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Cystic fibrosis drug trial design in the era of CFTR modulators associated with substantial clinical benefit: stakeholders' consensus view

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ABSTRACT

CFTR modulators associated with substantial clinical benefit are expected to rapidly improve the baseline condition of people with cystic fibrosis (PWCF) as well as decrease the rate of lung function decline, the occurrence of pulmonary exacerbations and likely even other disease complications. These changes in clinical status of PWCF introduced by clinically effective modulator therapy will have major repercussions on modalities of future CF drug development.

As part of its 'Strategic Plan to speed up Access to new Drugs', the European Cystic Fibrosis Society (ECFS) convened a meeting in Brussels on November 27th 2019 with relevant stakeholders (CF researchers and clinicians, patient organization and pharmaceutical company representatives, regulators, health technology assessors; see Acknowledgments for list of attendees) to discuss the future of clinical trials in cystic fibrosis (CF) in the context of HEMT entering the clinical arena. The following is the conclusion of the presentations and discussions. It is hoped that these concepts will be considered in future regulatory guidelines and may provide rationale and support for alternative trial designs.

1. Introduction

CFTR modulators, which treat the basic CF defect improve key clinical outcomes in PWCF, including quality of life (QoL). These drugs demonstrate disease modulation by decreasing pulmonary exacerbations as well as lung function decline, a correlate of survival [1–5]. Registry data already indicate survival benefit for the first of these [6].

CFTR mutations have been divided into different mutation classes, depending on the way they disturb CFTR protein synthesis, function or stability [7]. CFTR correctors improve protein folding and trafficking so that more CFTR protein reaches the cell surface; these drugs are required for the commonest CFTR mutation, the trafficking mutant, F508del. CFTR potentiators stimulate the function of CFTR protein already at the cell membrane; these are suitable as monotherapy for mutations leading to cell surface protein with poor function. Potentiators are also used in combination with correctors to further increase function of pharmacologically-rescued, mutant CFTR. Three CFTR modulators have so far obtained EMA approval: Kalydeco™ (ivacaftor) for patients with class III mutations (i.e., those affecting gating) and adults with the R117H mutation; Orkambi™ (corrector lumacaftor plus potentiator ivacaftor) for subjects homozygous for mutation F508del and Symkevi™ (corrector tezacaftor plus potentiator ivacaftor) for subjects homozygous for F508del or heterozygous for F508del and selected residual function (RF) mutations, namely from classes IV, V and VI and mainly affecting conductance, expression levels and cell surface stability, respectively. These drugs also have FDA approval for the same mutations plus a longer list of rare *CFTR* mutations based on clinical or *in-vitro* data from a Fisher Rat Thyroid (FRT)

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Table 1
Overview of currently approved CFTR modulator drugs.

	EMA approval		FDA approval (mutations additional to EMA italicized)	
	Mutations	From age:	Mutations	From age:
Kalydeco™ (ivacaftor)	G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R	6 mo	G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R	6 mo
	R117H	18 yrs	R117H *E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A>G, E831X, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, 2789+5G>A, 3272-26A>G, 3849+10kbC>T	
Orkambi™ (lumacaftor + ivacaftor)	F508del homozygous	2 yrs	F508del homozygous	2 yrs
Symkevi™, Symdeko™ (tezacaftor + ivacaftor)	F508del homozygous	12 yrs	F508del homozygous	6 yrs
	Heterozygous for F508del and one of following: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A>G, S945L, S977F, R1070W, D1152H, 2789+5G>A, 3272-26A>G, or 3849+10kbC>T		*E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A>G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G>A, 3272-26A>G, 3849+10kbC>T	
Trikafta™ (elexacaftor + tezacaftor + ivacaftor)	Not yet approved	N/A	At least one F508del mutation	12 yrs

Sources: https://www.ema.europa.eu/en/medicines/human/EPAR/kalydecoand/orkambiand/symkevi; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207925and&ApplNo=211358and&ApplNo=210491.

* Approved on basis of clinically and/or *in vitro* responsiveness.

system; in some cases, the drugs are also approved in younger age (Table 1).

