-fold over placebo, but 2.7-fold more adverse events, leading to discontinuation of the treatment [48]. These data emphasize the need to find better drugs, which are on their way to the clinic. But, they also highlight the necessity to (i) find better cell models to correlate *in vitro* responses to clinical outcomes [49]; (ii) identify new biomarkers to better predict clinical outcome (e.g. bicarbonate secretion, microbiome analysis, mucus rheology and the analysis of other organs beyond the lungs [50] and (iii) discover exogenic markers to identify high- and non-responding individuals (e.g. the complex allele F87L-I1027T-F508del, which is unresponsive to Lumacaftor [51]). Intensified efforts in all these directions are needed to increase our understanding of how allosteric CFTR modulation in the larger CF population improves clinical parameters. This is especially important for life-long personalized treatment of CF.

The future for CF is bright, but we should not let our guard down!

A game-changer in CF treatment is the triple-combination therapy Tezacaftor-Elexacaftor-Ivacaftor [29], which will likely be launched soon for all individuals heterozygous for F508del (Table 2) (Vertex press release). This treatment shows a remarkable *in vitro* increase in F508del-CFTR function up to 85% of wild-type and *in vivo* lung function of about 14% (FEV_1) [29,36]. In theory, this triple-combination therapy should improve CFTR function in individuals homozygous for F508del above that of a non-disease heterozygous CF carrier with 50% normal CFTR function. However, time will tell whether theory meets practice, and above all, whether this treatment has sufficient clinical benefit in heterozygous F508del patients carrying a poorly responding (e.g. N1303K, [39]) or non-responding mutation (e.g. premature termination codon mutations) on the other allele.

At the pre-conference meeting the important issue of life-long daily drug treatment with combinations of CFTR modulators was discussed (IS-G, PCM). On top of this, studies of CF ferrets with the G551D mutation administered Ivacaftor suggest that newborns with CF or even pregnant women carrying CF fetuses should be treated to prevent early organ damage, especially of the pancreas [52]. However, caution is urged because of the possibility of unpredictable long-term adverse effects (Table 1). Moreover, there might be differential responses to CFTR modulators because of yet unclear mechanisms [51,53]. Therefore, we need more drugs on the 'shelf' to secure life-long CF treatments. We certainly should not let our guard down and stop all discovery pipelines now that the triple-combination treatment [29] is about to enter the clinic.

Will the triple combination therapy fully cure CF (Table 1)? Perhaps at some point in the future gene-repair using CRISPR/Cas9 or mRNA-directed antisense oligonucleotide strategies will tackle the

disease directly at the level of the faulty gene or its transcribed product [54], sweeping away the above-mentioned concerns. But, before we can safely and precisely target the CF gene, while upholding all ethical standards, we depend on the success of small molecule treatments and improved knowledge of CFTR structure-function relationships to identify new therapeutic opportunities. Thus, this is the important direction we should take at least until the 2025 ECFS Basic Science Conference (Table 1).

Conflict of interest statement:

DNS is the recipient of a Vertex Innovation Award, IS-G is the recipient of two Vertex Innovation Awards and a member of the scientific boards of Eloxx, PTC Therapeutics and Vertex Therapeutics.

Author contributions:

BK wrote the commentary, which the other authors revised critically for important intellectual content. SH made the overview of clinical studies shown in Table 2. All authors approved the final version of the commentary.

