The combination of tezacaftor and ivacaftor in the treatment of patients with cystic fibrosis: clinical evidence and future prospects in cystic fibrosis therapy

Ther Adv Respir Dis
2019, Vol. 13: 1–13
DOI: 10.1177/1753466619844424

Sherstin T. Lommatzsch and Jennifer L. Taylor-Cousar

Correspondence to:
Jennifer L. Taylor-Cousar
National Jewish Health, 1400 Jackson Street, J318, Denver, CO 80206, USA
taylorcousarj@njhealth.org

Abstract: Years of tremendous study have dawned a new era for the treatment of cystic fibrosis (CF). For years CF care was rooted in the management of organ dysfunction resulting from the mal-effects of absent anion transport through the CF transmembrane regulator (CFTR) protein. CFTR, an adenosine triphosphate binding anion channel, has multiple functions, but primarily regulates the movement of chloride anions, thiocyanate and bicarbonate across luminal cell membranes. Additional roles include effects on other electrolyte channels such as the epithelial sodium channel (ENaC) and on pulmonary innate immunity.

Inappropriate luminal anion movement leads to elevated sweat chloride concentrations, dehydrated airway surface liquid, overall viscous mucous production, and inspissated bile and pancreatic secretions. As a result, patients develop the well-known CF symptoms and disease-defining complications such as chronic cough, oily stools, recurrent pulmonary infections, bronchiectasis, chronic sinusitis and malnutrition.

Traditionally, CF has been symptomatically managed, but over the past 6 years those with CF have been offered a new mode of therapy; CFTR protein modulation. These medications affect the basic defect in CF: abnormal CFTR function. Ivacaftor, approved for use in the United States in 2012, is the first medication in CF history to improve CFTR function at the molecular level. Its study and approval were followed by two additional CFTR modulators, lumacaftor/ivacaftor and tezacaftor/ivacaftor.

To effectively use currently available CF therapies, clinicians should be familiar with the side effects of the drugs and their impacts on patient outcomes. As many new modulators are on the horizon, this information will equip providers to discuss the benefits and shortcomings of modulator therapy especially in the context of limited healthcare resources.

Keywords: amplifier, corrector, cystic fibrosis, cystic fibrosis transmembrane conductance regulator, ivacaftor, lumacaftor, tezacaftor, potentiator

Received: 3 December 2018; revised manuscript accepted: 19 December 2018.

Historical background and clinical recognition

Cystic fibrosis (CF) symptoms have been described in children for hundreds of years.[1] Early medical literature bemoans afflicted infants as living in a 'cursed' state because a 'child who tastes salty [when kissed]… soon must die'.[2] Today, however, those with CF can anticipate a median predicted survival of 44 years.[3]

Despite medieval recognition of a link between an infant's salty skin and infant mortality, true understanding of CF did not begin until the late 19th and early 20th centuries. While now widely recognized primarily as a pulmonary disease, CF manifestations were initially described in the gastrointestinal (GI) tract; meconium peritonitis in 1838 by Carl von Rokitansky and meconium ileus in 1905 by Karl Landsteiner. Many children with intestinal

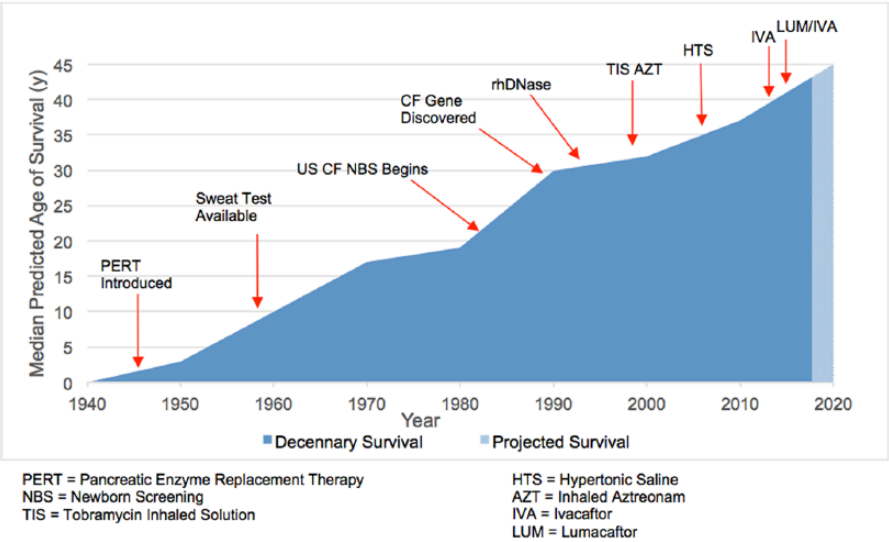


Figure 1. Change in cystic fibrosis survival as related to therapies and scientific advancement.[9–12]

obstruction, oily stools, and malnutrition were felt to have a form of celiac disease. In 1930 however, Margaret Harper, an Australian pediatrician at the Royal Alexandra Hospital for Children, distinguished CF intestinal disease from celiac disease.

Despite these early reports, exploration of a newly described disease did not take foot until 1938 when Dr Dorothy H. Andersen, Chief of Pathology at the Babies Hospital of Columbia Presbyterian Medical Center described 'cystic fibrosis of the pancreas'.[4] As a result, work during the 1940s revealed that CF was a multiorgan disease. The 1948 heat wave in New York city, USA, led pediatricians Kessler and Anderson to report that patients with CF were more prone to the ill effects of sweating during heat prostration.[5] Dr Paul di Sant'Agnese, founder of the United States (US) Cystic Fibrosis Foundation, performed several studies in the early 1950s demonstrating the altered electrolyte concentration in CF sweat.[6,7] These data resulted in Gibson and Cooke's 1959 description of pilocarpine iontophoresis.[8] Their method of sweat collection replaced placing babies in heated blankets and bags (which led to death in some cases) and supplanted duodenal intubation for measurement of duodenal trypsin concentration. In 1979, measurement of immunoreactive trypsinogen on a blood spot made universal screening for CF feasible, and in 1982 Colorado was the first US state to place CF on its newborn screening panel.[9] A new frontier of research opened later that decade when, in 1989, the CF gene was discovered by Canada's Dr Lap-Chee Tsui.[10] This unprecedented genomic understanding combined with organ-specific targeted therapies, has led to an exponential increase in CF survival (Figure 1).