In October 2019, the triple drug combination Trikafta™ (2 CFTR correctors with different mechanisms of action, plus one CFTR potentiator) obtained expedited FDA approval. This clinically very effective modulator therapy substantially improved lung function, nutritional status and respiratory patient-reported outcomes of PWCF from age 12 years either homozygous [8] or heterozygous for F508del plus a mutation leading to a CFTR protein with no detectable function (also termed minimal function) [9]. In subjects heterozygous for F508del, triple drug activity is purely derived from the F508del allele, as the other mutation leads to a modulator-insensitive protein. In the US modulator therapy associated with substantial clinical benefit is thus available for 90% of PWCF comprising all those with at least one F508del. In Europe, approval of Trikafta™ (probably under the name of Kaftrio™ but for simplicity we will further refer to this triple combination as Trikafta™) is forecast for 2020. However, due to the high cost, clinical availability of CFTR modulators has lagged behind (and might continue to do so) in many regions of Europe and beyond [10]. Furthermore, the genetic diversity of the European CF population is higher, with more people without an F508del mutation on either allele [11]; an estimated ~20% of subjects will not be eligible for current HEMT.

The success of CFTR modulators has attracted more pharmaceutical companies to the field of CF, each with their own modulator pipeline. The high diversity of *CFTR* mutations, with many at present not targeted by modulators, demands alternative strategies [12]. These new treatment modalities such as DNA/ mRNA addition, stop codon read through and antisense oligonucleotides are emerging into the clinical research pipeline.

Despite major progress, CF continues to be a life shortening disease, with many adults and a proportion of children having very low lung function and thus being in high need not only of CFTR modulators but also of symptomatic treatments [11]. This supports the continued focus also on the non CFTR modulator pipeline, which at present is very congested [13].

Large differences between PWCF exist across Europe: the frequency of the F508del mutation ranges from 60 to > 80% of CF alleles in Northern European countries down to <40 to 60% in southern European regions [11]. Access to CF standards of care, symptomatic treatments and follow-up also varies greatly between European countries, [14] which is reflected in the marked disparity in outcomes [11]. Since the development of CFTR modulators, this disparity might further increase. A few countries have rapid access to all licensed modulators whilst others, including at least half of the Eastern European countries, still have no access to any of these drugs [10]. Hence the European CF landscape, which is already very heterogeneous, is expected to become even more so when Trikafta™ will become available. The development of new drugs for PWCF in Europe is essential, but the challenges are clear when viewed against this complex background (see also summary points in Table 2).

The ECFS Task Force focused on speeding up access to new treatments has previously published two manuscripts arising from its first workshop; these were focused on clinical trial design and ex-vivo testing for rare mutations [15,16]. In November 2019, the second workshop was convened. The Task Force members (authors) invited representation from the ECFS Clinical Trials Networks, patient organisations, pharmaceutical companies active in this space, experts in Health Technology Assessment (HTA and from the European Medicines Agency (EMA). The full list of attendees can be seen in the Acknowledgements list. The workshop took the form of group discussions of the issues outlined in this manuscript. At the end of each topic section, the moderator asked for comments, consensus or dissent on statements which have been incorporated into this text. All attendees were asked for comments on a draft of this manuscript, which were incorporated. The topics discussed here therefore reflect the consensus opinions of the multidisciplinary group.

2. CFTR modulator trials

2.1. Where to perform future modulator trials?

As highlighted, the pipeline of CFTR modulator trials is very promising [13], but the pool of CFTR modulator naïve patients is shrinking rapidly. Based on their major impact on outcomes in PWCF, 2 CFTR modulator combinations are currently considered

Table 2
Future drug trial design consensus summary points.