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Figure 1: Kleizen et al PCM

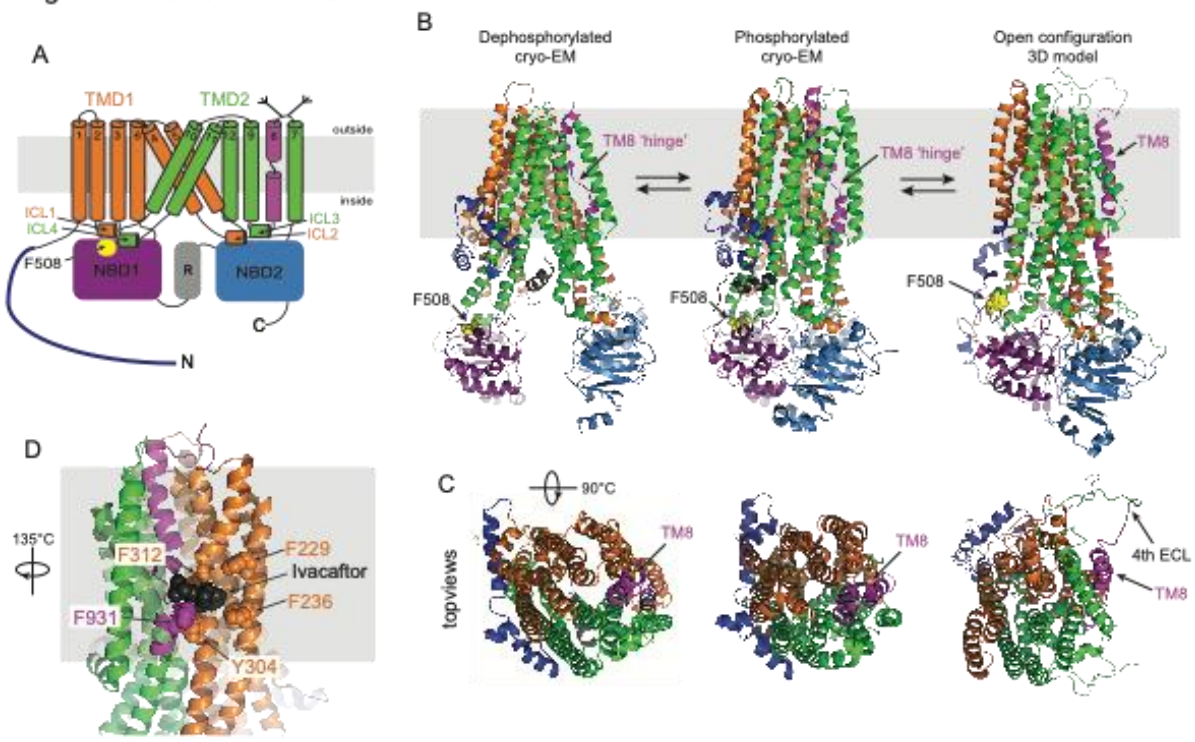

Figure 1: Open and closed structures and models of CFTR (A) Schematic representation of CFTR with its characteristic ABC transporter architecture. The positions of the plasma membrane (grey) and F508 are indicated; numbers identify individual transmembrane segments. Two N-glycans are present on the fourth extracellular loop between TM7 and TM8. **(B and C)** Orthogonal and outside views of PyMOL representations of the cryo-EM structures of human CFTR (left: dephosphorylated [PDB id: 5UAK]; centre: phosphorylated [PDB id:6MSM]) and 3D model of the open-channel configuration [9] with domains colour-coded according to the schematic in A. **(D)** Magnified view of the Ivacaftor-bound cryo-EM structure [PDB id: 6O2P] rotated 135 degrees compared to the structures in B to highlight residues interacting with the drug in this structure [12,16]. Abbreviations: ICL, intracellular loop; NBD, nucleotide-binding domain; R, Regulatory (R)-region; TMD, transmembrane domains.

Session 1 (n=49)				
Does structural insight lead to better CFTR modulators?	89% yes	11% no		
Can we do structure-based drug design on CFTR?	60% yes	17% no	23% no opinion	
How many drugable sites does CFTR have?	60% ≥6	11% 4-5	6% ≤3	23% no opinion
Should we understand the structural defects of other CF mutations?	81% yes	4% no	15% no opinion	

Session 2 (n=47)			
Will the triple-combo treatments cure CF?	14% yes	82% no	6% no opinion
Should we keep investing in mutation-specific therapies?	88% yes	6% no	6% no opinion
Can we expect adverse effects with life-long CF modulator treatments?	39% yes	53% no	8% no opinion
Will we still have an ECFS Basic Science meeting in 2025?	88% yes	4% no	8% no opinion

Table 1: Results of two live e-voting polls held at the PCM. The summary results provide an interesting overview of expert opinions about important considerations and future directions for the CF community.