CFTR protein dysfunction

CF occurs in persons with two pathologic CFTR genes located in trans; that is, one mutation on each allele. Currently more than 2000 genetic variations are described, but only about 300 are known to cause clinical disease.[12] Mutations often affect both CFTR synthesis and function, but each is classified by the primary mechanism leading to protein malfunction.[13] Mutations affecting synthesis and processing (Class I-II) result in more severe disease because no or nominal numbers of proteins reach the cell surface.[14] Abnormal proteins maintaining some residual function (RF), that is, conduct some anions, are processed by the endoplasmic reticulum (ER) and trafficked to the luminal surface. Individuals with these mutations often experience less severe symptoms as the abnormal proteins maintain some open probability or transport some anions (classes III–IV respectively).[14]

Representing approximately 10% of mutations,[15] class I (often delineated with an 'X' such as G542X) refers to defects in biosynthesis such as frameshift mutations, insertions and nonsense mutations. Also, in this class are canonical splice mutations and chromosomal deletions.[13] Many of

these ultimately result in premature termination codons (PTCs).[16] The most common mutation, F508del, belongs principally to class II. It is present in almost 90% of the CF population and 46% of people with CF are homozygous for this mutation.[17] These abnormalities result in an improperly folded CFTR that is poorly processed or insufficiently trafficked to the cell surface. The few that are trafficked function poorly and are quickly turned over.[18]

Class III and IV abnormalities yield proteins that, although present in the membrane, transport inadequate numbers of anions. As there is some appreciable movement of anions (i.e. there is some RF of the protein), those with these mutations tend to have less severe disease than those with class I and II mutations.[3] Class III mutations, known as gating mutations, do not open with sufficient frequency. Class IV, termed conductance mutations, fail to conduct adequate quantities of chloride ions. Splice mutations (the insertion or deletion of nucleotides in regions of DNA coding for protein cuts), belong to class V. Finally, class VI refers to abnormalities resulting in protein instability once inserted into the epithelial surface.

CFTR mutations affect distinctive stages of protein synthesis and function. Thus, to rescue CFTR, modulator therapy targets a specific source of the protein's malfunction. As some proteins result in multiple defects, more than one modulator is required to render sufficient protein activity. For example, ivacaftor, subclassified as a CFTR protein potentiator, augments chloride secretion of membranal CFTR.[19] Augmentation results in clinical improvement for persons with specific gating and conductance mutations (classes III and IV).[20–23] Consequently, for those who are F508del homozygous, ivacaftor monotherapy is clinically ineffective[24] as F508del produces a CFTR protein that is not adequately expressed on the luminal surface. If present on the luminal surface, however, its conductance is responsive to potentiator therapy.[19] As a protein corrector increases the concentration of F508del in the membrane by improving ER processing and subsequent protein trafficking, the combination of a corrector and potentiator results in clinical benefit for those F508del homozygous and most recently those with F508del/RF mutations.[25–27] Currently in development is a third modulator class, termed 'amplifier', that increases the steady-state levels of the CFTR. It is mutation-agnostic and independently compliments the activity of both correctors and potentiators.[28]

Consequently, as historical therapies could only affect complications of disease, current therapies target the underlying cause of the disease. Thus, as 97.7% of those in the US CF Registry have been genotyped, a person's genetic mutations are used to direct therapeutic changes.[3,29]

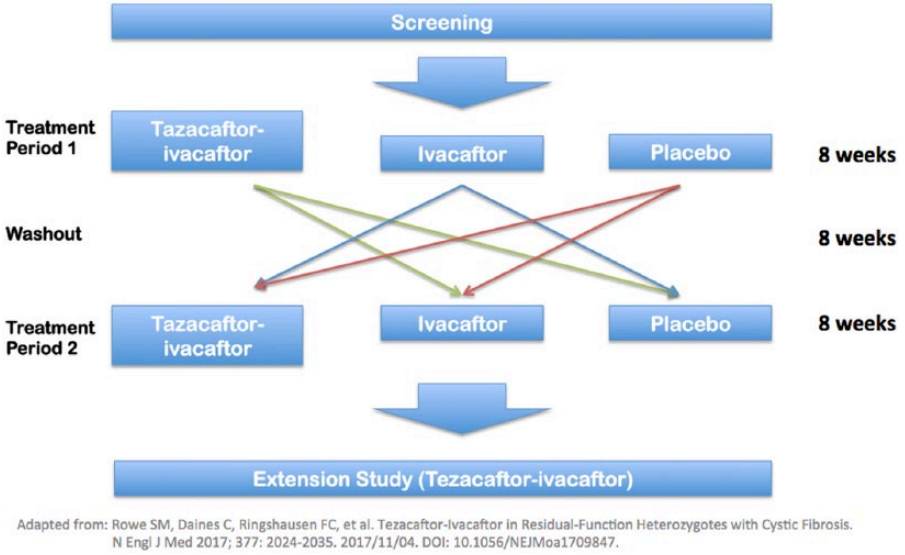
CFTR modulators: safety, effectiveness and use

Safety, effectiveness and use

Presently, three CFTR modulators are approved on the international market: ivacaftor, lumacaftor/ivacaftor and most recently tezacaftor/ivacaftor. Although the effect of modulators on long-term survival can only be estimated,[30,31] short-term improvements such a decrease in sweat chloride, fewer pulmonary exacerbations (PExs), increases in percentage of predicted forced expiratory volume in 1 second ($ppFEV_1$) and increases in body mass index (BMI) have been well documented in several phase III clinical trials.[20,25–27]