Future cystic fibrosis drug trial design in the context of highly effective CFTR modulators: Consensus views of cystic fibrosis stakeholders: Summary Points	
CFTR Modulator Trials	• Further CFTR modulator studies are needed, including for PWCF with access to HEMT • For PWCF already taking HEMT, only studies with a short washout followed by short (2-4 weeks) placebo-controlled assessment followed by long open-label extension, are likely to be acceptable and feasible • During the short placebo-controlled study, sweat chloride and FEV1 are key well-established endpoints with sufficiently early response, but using additional biomarkers is recommended for their future validation • Data from open-label extension can be compared with pre-trial participant-specific data, historical data in patient registries, previous clinical trial data, or contemporaneous matched controls for multiple long-term safety and efficacy outcomes to meet both regulatory and HTA requirements • Open label non-inferiority trials with a wide non inferiority margin are feasible if the comparator drug is supplied via doctor presciption • For PWCF with rare mutations, efficacy extrapolation from celular models acceptable to regulators and payers will be necessary • In young children, an effort must be made to prove efficacy; safety assessment is more informative when a short placebo period is included.
Anti-Infective Trials	• Key priority will be those PWCF still experiencing clinical decline due to chronic significant pathogens such as *Pseudomonas aeruginosa, Mycobacterium abscessus* • Trials of new agents for eradication of new or early *Pseudomonas aeruginosa* infection are not a priority • Studies with a maximum 4 week placebo-controlled period, followed by longer open-label extensions, are likely to be acceptable and feasible, given current standards of care • Sputum bacterial density and FEV_1 are likely the best endpoints • In PWCF taking HEMT rate of/time to pulmonary exacerbation as currently defined is no longer likely to be a feasible endpoint • Sputum production is less consistent post-HEMT; sputum induction may be necessary
Anti-inflammatory Trials	• Studies of anti-inflammatories are still important for PWCF taking HEMT • As the optimal biomarker is uncertain, we recommend to measure more than just the directly targetted biomarker • In PWCF taking HEMT rate of/time to pulmonary exacerbation as currently defiined may no longer be a feasible endpoint
Mucolytic Trials	• Possibly still important post-HEMT, but rate of/time to pulmonary exacerbation no longer likely to be a feasible endpoint • Sputum rheology may be a relevant biomarker, but needs to be reproducible with sputum induction

as modulator therapy associated with substantial clinical benefit namely Kalydeco™ for patients with a class III mutation and Trikafta™ for patients with at least one F508del (see further). Post-approval of Trikafta™ by the EMA, the major clinical impacts of drug availability will create diverging European patient cohorts. Based on modulator approval history plus the numbers of PWCF in the different countries, we have estimated the size of the different populations:

- access within the year post approval (~15%)
- access within several years post approval (~50%)
- very delayed or no access (~20%)
- not eligible for current modulators based on genotype (~18%).

We hope this is a 'worst case scenario' as discussions about reimbursement may be easier for triple modulator therapy than they have been for dual modulators given the much superior efficacy. Whilst a positive scenario will be of great benefit to PWCF receiving the drugs, the remaining pool of modulator naïve subjects in whom new molecules can be tested will even be smaller.

Patients with late or no access to triple modulator therapy will mainly reside in low resource areas. On average, their standard of CF care is lower than in other regions and this is reflected by worse baseline clinical parameters: lower proportion of adult PWCF, lower age-specific mean lung function (FEV_1), higher proportion with really low lung function and with chronic *P. aeruginosa* infection, worse nutritional status, lower use of standard symptomatic CF treatments [11]. Most centres in these low resource areas are very eager to assist with trials ofnew CFTR modulators, but many of them are less trial-ready and less trial-experienced. Because of baseline differences, extrapolating data from trials in these regions may be complex. Nothwithstanding continuous improvements in CF center care in lower resource areas in Europe, it is not realistic to expect that the local trial infrastructure can be boosted rapidly. Therefore, pharma companies may be unwilling to take that route. Performing modulator trials in these countries may also raise ethical issues and further increase inequality within the country; if ultimately drug reimbursement is unlikely, then the small cohort of trial participants may be the only PWCF with access to the drugs.

It thus seems most appropriate to run future CFTR modulator trials mainly in countries with access to modulators within the year(s) after drug approval. It is however uncertain whether patients who already have access to clinically very effective modulators will agree to participate in trials of new drugs. We have little experience in withdrawingmodulator therapy, whether this can be done safely and how long it will take for these subjects to regain a stable baseline [17,18]. In those regions where clinically effective modulator reimbursement is pending, the anxiety related to this wait may negatively influence patients' decision to participate in a trial with a new modulator.