Substance	Product name	Approval date	Mutation	Approval Age	Clinical trial and publications
Ivacaftor (VX-770)	**Kalydeco Pill** **150 mg**	EU: July 2012 US: Jan 2012	G551D	> 12 years	Phase III: STRIVE (> 12 y) Ramsey NEJM 2012
Ivacaftor (VX-770)	**Kalydeco Pill** **150 mg**	EU: July 2012 US: Jan 2012	G551D	> 6 years (25 kg)	Phase III: ENVISION (children 6-11 y) Davies Am J Respir Crit Care Med. 2013 Phase III: PERSIST as extension from STRIVE and ENVISION (> 6 y and >12y) McKone EF Lancet Respir Med. 2014
Ivacaftor (VX-770)	**Kalydeco Pill** **150 mg**	EU: July 2014 US: Feb 2014	Other gating mutations: G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P and G1349D	> 6 years	Phase III: KONNECTION (Gating-Mut.; > 6 y) De Boeck JCF 2015
Ivacaftor (VX-770)	**Kalydeco Pill** **150 mg**	EU: Nov 2015 US: Dec 2014	R117H heterozygotes	> 18 years (EU) > 6 years (US)	Phase III: KONDUCT (> 6 y) (R11H heterozygotes) Moss et al Lancet Respir Med 2015
Ivacaftor (VX-770)	**Kalydeco Granules** **50 mg/75 mg**	EU: Nov 2015 US: March 2015	G551D and other gating mutations: G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P	2-5 years	Phase III: KIWI (2-5 y; 24 weeks) Davies Lancet Resp Med 2016 Phase III: KLIMB (2-5 y; 84 weeks) Rosenfeld et al.; JCF 2019

			and G1349D		
Ivacaftor (VX-770)	**Kalydeco Granules** **50 mg/75 mg**	EU: Nov 2018 US: Aug 2018	G551D and other gating mutations: R117H, G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P, G1349D	12-24 months	Phase III: ARRIVAL (Gating Mutations, 12 months to < 24 months) Rosenfeld et al; Lancet July 2018
Ivacaftor (VX-770)	**Kalydeco Granules** **25 mg/50 mg/ 75 mg**	EU: not yet approved US: April 2019	G551D and other gating mutations: R117H, G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P and G1349D	> 6 months	ARRIVAL, not yet published
Lumacaftor (VX-809)/ Ivacaftor (VX-770)	**Orkambi Pill** **200 mg LUM/ 125 mg IVA**	EU: Nov 2015 US: July 2015	F508del homozygotes	> 12 years	Phase III: TRAFFIC, TRANSPORT (> 12 y; 24 weeks) Wainwright NEJM 2015 Phase III: PROGRESS (> 12 y; 96 weeks); Konstan et al in Lancet Respir Med 2017
Lumacaftor (VX-809)/ Ivacaftor (VX-770)	**Orkambi Pill** **100 mg LUM/ 125 mg IVA**	EU: Jan 2018 US: Sep 2016	F508del homozygotes	6-11 years	Phase III: VX15-809-109 (6-11 y; 24 weeks; FEV_1pp and LCI measurements) Ratjen et al; Lancet Respir Med 2017
Lumacaftor (VX-809)/ Ivacaftor (VX-770)	**Orkambi Granules** **100 mg LUM/ 125 mg IVA** **150 mg LUM/ 188 mg IVA**	EU: Jan 2019 US: Aug 2018	F508del homozygotes	2-5 years	Phase II: VX16-809-121 (2-5 y; recruiting) NCT03625466
Tezacaftor (VX-661)/ Ivacaftor (VX-770)	**Symdeko Pill** **TEZA 100 mg/**	US: Feb 2018	F508del homozygotes or F508del heterozygotes plus plus a mutation	> 12 years	Phase III: EVOLVE (> 12 y; 24 weeks; F508del homozygotes)