Although ivacaftor was initially approved only for people with CF and a G551D mutation,[32] clinical trial data and cell models of CF[33] supported the US Food and Drug Administration (FDA)'s indication expansion to include 38 mutations for people >1 year of age. Lumacaftor-ivacaftor was approved in the US for use in people with CF homozygous for the F508del mutation in 2015.[34] Chest tightness and its multiple drug interactions (such as rendering hormonal contraceptives ineffective and significantly interfering with rifampin), further limit its use.[35,36] Tezacaftor/ivacaftor is a new combination modulator (corrector and potentiator) that expands the population for which modulator therapy is available; those heterozygous for F508del and a RF mutation, and it is a second option for those homozygous for F508del. The two large phase III clinical trials, EVOLVE[25] and EXPAND,[26] were designed to expressly demonstrate the effectiveness of the new corrector tezacaftor and known potentiator ivacaftor in these different CF populations.

EVOLVE was a 24-week, randomized, double-blind, placebo-controlled, parallel-group trial studying tezacaftor/ivacaftor in F508del homozygotes. Persons



Adapted from: Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. N Engl J Med 2017; 377: 2024-2035. 2017/11/04. DOI: 10.1056/NEJMoa1709847.

Figure 2. EXPAND study design[26].

12 and older with stable CF disease and a $ppFEV_1$ between 40% and 90% at screening, were randomized 1:1 to receive either tezacaftor 100 mg daily with ivacaftor 150 mg twice daily or placebo twice daily. The primary endpoint was the absolute change in $ppFEV_1$ from baseline though week 24. Secondary endpoints over the same timeframe included the relative change in $ppFEV_1$, total number of PExs, the absolute change in BMI, and absolute symptom change as measured using the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a validated CF-specific quality of life measure for which increased scores represent improved patient-reported quality of life; the established minimal clinically important difference for the respiratory domain score is 4 points.[31]

EXPAND was a randomized, multicenter, placebo-controlled, crossover trial describing the effect of tezacaftor/ivacaftor in 248 patients heterozygous for F508del and a RF mutation. The inclusion criteria were identical to EVOLVE, except that in addition to being heterozygous for a RF mutation, candidates also needed to have a sweat chloride of greater than or equal to 60 mmol/l or, if lower, evidence of chronic sinopulmonary disease. The primary endpoint was the absolute change in $ppFEV_1$ and secondary endpoints included CFQ-R respiratory domain scores, relative change in $ppFEV_1$, and absolute change in sweat chloride. The investigators chose a crossover design (Figure 2) because there are an insufficient number of patients with RF mutations to conduct a sufficiently large parallel-group trial (as fewer than 400 CF mutations have been fully characterized[11] and the majority of those mutations are incredibly rare).[3]

Both studies demonstrated a significant improvement in their primary (absolute change in ppFEV1) endpoints. In EVOLVE (F508del homozygote population) the ppFEV1 increased by 4% . In EXPAND (F508del heterozygote population) the ppFEV1 improved by 6.8%. An important secondary endpoint was the CFQ-R respiratory domain score. In EVOLVE, although nominally significant, there was a 5.1 point improvement in the CFQ-R respiratory domain score, and in EXPAND, the CFQ-R respiratory domain score increased by 11.1 points when compared with placebo. Additionally, in EXPAND, use of tezacaftor-ivacaftor was associated with a statistically significant 2.1% improvement in ppFEV1 when compared with ivacaftor alone. This finding is important as it demonstrates the increased effectiveness of dual corrector/potentiator therapy over an already available monotherapy (ivacaftor) for many in the heterozygous F508del/RF population.

Secondary endpoints, including the effect of tezacaftor/ivacaftor on the rate of pulmonary exacerbations were generally encouraging in both studies. EXPAND demonstrated a 10% reduction in risk for PExs. Although a supportive endpoint, persons in EVOLVE experienced a 35% reduction in infective PExs. Thus, as more frequent PExs have been associated with an increased rate of $ppFEV_1$

Table 1. Brief description of referenced CFTR protein modulator studies.

Study	Description
STRIVE[20]	A randomized, double-blind, placebo-controlled trial studying ivacaftor in patients ≥12 years with at least one G551D-CFTR mutation
EVOLVE[25]	A phase III randomized, double-blind, placebo-controlled, multicenter, parallel trial evaluating the effects of tezacaftor-ivacaftor in patients ≥ 12 years homozygous for F508del
EXPAND[26]	A phase III randomized, double-blind, placebo-controlled, crossover trial examining the efficacy and safety of ivacaftor monotherapy or in combination with tezacaftor in those ≥ 12 years heterozygous for F508del and an RF mutation
Phase II LUMACAFTOR-IVACAFTOR[40]	A phase II randomized control trial in patients ≥ 18 years studying the effects of lumacaftor combined with ivacaftor
TRAFFIC/TRANSPORT[34]	Two phase III, randomized, double-blind, placebo-controlled studies studying the effects of lumacaftor combined with ivacaftor in patients ≥12 years of age F508del homozygous
LUMACAFTOR-IVACAFTOR Open-Label 6–11y/o[41]	An open-label phase III trial, evaluating the safety, tolerability, pharmacodynamics, and efficacy of lumacaftor/ivacaftor in patients 6–11 years homozygous for F508del
LUMACAFTOR-IVACAFTOR Randomized 6–11y/o[42]	A phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of lumacaftor/ivacaftor combination in F508del homozygotes 6–11 years of age
PROSPECT[43]	Two-part multicenter prospective, longitudinal study of CFTR-dependent disease profiling in CF to explore biomarkers, clinical, and physiological characteristics across various degrees of CF severity
LUMACAFTOR-IVACAFTOR 24 Week Open Label[44]	A safety, tolerability, and efficacy study of lumacaftor/ivacaftor 400 mg/200 mg Q12 hours in patients ≥ 12 years homozygous for F508del with $ppFEV_1 < 40\%$

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second; RF, residual function.

decline, a sustained effect of tezacaftor/ivacaftor could decrease this complication.[37] On a functional level, when compared with placebo, the absolute change in sweat chloride concentration from baseline was -10.1 mmol/l (EVOLVE) and -9.5 mmol/l (EXPAND). Surprisingly, although patients in both studies gained weight over the 6-month study period, there was no statistically different improvement in BMI in the treatment arms.