What is therefore clear is that whilst is has been easy to enroll patients in large scale trials and prove efficacy of first in class triple modulator therapy [1,8,9], this will be much more difficult for modulators in the pipeline. Hence a different trial paradigm will be needed.

2.2. What are feasible and meaningful comparators to test new CFTR modulators?

Until now the strategy has been to add a new modulator or modulator combination to the patient's existing treatment plan. For patients already ontriple combination therapy, this cannot be advised for safety reasons, the possibility of complex drug-drug interactions and the potential for 'blunting/ masking' of any efficacy response to the new drug by the existing agent.

Comparing a new modulator to placebo will only be possible in the pool of patients waiting for Trikafta™ approval or willing to washout from previous treatment. For the latter group, only study

designs with a short washout and short double-blind placebo period will be acceptable and feasible [19]. It is also not ethical to deprive patients of highly effective treatment for long periods. It is our view that this should not pose too great a problem as short placebo studies will be sufficiently informative: the effect of modulator therapy on sweat chloride can be seen within days and the effect on FEV_1 within days or weeks. CFTR modulator trials, especially the trials with modulators associated with a substantial clinical benefit, have not demonstrated a long lag period between drug commencement and pulmonary function impact, and therefore continuing beyond these short time points in the expectation of a 'delayed' response is unjustified. Incorporation of short washouts or placebo periods, whilst probably justifiable, does raise other issues. The first is that we need to be certain that a short washout is sufficient to reach a steady baseline and avoid a carry over effect of the previousclinically effective modulator therapy . Secondly, there is a possibility that PWCF willing to discontinue triple modulator therapy are different from those who are not and that results may not be completely extrapolatable. Short placebo controlled studies also require new paradigms of how to establish mid to longer term drug efficacy. Historically, benefits on outcomes such as pulmonary exacerbations and nutritional status have been demonstrated in large randomized double blind, placebo controled trials of at least 6 months duration. These will now become unfeasible for the reasons above plus the fact that the large numbers of participants needed will not be available [4]. We therefore consider that extending any placebo period beyond the 2-4 weeks' duration required for sweat chloride and FEV_1 to change will not provide additional information. Rather it will further compromise the already limited study feasibility. We would propose instead that data on these other important outcomes should be obtained during open-label extension periods. These can be compared with either pre-trial participant-specific data, historical data in patient registries or data from previous clinical trials. In this context, the EMA's qualification procedure and positive opinion of the European CF Society Patient Registry (ECFS-PR) is hugely relevant and supportive of such a strategy [20]. The conclusion was that "the current status of ECFS-PR (coverage, core dataset, governance, quality assurance approaches and completeness of core variables) may allow its use for drug utilisation studies for total recorded population and subgroups, drug efficacy/effectiveness studies (concurrent assessment of effectiveness in specific circumstances or source of historical control data for comparative purposes in the context of RCTs when this would be the only reasonable) and for drug safety evaluation with focus on important identified and potential risk".

Also when novel modulator agents are being compared with best standard of care (i.e.triple modulator therapy), new trial strategies are needed. Superiority trials are highly unlikely to be feasible as the bar for acute improvement in FEV_1 with Trikafta™ is at present set around +14% predicted. We might even have reached the maximum possible acute improvement in FEV_1 as there was no difference in total FEV_1 improvement between F508del-homozygous and heterozygous subjects [8,9]. We do not yet know whether differences between these two genotype groups exist in outcomes like FEV_1 rate of decline and complications. Non-inferiority trials remain a possibility. Trials with generally a wide non-inferiority limit make sense in this setting: the drug benefit of the new test combination will then still be superior to the previous standard i.e. 2 drug modulator therapy (Orkambi™ and Symkevi™/Symdeco™); the inclusion number needed will be achievable. Unless the sponsor is comparing two of its own drugs, any trial comparing a new agent with best standard of care will only be possible with an open-label design: the costs associated with the triple modulator comparator arm will only be feasible by including patients being prescribedthis therapy. This will pose extra challenges of adherence to therapy and maybe moves us more towards real world evidence [21] and comparative effectiveness studies [22].