	IVA 150 mg **additional: 150 mg IVA Monotherapy tested in heterozygotes**		with residual function: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, 711+3A→G, R347H, R352Q, A455E, D579G, E831X, 2789+5G→A, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, 3272-26A→G, D1152H, D1270N, 3849+10kbC→T		Taylor-Cousar N Engl J Med 2017 Phase III: EXPAND (> 12 y; 24 weeks; F508del heterozygotes) Rowe N Engl J Med 2017
Tezacaftor (VX-661)/ Ivacaftor (VX-770)	**Symkevi Pill** **TEZA 100 mg/ IVA 150 mg**	EU: Nov 2018	F508del homozygotes or F508del heterozygotes plus a mutation with residual function: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272- 26A→G, 3849+10kbC→T	> 12 years	Phase III: EVOLVE (> 12 y; 24 weeks; F508del homozygotes) Taylor-Cousar N Engl J Med 2017 Phase III: EXPAND (> 12 y; 24 weeks; F508del heterozygotes) Rowe N Engl J Med 2017
Tezacaftor (VX-661)/ Ivacaftor (VX-770)	**Symdeko Pill** **TEZA 50 mg/ IVA 75 mg (< 25 kg)** **TEZA 50 mg/ IVA 150 mg (> 25 kg)**	US: June 2019	F508del homozygotes or F508del heterozygotes plus same mutation with residual function as approved for >12 y	6-11 years	Phase III: VX15-661-113; (6-11 y; 24 weeks; F508del homozygotes or F508del heterozygotes plus residual function mutation) Walker et al in JCF 2019
Elexacaftor (VX-445)/		Not yet approved;	F508del homozygotes or	> 18 years	Phase II: VX-445 + Tezacaftor +

Tezacaftor (VX-661)/ Ivacaftor (VX-770)		submission to FDA expected by 3rd quarter of 2019 and to EMA by 4th quarter of 2019	F508del heterozygotes plus mutation with minimal-function		Ivacaftor Keating et al; N Eng J Med 2019 Phase III study recruiting: NCT03525444

Guidelines and reviews on modulator studies

Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. Ren et al Ann Am Thorac Soc. 2018

Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis; Southern et al, Cochrane Database Syst Rev. 2018 Aug 2

A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis; Habib et al., Sci Rep. 2019 May 10

Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis; Skilton et al, Cochrane Database Syst Rev. 2019 Jan 7

A systematic Cochrane Review of correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. Southern et al, Paediatr Respir Rev. 2019 Apr;30:25-26.

Registry studies / real life data on CFTR modulators:

Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries, Volkova N. et al., J Cyst Fibros. 2019 Jun 10.

Longitudinal Trends in Real-World Outcomes after Initiation of Ivacaftor. A Cohort Study from the Cystic Fibrosis Registry of Ireland, Kirwan et al., Ann Am Thorac Soc. 2019 Feb

Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor, Bessanova L. et al, J Cyst Fibros. 2017 May

Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease., Hubert D. et al, J Cyst Fibros. 2017 May

Real-life acute lung function changes after lumacaftor/ivacaftor first administration in pediatric patients with cystic fibrosis, Labaste et al., J Cyst Fibros. 2017 Nov

Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data., Sawicki GS et al, Am J Respir Crit Care Med. 2015 Oct 1

Table 2: Clinically-approved CFTR modulators. This table presents all the clinically-approved substances, their product names and dosages, approval dates and patient ages, types of CF mutations and the names of clinical trials with references. Additional references to guidelines, reviews of clinical studies and real-life data on CFTR modulators are provided.