Use

The US FDA, delineates the genetic mutations for which each CFTR protein modulator may be prescribed, despite some persons being clinically found to respond to the approved therapies.[38] For an individual person, the results of EXPAND and EVOLVE should be evaluated in the context of prior studies involving CFTR protein modulators, noting medication side effects (SEs), patient co-morbidities, differences in measured outcomes and US FDA approval criteria (See Tables 1 and 2 for a brief description of important studies and side effects referenced in the following text). For example, although immediate effects of modulator therapy include improvements in $ppFEV_1$ and rates of PExs, markers of cellular efficacy such as changes in sweat chloride suggest improved baseline physiology. The clinical consequences of the latter finding are not yet clear as individual sweat chloride responses do not predict outcomes related to $ppFEV_1$ or PExs.[39] Perhaps sustained exposure to a more improved clinical milieu could retard organ dysfunction.

Table 2. Summary of modulator effects on clinically important outcome measures#.

Study (drug used)	Mutations	Week 24 Δ sweat chloride (mmol/l) [CI]	Week 24 absl Δ ppFEV$_1$ (%) [CI]	Week 24 Δ BMI (kg/m^2) [CI]	Week 24 PEx rate reduction (%) [CI]
STRIVE[20]	G551D	-47.9 [-51.3 to -44.5]	10.6 [8.6–12.6]	2.8 (kg) (BMI NM) [1.8–3.7]	60 [36–78]
EXPAND[26]	F508del/RF	-9.5@ [-11.7 to -7.3]	6.8@ [5.7–7.8]	NS	NS
Phase 2 Lumacaftor/ Ivacaftor[40]	F508del homozygotes	-11.1* [-18.5 to -3.7]	NS*	NM	NM
TRAFFIC/ TRANSPORT[34]	F508del homozygotes	NM See Phase II lum/iva	2.8≠ [1.8–3.8]	0.24 [0.11–0.37]	39 [24–51]
Lumacaftor/ Ivacaftor-Open Label 6–11y/o[41]	F508del homozygotes	-24.8+ [-29.1 to -20.5]	NS	0.64+ [0.46–0.83]	NM
Lumacaftor/ Ivacaftor Phase III Randomized **6–11y/o**[42]	F508del homozygotes	-20.8++ [-23.4 to -18.2]	2.4 [0.4–4.4]	NS	NM
PROSPECT[43]	Variable	-17 [NR]	1.6 [NR]	0.6 [NR]	NM
Lumacaftor/ Ivacaftor 24 Week Open-Label [44]	F508del homozygotes	-20.2 [-24.3 to -16.1]	NS	NS	NM
EVOLVE[25]	F508del homozygotes	-10.1 [-11.4 to-8.8]	4.0 [3.1–4.8]	NS	35 [12–52]

#Outcomes at week 24 *versus* placebo unless otherwise noted.
*Day 56, lumacaftor 400 mg every 12 hours.
≠For patients who received approved lumacaftor-ivacaftor dose.
@change from the baseline to the average of the week 4 and week 8 measurement compared with placebo.
+change from baseline to week 24.
++change at day 15 and week 4.
BMI, body mass index; CI, confidence interval; CF, cystic fibrosis; iva, ivacaftor; lum, lumacaftor; NM, not measured; NR, not reported; NS, not statistically significant; ppFEV$_1$, percentage of predicted forced expiratory volume in 1 second; PEx, pulmonary exacerbation.

Tezacaftor-ivacaftor is available in the US (and approved for use in Canada) for those 12 years and older who are either F508del homozygotes or are heterozygous for F508del and one of several RF mutations (US approval only; Table 3).[45] There are two advantages that favor use of tezacaftor-ivacaftor *versus* lumacaftor-ivacaftor: Tezacaftor-ivacaftor is associated with an improved SE profile and has fewer medication interactions than lumacaftor-ivacaftor. For example: In the EXPAND and EVOLVE, no patients discontinued the study due to respiratory SEs. Also, no increase in dyspnea was noted with tezacaftor-ivacaftor initiation as had been with lumacaftor-ivacaftor.[25–27] Importantly, females can reliably use hormonal contraception

Table 3. CFTR mutations beyond F508del homozygous approved for tezacaftor/ivacaftor use.*

Symdeko indicated mutations • **F508del/F508de1 or** • **At least one responsive mutation from the following list:**			
711+3A→ G	2789-5G → A	3272-26A → G	3846+10kbC →T
A455E	A1067T	D110E	D110H
D579G	D1152H	D1270N	E56K
E193K	E831X	F1052V	F1074L
K1060T	L206W	P67L	R74W
R117C	R347H	R352Q	R1070W
S945L	S977F		

*These CFTR mutations have been shown to yield a clinical FEV_1 response or *in vitro* data demonstrating an increase in chloride transport to at least 10% of untreated normal over baseline in response to tezacaftor/ivacaftor.[45]
CFTR, cystic fibrosis transmembrane regulator; FEV_1, forced expiratory volume in 1 second.

with tezacaftor-ivacaftor.[45] However, as with lumacaftor-ivacaftor, use of rifampin and other strong CYP3A inducers is not recommended and the dose of azole antifungals should be reduced when co-administered tezacaftor-ivacaftor.[45] Important for pregnancy counseling, although animal data are not highly concerning (Table 4) and there are scattered case reports of successful human pregnancy following use of ivacaftor alone or ivacaftor-lumacaftor during the pregnancy,[45,33,35–42] the effects of these modulators on human fetal development and lactation are largely unknown. The older adult population presents a different set of prescribing concerns as comorbid conditions require treatment with medications not historically encountered in CF care. Serum digoxin concentrations, for example, are variably affected by combination therapy and may need to be followed more closely.[45] Finally, combination therapy also alters serum levels of several commonly used immunosuppressive medications such as cyclosporine, everolimus, sirolimus, and tacrolimus.[45]