2.3. What are the trial endpoints needed?

In the context of trials with CFTR modulators the sweat chloride concentration has proven to be a key biomarker. The sweat test is non-invasive, widely available and well standardized [23] with known variability [24–27]. Sweat chloride concentration is a reliable biomarker of CFTR function and correlates well with the clinical phenotype [28]. Changes in sweat chloride concentration occur within days of starting treatment with CFTR modulators [17,29]. There is a non-linear correlation between sweat chloride concentration and %CFTR function as assessed *in vitro,* and changes in sweat chloride concentration seen during treatment with CFTR modulators move along this correlation line [30]. Although rather poorly correlating on an individual patient basis, mean changes in sweat chloride concentrations during treatment with ivacaftor in different studies and populations correlate well with mean changes in FEV_1 % predicted in these same populations [31]. Therefore, sweat chloride concentration has proven to be a reliable biomarker of efficacy during modulator trials at all stages of clinical development. Sweat chloride can of course not be used to assess efficacy of non systemic treatments that treat the underlying defect, e.g. nebulized mRNA.

Other efficacy endpoints are FEV_1 for subjects above age 6 years and lung clearance index (LCI) for younger subjects and/or those with less advanced lung disease. This information can be obtained from short-term clinical trials as improvements level off after 2 to maximum 4 weeks [1–5,8,9,29]. As discussed above, reduction in the occurence of pulmonary exacerbations will have to come from open-label extension periods and the same is true for other mid to longer term endpoints like, nutritonal status, patient well-being, sustained improvement in FEV_1, FEV_1 rate of decline, extra-pulmonary benefits such as pancreatic function and decreased rate (or even prevention) of complications. Hence real world evidence data [21] and registry data will become increasingly important. To facilitate comparisons among studies, a core outcome set (specific outcomes at specific time points) can be developed [32]. As stakeholders we agreed more attention to endpoints suitable for HTA must be part of phase III study design in order to overcome the reimbursement hurdle. These outcomes can be gained from short controlled studies followed by sufficiently longer open-label extension as long as suitable matched control data either historical or contemporaneous are available, such as from the ECFS-PR. In general, HTA methods require longer term data with appropriate patient reported quality of life (QoL) measures focussing on more than just respiratory outcomes.

2.4. Specific issues in developing drugs for young children and infants

It is obvious that we want to take safe and effective treatments down to the younger age groups. The CFTR defect is already present during foetal life. As most infants have relatively healthy lungs, there is a window of opportunity for 'prevention' in early life. We already have indications that early treatment with ivacaftor can prevent or revert complications like pancreatic insufficiency [33]. The possible gain of benefit is thus huge and we know that current treatments come with a high burden and greatly impact the QoL of parents and growing children. On the other hand, new treatments may not be free from adverse effects. Hence we need to balance the urgency for triple modulator therapy in the young age group with the need for safety and efficacy data. Extrapolation of efficacy down to younger age groups and design of single-arm studies addressing only dosing and drug tolerability has benefits. Study design is simplified and recruitment easy as all

Table 3
Pros and cons of available *in-vitro*/ *ex-vivo* testing models for rare mutations.

	Selecting only a single model		Allowing flexibility to use more than one model
	FRT	Organoids	
Pros	Already in regulatory use in the US; simple fast	Extensive experience in Europe; standardized; accurate; patient-derived thus accounting for individual responses; endogenous (physiological) levels of CFTR expression	More accessibility across different sites; possibly faster
Cons	Prone to error, especially with correctors; not patient-derived thus does not account for both alleles contributing to individuals' responses; heterologous (non-physiological) CFTR expression	New model; no universally agreed cut-off; at present only emerging evidence that organoids predict the response in an individual; not yet approved by regulators; no precedent for use in drug approval	Possibility of contradictory results for the same drug in different models; more need for standardization and thus more difficult to be accepted by regulators and higher complexity in approval

children obtain early drug access. On the other hand, advocating extrapolation down to younger age groups may come with a lost opportunity of fully understanding safety signals (eg. liver function changes during ivacaftor treatment in young children) [34] and off-target effects. Even though patient numbers may be small, at least trying to collect blinded efficacy data (sweat chloride concentration, LCI, fecal elastase) may convince regulators, funders and clinicians of the real benefit of starting these new treatments early. Examples of such benefits might include delays in the development of pancreatic exocrine insufficiency, CF-related diabetes, bronchiectasis and other systemic long-term complications impacting on life expectancy or quality of life. Possible solutions to overcome this dilemma are: early licensing opportunities with single arm data but with the regulatory requirement to support efficacy and safety by collecting data in a subsequent (or simultaneous) controlled trial; investigator-led studies with commercial drug provision; registry data collection. Whatever method is selected, there is an imperative for long-term data to be collected in children and infants started on modulators.