As previously mentioned, ivacaftor provides substantial clinical efficacy in adults and children with RF mutations; typically gating and conductance abnormalities (Table 1 STRIVE).[20–22] It is now approved for use in those with CF 1 year of age or older with multiple gating and conductance altering mutations as delineated in the package insert.[33] It has not been associated with significant pulmonary symptoms,[20] but like each modulator, may cause hepatotoxicity.[33] Animal studies revealed development of non-congenital cataracts in the young, and thus children require serial ophthalmologic evaluation.[33] It also has several drug–drug interactions. Its dose needs to be reduced when co-administered with moderate and strong CYP3A inhibitors (such as azole antifungals)[33] and its concentration is significantly reduced in the presence of rifamycins. Whether used alone or in combination with ivacaftor or tezacaftor, it also may affect serum dioxin levels and commonly used immunosuppressants.[33] Uniquely, as the modulator with the longest commercial experience, long-term safety and efficacy have been better established; no new significant safety concerns have arisen and its use continues to be associated with fewer PExs, decreased need for transplantation and lower risk of death.[47]

Lumacaftor/ivacaftor, the first approved combination modulator, may be prescribed for those who are F508del homozygous and 2 years or older. While it provides improvement in clinically important endpoints such as $ppFEV_1$ and PExs, it remains a challenging drug to use in some patients. Initiation is sometimes associated with significant chest tightness, wheezing and increased pulmonary events in those with advanced lung disease.[27,35,48] As a strong CYP3A inducer, lumacaftor has the highest number of drug–drug interaction of all the modulators[49]; hormonal contraception is unreliable, serum concentrations

Table 4. Drug use in specific populations.

Organ	Ivacaftor[33,35]	Lumacaftor-ivacaftor[35]	Tezacaftor-ivacaftor[45]
Renal insufficiency			
Mild	No dose adjustment	No dose adjustment	No dose adjustment
Moderate	No dose adjustment	No dose adjustment	No dose adjustment
GFR < 30 ml/min or ESRD	Caution with use	Caution with use	Caution with use
Hepatic insufficiency			
CP class A	No dose adjustment	No dose adjustment	No dose adjustment
CP class B	Dose adjustment recommended	Dose adjustment recommended	Dose adjustment recommended
CP class C	Not studied[a]	Not studied[a]	Not studied[a]
Fertility	No significant effect in animals at nontoxic dose[c]	No significant effect in animals at toxic dose[35] (lumacaftor alone)	No significant effect in animals at toxic dose[45] (tezacaftor alone)
Pregnancy/ teratogenicity	No significant effect in animals at nontoxic dose[e]	No significant effect at toxic dose[f] (lumacaftor alone, not tested in combination)	Varied effects at different dosing[g] (tezacaftor alone, not tested in combination)
Miscarriage	Unknown	Unknown	Unknown
Lactation (humans)	Present [46, h]	Present [46, h]	Unknown[h]

CP, Child–Pugh; ESRD, end-stage renal disease; GFR, glomerular filtration rate; LFBW, low fetal birth weight; MRHD, maximum recommended human dose.
[a]Use with caution and monitor liver function closely.
[b]Rats: none at three[33], four[45], or five-times[35] (females) and six[45,34], eight-times[35] (males) the MRHD receiving 100 mg/kg/day.
[c]Rats: none at three[33], four[45], or five-times[35] (females) and six[45,33], eight-times[35] (males) the MRHD receiving 100 mg/kg/day. Reduced fertility noted at 6[45], 7[35] and 8[33] (females) and 9[45] or 15-times[33,37] (males) the MRHD receiving 200 mg/kg/day.
[d]Rats: none at eight-times (females) and three-times (male) the MRHD.
[e]Rats: none at three-times[33] the MRHD receiving 100 mg/kg/day. LFBW noted at five-times (toxic dose)[33] the MRHD receiving 200 mg/kg/day.
(1) Rats: none at three-times the MRHD receiving 100 mg/kg/day based on embryo-fetal development, but LFBW at two-times the MRHD receiving 50 mg/kg/day based on pre and postnatal development.
(2) Rabbits: based on embryo-fetal development, none at 0.2-times the MRHD receiving 25 mg/kg/day, but LFBW at 0.4-times the MRHD receiving 50 mg/kg/day.
(3) Noncongenital lens opacities/cataracts have been reported in pediatric patients. Rats: Noncongenital cataracts noted in rats from postnatal days 7 to 35, cataracts were observed at all dose levels.
[f]Rats and Rabbits: during organogenesis, no teratogenicity or adverse effects on fetal development at doses up to approximately eight (rats) and five (rabbits) times the exposure at the MRHD. Rats: from organogenesis to lactation, no developmental adverse events at eight-times the MHRD.[37]
[g]Rats and Rabbits: during organogenesis, no teratogenicity or adverse developmental effects at three-times (MRHD) in rats and 0.2 times the MRHD in rabbits. Please see package insert for more details at higher doses.[45]
[h]Present in milk of lactating rats. Due to species-specific lactation physiology animal data may not reflect human findings.

of many selective serotonin reuptake inhibitors are reduced, and a rifampin-based nontuberculous mycobacteria treatment regimen is not recommended.[35] Importantly, it may decrease the serum concentration of corticosteroids which has direct implications when concomitantly treating allergic bronchopulmonary aspergillosis or an acute asthma exacerbation.[35]

An interesting finding is the change in sweat chloride seen with lumacaftor-ivacaftor compared with the changes seen with other CFTR modulators. Notably, patients with the G551D mutation had a robust decrease in sweat chloride of 48.1 mmol/l, but such marked improvement was not matched in dual combination modulator trials including in those with other RF mutations[26] (Table 2, EXPAND). The lumacaftor/ivacaftor phase II study documented improvement in sweat chloride of approximately 11 mmol/l (changes in sweat were not measured in the lumacaftor/ivacaftor phase III studies).[40,36] Data from lumacaftor/ivacaftor phase IV studies demonstrate that the average improvement in sweat chloride in children $\geq$ 6 years is approximately 20 mmol/l. Recently, Graeber and colleagues described changes in sweat chloride, nasal potential difference (NPD) and intestinal current measurement (ICMs) in 53 patients homozygous for F508del.[50] Their work demonstrated improvement in NPD and ICMs to 10–20% of wildtype function. Most intriguing is that the extent of CFTR rescue found was comparable to that present in pancreatic sufficient F508del/RF heterozygotes. This finding suggests that lumacaftor/ivacaftor combination therapy may provide sufficient CFTR rescue to improve pancreatic exocrine dysfunction. Data from the study of lumacaftor-ivacaftor in children ages 2–5 years who are homozygous for F508del demonstrated improvements in fecal elastase (a measure of pancreatic function) of −262.1 ng/ml [standard deviation (SD) 343.1] in patients <14 kg and an improvement of −71.1 ng/ml (SD 120.5) in children >14 kg following 24 weeks of lumacaftor-ivacaftor therapy (ClinicalTrials.gov identifier: NCT02797132). These findings suggest that early combination therapy may have a bearing beyond $ppFEV_1$ outcomes; for example: the potential to decrease overall management burden by supporting $ppFEV_1$ through improved nutrition. How the differences in improvement in sweat chloride between lumacaftor-ivacaftor and tezacaftor-ivacaftor will impact clinical outcomes over longer periods of study is unclear, but is being evaluated (ClinicalTrials.gov identifier: NCT03445793).

Given the similarities and differences between the two drugs, there are some patients for whom the rationale for a change in therapy from lumacaftor-ivacaftor to tezacaftor-ivacaftor is clear. For example, a patient who had chest tightness and $ppFEV_1$ decline in spite of a step-up approach to therapy would be an excellent candidate for tezacaftor-ivacaftor. However, for other patients who have been stable or had markedly improved lung function or other outcomes on lumacaftor-ivacaftor, the decision to change therapy remains unclear. Other additional questions also remain: When should a modulator be prescribed outside of the indication label? (e.g. in the case of a rare RF mutation). Might the greater improvement in sweat chloride noted with lumacaftor-ivacaftor provide better pulmonary protection and prolong endocrine pancreatic function such that the SE profile of lumacaftor-ivacaftor is more acceptable? How should CFTR modulator use be managed when a patient requires an antifungal or nontuberculous mycobacterial (NTM) therapy? These challenges will continue to require thoughtful, informed discussions between clinician and patient.

Cost–utility analysis

The lifetime cost of CF care (considering equipment, dietary needs, and maintenance therapies, alone) is expensive and rises as new therapies become available. For example, in 1997, the total lifetime cost in Germany was €396,000/patient and rose to €858,604/patient in 2007.[51] In 2006, the US spent €39,278/patient (US$48,098) of which 40% was delegated to medication costs.[51] In this decade, that percentage will rise significantly as the annual patient cost of ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor is approximately US$260,000–300,000.[52,53]

As a result, payment for CFTR modulators has spurred substantial debate as these therapies are amongst some of the most highly priced medications on the US market.[52] Viewpoints range between two extremes: a utilitarian approach in which expenditures benefit the greatest portion of a population and a ‘right-to-health’ approach in which all members of a population are provided with a defined minimum quality of life.[54] To syncretize these two vantagepoints some suggest one evaluate drug cost in terms of a weighted quality of life adjusted life year (QUALY). Cost-effectiveness is thus evaluated in terms of direct and indirect costs with a greater value assigned to health gain but respecting a maximum monetary expenditure.[54] This year, the Institute for Clinical and Economic Review (ICER; an independent, nonprofit research institute) evaluated the addition of CFTR protein modulators to standard CF

care.[55] They reported that despite improvement in health outcomes the current price of modulators needed at least a 40% price reduction to be cost-effective. Of note, lumacaftor-ivacaftor and tezacaftor-ivacaftor have not been available for a sufficient amount of time to assess their effect on QUALY, so their analysis is premature. Furthermore, the application of their analysis type to therapies for very rare diseases has been questioned.[56] Nevertheless, the findings highlight the high cost of personalized medicine which has led to more limited use of CFTR modulators in countries with universal health care coverage,[57–59] and thus may impact the immediate use of tezacaftor-ivacaftor outside the US.

Future prospects

The effects of currently available modulator therapy are exciting because of their potential short and long-term impact on both quality and longevity of life, but many questions remain: What might the sustained effects of currently available modulators be? How can current protein targeted therapy be expanded to include more genetic variants and age groups? In which populations might additional classes of modulators provide benefit? Could greater clinical and functional affect be obtained with multiple correctors in combination with potentiators?

These pressing questions are being addressed in multiple studies several of which use tezacaftor/ivacaftor as the backbone on which new hypotheses or new modulators are tested. For example: Vertex Pharmaceuticals, has launched two phase III trials evaluating the efficacy in patients 12 years and older of the combination tezacaftor/ivacaftor with one of two additional correctors: VX-659 or VX-445 (ClinicalTrials.gov identifier: NCT03447249 and NCT03525444 respectively). Additionally, pharmacokinetic studies of VX-659 and VX-445 with tezacaftor/ivacaftor are ongoing in patients ages 6 to 11 years (ClinicalTrials.gov identifier: NCT03633526 and NCT03691779 respectively). In December 2018, the University of Alabama in November 2018 plans to launch a phase I study looking at tezacaftor/lumacaftor in a novel population; those with the PTC W1282X (ClinicalTrials.gov identifier: NCT03624101).