2.5. How to foster progress in modulator development for the patient population with rare CFTR mutations ?

Progress has mainly been made for the largest group of subjects, i.e., those with at least one F508del (around 82% in the European cohort), for the subjects with class III mutations (4% of the European cohort, but mainly overlapping with the former group) and in a limited number of cases with selected rare, but well-understood, mutations. With more than 2000 different *CFTR* variants described so far, it is a challenge to bring treatment to these remaining subjects. So far, FRT cells heterologously expressing *CFTR* mutations have been used to detect rare mutations responsive to ivacaftor and tezacaftor/ivacaftor for label-expansion through FDA regulatory approval [35]. But, in our opinion, FRT cells have several limitations. Only cDNA is expressed in these cell lines and they are prone to error for splice mutations [36]. Since they are rat and thyroid cells, they are less reliable to test the efficacy of correctors, which have been demonstrated to be very sensitive to cell specificity [37,38]. So far, the largest experience with predicting CFTR modulator efficacy has been with primary cultures of human bronchial epithelial cells analysed in the Ussing chamber, which is considered the 'gold-standard' in the field [39,40]. However, bronchial epithelial cells are mainly derived from lung explants and are not a practical way forward for patients with rare mutations. The development of patient-specific biomarkers of CFTR function to predict efficacy of modulators in nasal and intestinal cells has helped to identify therapies useful for patients with rare *CFTR* mutatons [41–44]. In Europe especially, there is growing expertise with intestinal organoids using the forskolin-induced swelling (FIS) assay [43,45]. For a comparative review of test models see Amaral et al [16] .

There are advantages to going forward with consensus on only one predictive model as it would allow greater standardization and improve consistency of results. Conversely, downsides include the model not being accessible to all sites and likely requiring an approach centralized in a few sites, with the complexities related to shipping of samples. Table 3 illustrates the available options with their pros and cons. Whatever the model chosen, we have previously outlined a possible path forward for patients with rare *CFTR* mutations: testing drug efficacy in patient-specific material with responders moving forward to N-of-1 trials or basket trials [16,46]. Once regulators have approved any of the *in vitro* models discussed above, the extrapolation of data across genotypes becomes possible.

3. Non Modulator Trials: Anti-infectives, Anti-inflammatory drugs, Mucolytic/Airway Surface Liquid Restoring Durgs

If development of new modulator programs will become increasingly difficult in the era ofmodulators associated with substantial clinical benefit, the challenges are even greater for the rest of the clinical pipeline. Although improved non-modulator therapies will continue to be needed, at least for decades, there are 2 major hurdles: the current focus of patients and physicians on modulator trials and the uncertainty as to how clinically very effective modulator therapy will reset the symptom baseline, and therefore trial outcome measures, for PWCF.

3.1. Anti-infective drugs

For anti-infective drugs, the greatest need is to find better treatments for PWCF with ongoing clinical decline despite standard of care treatment of chronic *Pseudomonas aeruginosa* (Pa) infection [47]. We have effective treatments for eradication of initial/early *Pa*, and trials would be cumbersome (needing both very large n and slow to recruit as based on occurrence of new infection); hence, we agree with Nichols et al that this is not a priority [47]. However, interventions designed to eradicate other airway pathogens such as MRSA, *Burkholderia, Achromobacter, Stenotrophomonas species* and *mycobacteria* [47] do deserve attention.