Proteostasis Therapeutics INC is conducting a phase I multicenter, randomized, placebo-controlled, study evaluating safety, tolerability, and pharmacokinetics of triple therapy with lumacaftor-ivacaftor and PTI-801 (a third-generation corrector) in healthy volunteers and persons with CF (ClinicalTrials.gov identifier: NCT03140527). Additionally, in a phase II evaluation, this company is studying the effects of once-daily triple therapy using PTI-428 (a novel amplifier), PTI-808 (CFTR potentiator) and PTI-801 (corrector; ClinicalTrials.gov identifier: NCT03500263).[60] Other companies conducting early phase studies of CFTR modulators through the CF pipeline include Galapagos, Novartis and Flatley.[61]

In addition to CFTR modulators, investigators are exploring use of CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats associated with Cas9 nuclease technology). This novel approach to the treatment of CF uses a protein-RNA complex that identifies defective CFTR DNA. The defective DNA is removed and replaced with a normal sequence. In 2016, the Cystic Fibrosis Foundation Therapeutics established a collaboration with Editas Medicine to develop a CRISPR-Cas9 therapy that would identify and correct the most common CFTR mutations as well as those mutations not approved for current protein modulator therapy.[62]

The effects of CFTR modulators on short-term (and in the case of ivacaftor, longer-term) outcome measures present significant challenges regarding design of future clinical trials. First, it may not be ethical or feasible to ask volunteers to discontinue an effective medication to substantiate potential effectiveness of another.[63] Second, as current molecular therapy has resulted in robust short-term typical outcome measures, future trials will need other measures of functional improvement and creative designs to demonstrate efficacy.

Conclusion

Over the last century CF has been transformed from a fundamentally unrecognized and misunderstood disease to one that is approaching a cure. Virtually each decade since 1930 has passed with a novel intervention extending the life expectancy of those afflicted with this disorder. By addressing the multiorgan consequences of compromised chloride anion transport with first generation potentiators and correctors, the CF median predicted life expectancy has increased

from school-age to the mid-40s. In the near future, early introduction of next generation CFTR protein modulators may, for the first time, offer the CF community a future in which CF is no longer the most common lethal autosomal recessive disease in Caucasian individuals, but a chronic disease with a normal life expectancy.

Acknowledgements

Assistance with table and figure designs was provided by both authors as well as Evelyn Zillmer and Steven E. Lommatzsch.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares that there is no conflict of interest.

References

1. Peckham D and Littlewood JM. A history of cystic fibrosis. www.cfmedicine.com (2011, accessed 18 June 2018).
2. Quinton PM. Physiological basis of cystic fibrosis: a historical perspective. *Physiol Rev* 1999; 79: S3–S22.
3. Cystic Fibrosis Foundation. *Patient registry 2016 annual data report*. Bethesda, MD: Cystic Fibrosis Foundation, 2017.
4. Andersen DH. Cystic Fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* 1938; 56: 344–399.
5. Kessler WR and Andersen DH. Heat prostration in fibrocystic disease of the pancreas and other conditions. *Pediatrics* 1951; 8: 648.
6. Darling RC, di Sant'Agnese PA, Perera GA, *et al*. Electrolyte abnormalities of the sweat in fibrocystic disease of the pancreas. *Am J Med Sci* 1953; 225: 67–70.
7. Di Sant'agnese PA, Darling RC, Perera GA, *et al*. Abnormal electrolyte composition of the sweat in cystic fibrosis: clinical significance and relationship to the disease. *Pediatrics* 1953; 12: 549–563.
8. Gibson LE and Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959; 23: 545–549.
9. Grosse S. Newborn screening for cystic fibrosis; Evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep* 2015; 53(RR13): 1–36.
10. Kerem B, Rommens JM, Buchanan JA, *et al*. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989; 245: 1073–1080.
11. cftr2.org. Accessed December 2018.
12. Clancy JP and Jain M. Personalized medicine in cystic fibrosis: dawning of a new era. *Am J Respir Crit Care Med* 2012; 186: 593–597.
13. Boeck MP and De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med* 2013; 1: 158–163.
14. Cystic Fibrosis Foundation Patient Registry. *2016 Annual data report*. Bethesda, MD: Cystic Fibrosis Foundation, 2016.
15. Peltz SW, Morsy M, Welch EM, *et al*. Ataluren as an agent for therapeutic nonsense suppression. *Annu Rev Med* 2013; 64: 407–425.
16. Grasemann H. CFTR modulator therapy for cystic fibrosis. *N Engl J Med* 2017; 377: 2085–2088.
17. Cystic Fibrosis Trust. *Antibiotic treatment for cystic fibrosis*. 3rd ed. Report of the UK Cystic Fibrosis Trust Antibiotic Working Group, 2009.
18. Dalemans W, Barbry P, Champigny G, *et al*. Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. *Nature* 1991; 354: 526–528.
19. Van Goor F, Hadida S, Grootenhuis PDJ, *et al*. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci USA* 2009; 106: 18825–18830.
20. Ramsey BW, Davies J, McElvaney NG, *et al*. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011; 365: 1663–1672.
21. Davies JC, Wainwright CE, Canny GJ, *et al*. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013; 187: 1219–1225.
22. De Boeck K, Munck A, Walker S, *et al*. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros* 2014; 13: 674–680.
23. Moss RB, Flume PA, Elborn JS, *et al*. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation:

a double-blind, randomised controlled trial. *Lancet Respir Med* 2015; 3: 524–533.