For studies targetting chronic *Pa* infection in patients treated with alternate months of e.g. nebulised tobramycin the "off" month could be used to study a new antibiotic. Effects on lung function and sputum bacterial density have been seen within 14 days in previous trials, perhaps supporting the notion of a 1 month

placebo-controlled study followed by a long open-label extension period. However, when participants' pulmonary status has been improved byclinically very effective modulator therapy, these changes may be more difficult to detect. In addition, studies in subjects on continuous cycling nebulised antibiotics are more challenging [47,48]. Blinding is difficult or even impossible, especially if a licensed delivery device is needed. There are challenges with the traditional endpoints in addition to those mentioned above. Clinically effective modulator therapy may diminish or even abolish sputum production, hence induced sputum will likely be necessary for sampling. As exacerbations will become much less frequent, rate or time to next exacerbation will likely become endpoints requiring unfeasibly large and long studies. The value of LCI as a regulatory endpoint is not yet established and, especially in more severely affected lungs, mucus shifts may give lead to paradoxical change as more diseased lung units are revealed and contribute to the signal. This is the likely explanation of the noise observed in studies of intravenous antibiotics for exacerbations. One option could be to take antibiotic trials to countries without access to triple modulator therapy, but it is unlikely that results can be extrapolated to PWCF treated with triple modulatorsfor the reasons discussed earlier.

3.2. Anti-inflammatory drugs

There is at present no marketing approval for any CF-specific anti-inflammatory drug. Ivacaftor registry data [49] and GOAL study data [50] demonstrate ongoing lung function decline despite HEMT. Hence anti-inflammatory drugs are likely still important [51]. Complications including CF arthropathy [52] and increased gastro-intestinal cancer risk [53,54] suggest systemic anti inflammatory drugs may also be needed.

Changes in FEV_1 or biomarkers were not often seen in 28-day phase 2 trials with anti inflammatory drugs; demonstrating such change may be even be less likely in populations treated withmodulators associated with substantial clinical benefit. Knowledge is lacking on optimal biomarkers for anti-inflammatories and the degree of change required in them (in part due to the absence to date of an effective drug). Hence, we would propose the inclusion of more than just the directly targeted biomarker eg. sputum neutrophil elastase and serum calprotectin. The use of anti-inflammatories as acute adjuncts during exacerbations is worthy of study, but may be less attractive to pharmaceutical companies compared to maintenance treatment.

3.3. Mucolytic drugs

Here, the problems are similar to those described above. At least if commenced once lung disease is already established, current modulator therapydoes not lead to complete normalisation of mucus/ sputum production and lung function continues to decline. Mucolytic and airway surface liquid restoring drugs are likely still important for this and possibly broader cohorts. Again, the problem comes when calculating the sample size requirement for trials: clinically effective modulator therapywill increase the number needed to assess changes in FEV_1 or reduction in rate of pulmonary exacerbations. Measuring sputum rheology [55] can be a useful biomarker, but sputum may be increasingly difficult to obtain posttriple modulator therapy. LCI can be used as a more sensitive measure of lung function, but will likely be most informative (and acceptable to participants) in patients with mild-moderate lung disease.

4. Conclusions

The recent progress in clinically very effective CFTR modulator therapies is unprecendented and is excellent news for those PWCF able to access drugs. Challenges remain including the need for alternative modulators to be trialled, and for drugs in other groups (targetting infection, inflammation and mucus clearance) to be developed and tested. The multi-stakeholder group brought together by the ECFS Task Force provided a valuable opportunity to discuss many of these challenges, and to provide a number of recommendations based on consensus. We hope that these will form a valuable resource to guide future trial design and approval, allowing us to maximise further improvements to the health of people with CF worldwide.

CRediT authorship contribution statement

K. De Boeck: Conceptualization, Writing - original draft, Writing - review & editing. **T. Lee:** Conceptualization, Writing - original draft, Writing - review & editing. **M. Amaral:** Conceptualization, Writing - original draft, Writing - review & editing. **P. Drevinek:** Conceptualization, Writing - original draft, Writing - review & editing. **J.S. Elborn:** Conceptualization, Writing - original draft, Writing - review & editing. **I. Fajac:** Conceptualization, Writing - original draft, Writing - review & editing. **E. Kerem:** Conceptualization, Writing - original draft, Writing - review & editing. **J.C. Davies:** Conceptualization, Writing - original draft, Writing - review & editing.

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