24. Flume PA, Liou TG, Borowitz DS, *et al.* Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* 2012; 142: 718–724.
25. Taylor-Cousar JL, Munck A, McKone EF, *et al.* Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017; 377: 2013–2023.
26. Rowe SM, Daines C, Ringshausen FC, *et al.* Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med* 2017; 377: 2024–2035.
27. Wainwright CE, Elborn JS, Ramsey BW, *et al.* Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015; 373: 220–231.
28. Drew L, Green O, Villella A, *et al.* CFTR amplifiers: a new class of CFTR modulator that complements the substrate limitations of other CF therapeutic modalities. *C60 All About Cystic Fibrosis* 2016; 193: A5574-A.
29. Farrell PM, White TB, Ren CL, *et al.* Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr* 2017; 181S: S4–S15.e1.
30. Sawicki GS, McKone EF, Pasta DJ, *et al.* Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med* 2015; 192: 836–842.
31. Konstan MW, McKone EF, Moss RB, *et al.* Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017; 5: 107–118.
32. Accurso FJ, Rowe SM, Clancy JP, *et al.* Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010; 363: 1991–2003.
33. KALYDECO™. Kalydeco (ivacaftor) [package insert]. Cambridge, MA: Vertex Pharmaceutical Inc., 2012.
34. Quittner AL, Modi AC, Wainwright C, *et al.* Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest* 2009; 135(6): 1610–1618.
35. Orkambi (lumacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Inc., 2016.
36. Wainwright CE, Elborn JS, Ramsey BW, *et al.* Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015.
37. Waters V, Stanojevic S, Atenafu EG, *et al.* Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012; 40: 61.
38. Bratcher PE, Hunt KC, Pickard K, *et al.* Positive clinical response to ivacaftor treatment in an individual with the CFTR genotype F508del/V456A. *J Cyst Fibros* 2018; 18: e9–e10.
39. Durmowicz AG, Witzmann KA, Rosebraugh CJ, *et al.* Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest* 2013; 143: 14–18.
40. Boyle MP, Bell SC, Konstan MW, *et al.* A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respir Med* 2014; 2: 527–538.
41. Milla CE, Ratjen F, Marigowda G, *et al.* Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2017; 195: 912–920.
42. Ratjen F, Hug C, Marigowda G, *et al.* Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2017; 5: 557–567.
43. Sagel SD, Khan U, Heltshe SL, *et al.* Study design and clinical characteristics of subjects enrolled in the CFFT prospect study. *Pediatr Pulmonol* 2016; 51: S45.
44. Taylor-Cousar JL, Jain M, Barto TL, Haddad T, *et al.* Lumacaftor/ivacaftor (LUM/IVA) in patients (pts) with cystic fibrosis (CF) and advanced lung disease homozygous for F508del-CFTR: a 24-week open-label study. *J Cyst Fibros* 2018; 17: 228–235.
45. Symdeko (tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Inc., 2018.
46. Trimble A, McKinzie C, Terrell M, *et al.* Measured fetal and neonatal exposure to lumacaftor and ivacaftor during pregnancy and while breastfeeding. *J Cyst Fibros* 2018; 17: 779–782.

47. Bessonova L, Volkova N, Higgins M, *et al*. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018; 73: 731–740.

48. Taylor-Cousar JL, Jain M, Barto TL, *et al*. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. *J Cyst Fibros* 2018; 17: 228–235.

49. Symdeko (tezacaftor/ivacaftor and ivacaftor) Initiation Guide. Boston, MA: Vertex Pharmaceuticals Incorporated, 2018.

50. Graeber SY, Dopfer C, Naehrlich L, *et al*. Effects of lumacaftor-ivacaftor therapy on cystic fibrosis transmembrane conductance regulator function in Phe508del homozygous patients with cystic fibrosis. *Am J Respir Crit Care Med* 2018; 197: 1433–1442.

51. Angelis A, Tordrup D and Kanavos P. Socio-economic burden of rare diseases: a systematic review of cost of illness evidence. *Health Policy* 2015; 119: 964–979.

52. Ferkol T and Quinton P. Precision medicine: at what price? *Am J Respir Crit Care Med* 2015; 192: 658–659.

53. Kesselheim AS, Avorn J and Sarpatwari A. The high cost of prescription drugs in the United States: Origins and prospects for reform. *JAMA* 2016; 316: 858–871.

54. Hughes DA, Tunnage B and Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? *QJM* 2005; 98: 829–836.

55. Balk E, Trikalinos T, Mickle K, *et al*. Modulator treatments for cystic fibrosis: effectiveness and value. Final Evidence Report and Meeting Summary, May 2018. Institute for Clinical and Economic Review, Public Meeting.

56. Schlander M, Garattini S, Holm S, *et al*. Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders. *J Comp Eff Res* 2014; 3: 399–422.

57. Elborn S, Elston C and Haworth CS. Letter from CFPMG to Simon Stevens NHS England. In: Stevens S, Executive C and England NHS (eds) Cystic Fibrosis Trust, 2018.

58. The availability of Orkambi® (containing lumacaftor and ivacaftor) through the Pharmaceutical Benefits Scheme for patients with cystic fibrosis. Australian Government Department of Health, 2018.

59. Cohen-Cymberknoh M, Shoseyov D, Breuer O, *et al*. Treatment of cystic fibrosis in low-income countries. *Lancet Respir Med* 2016; 4: 91–92.

60. Proteostasis announces positive data from ongoing phase 1 study of PTI-801 in cystic fibrosis patients on background Orkambi® therapy. Proteostasis Therapeutics, Inc., 2018. http://ir.proteostasis.com/news-releases/newsrelease-details/proteostasis-announces-positive-dataongoing-phase-1-study-pti

61. Cystic Fibrosis Foundation. *Drug development* pipeline. Bethesda, MD: Cystic Fibrosis Foundation, 2018.

62. Lancastre J. CRISPR/Cas9 approach for cystic fibrosis treatment. *Cystic Fibrosis News Today* January 16, 2017. https://cysticfibrosisnewstoday.com/crisprcas9-approach-forcystic-fibrosis/

63. VanDevanter DR, Mayer-Hamblett N and Boyle M. Feasibility of placebo-controlled trial designs for new CFTR modulator evaluation. *J Cyst Fibros* 2017; 16: 496–498.