Journal of Cystic Fibrosis 19 (2020) e1–e2

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Correspondence

Letter to the editor: Challenges and opportunities in the development of future CFTR modulator options for people with CF

Dear editors,

For people with Cystic Fibrosis (pwCF) with genotypes responsive to Cystic Fibrosis Transmembrane Regulator Conductance (CFTR) modulators, use of such therapy is now standard of care. However, there are a number of issues that underscore the need for development of additional CFTR modulator treatment options. These issues include (1) variation in the magnitude of clinical benefit experienced among eligible pwCF (heterogeneity of response), (2) regional variation in access to treatment, and (3) populations of pwCF with genotypes that do not respond to currently approved CFTR modulators. Importantly, some of these same factors have altered the demographics of the study population eligible for enrollment in clinical trials of novel CFTR modulator combinations. This effect on the available population for clinical trials must be considered in the development of novel CFTR modulators.

CFTR modulator combinations of a corrector and potentiator are approved by regulatory authorities such as the Federal Drug Administration in North America and the European Medicines Agency in the EU. However, because reimbursement and approval do not go hand-in-hand outside of the US, pwCF have widely variable levels of access to CFTR modulators. In the US, where FDA approval and insurance reimbursement are closely linked, the overwhelming majority of eligible pwCF have access to CFTR modulator therapy. However, in Europe, there are many countries in which CFTR modulators are approved, but not reimbursed [1]. For subjects with CF participating in recent CFTR modulator trials, we hypothesized that differential access to therapy would affect the demographics of subjects enrolled in the trials.

Early studies evaluating the novel CFTR corrector PTI-801 enrolled adults with CF homozygous for the F508del CFTR mutation who were on stable background treatment with lumacaftor/ivacaftor (ClinicalTrials.gov Identifier: NCT03140527). Potential subjects were required to have been on treatment with lumacaftor/ivacaftor per both label indication and label dosing for a minimum of 3 months. Enrolled subjects were on treatment with lumacaftor/ivacaftor for an average of 2.4 years by the start of the treatment period of the study. Despite geographic differences, the US and non-US subjects who remained on background CFTR modulator treatment had similar baseline characteristics and frequencies of pulmonary exacerbations. (Table 1, PTI-801 add-on columns). However, in the CFTR modulator combination studies discussed herein, subjects in the US had a higher percentage of pulmonary exacerbations (80% versus 61%) and pulmonary exacerbations requiring treatment with intravenous antibiotics (72% versus 39%) or hospitalization (64% versus 18%) than subjects outside the US. ClinicalTrials.gov Identifiers: NCT03140527, NCT03251092, NCT03500263). Based on the most recent CF registry reports from the Cystic Fibrosis Foundation in the US and the UK Cystic Fibrosis Registry Annual Data Report, the percentages of adult patients experiencing a pulmonary exacerbation is similar within these regions (US: approximately 49% of pwCF 20–30 years of age, UK: 54% of pwCF $\geq$18 years of age) [2,3].

A retrospective review of study subjects' baseline characteristics from the initial trials of CFTR modulator combinations compared with data from the more recent studies of novel CFTR modulator combinations discussed herein reveal that the enrolled patients have similar baseline lung function and sweat chloride values. The evolving CFTR modulator treatment landscape was affecting the selection of study subjects by the time of the Phase 3 tezacaftor/ivacaftor studies. Recruitment for these studies was predominantly in non-US regions where access to approved CFTR modulator treatments was more limited [4]. However, as summarized in Table 1, the subjects in current novel CFTR modulator combination trials are older, and a substantial proportion of them received prior treatment with a CFTR modulator and subsequently discontinued treatment (Table 1, Proteostasis modulator combination columns) [4–6].

Treatment naïve patients are increasingly rare in regions where CFTR modulator treatments are approved and accessible. The first CFTR modulator trials were able to enroll treatment naïve subjects. Immediately following these initial trials, it was relatively simple to exclude subjects who had been previously treated with a CFTR modulator [4]. However, even these earlier studies recruited the majority of subjects from regions outside of the US where access to approved modulators was more limited. This approach, however, is no longer feasible in the current clinical landscape in which CFTR modulator treatment has become the standard of care for pwCF with approved genotypes. This change is responsible for the declining availability of treatment naïve patients and the growing ethical concerns shared by physicians and pwCF regarding longer duration placebo-controlled trials in populations that have access to approved CFTR modulator treatments [7].

Compared to subjects enrolled in previous CFTR modulator trials, subjects enrolled in recent trials are older and more likely to have discontinued prior treatment with a CFTR modulator. Additionally, based on pulmonary exacerbation history, subjects enrolling in current studies appear to have a higher burden of disease. Some of these subjects have an increased incidence of pulmonary exacerbations in spite of ongoing treatment with approved CFTR modulators. As novel CFTR modulator treatments continue to be developed for pwCF, these factors must be considered in clinical trial design, study execution, and study result interpretation.

https://doi.org/10.1016/j.jcf.2019.10.010

Table 1
Demographics, baseline characteristics, and history of pulmonary exacerbations in subjects with cystic fibrosis who participated in a clinical trial evaluating PTI-801 and combinations of PTI-801, PTI-808 and PTI-428

	Lumacaftor-Ivacaftor Traffic-Transport Studies [5] N=1108	Tezacaftor-Ivacaftor Evolve Study [6] N=504	Proteostasis Modulator Combination US[a] N=25	Proteostasis Modulator Combination Non-US[b] N=28	PTI-801 Add-on US[c] N=47	PTI-801 Add-on Non-US[c] N=10
Demographics and Baseline Characteristics						
Age, mean (range or SD), years	25.0 (12-64)	26.3 (±10)	30.9 (±10.5)	31.9 (±11.1)	30.4 (±10.5)	28.0 (±7.1)
Body mass index, mean (range or SD), kg/m^2	21.2 (14.1-35.1)	21 (±3)	22.0 (±3.7)	21.6 (±2.2)	22.6 (±3.1)	21.3 (±2.2)
Prior modulator use, percentage of subjects	N/A	0%	48%	14%	100%	100%
FEV_1 (% predicted)	60.6 (31.1-99.8)	60 (±15)	61.9 (±13.9)	59.2 (±14.3)	60.4 (±12.2)	64.7 (±13.6)
Sweat chloride concentration (mmol/L)	N/A	101 (±11)	102.5 (±10.1)	97.1 (±10.3)	76.8 (±17.0)	86.8 (±14.3)
P. aeruginosa positive, percentage of subjects	N/A	73%	72%	46%	68%	70%
Geographic region, percentage of subjects	N/A	20% US, 80% Non-US	47%	53%	82%	18%
Pulmonary Exacerbation History (during 12 months prior to study entry)						
Percentage of subjects with at least one exacerbation*	N/A	N/A	80%	61%	79%	80%
Percentage of subjects with at least one exacerbation requiring intravenous antibiotics	N/A	N/A	72%	39%	53%	50%
Percentage of subjects with at least one exacerbation requiring hospitalization	N/A	N/A	64%	18%	38%	10%

* Number of exacerbations based on clinical events as captured in subjects' medical history
[a] ClinicalTrials.gov Identifiers: NCT03140527, NCT03251092
[b] ClinicalTrials.gov Identifiers: NCT03140527, NCT03251092, NCT03500263
[c] ClinicalTrials.gov Identifier: NCT03140527Abbreviations: F508del, deletion of phenylalanine at position 508 in the gene encoding for cystic fibrosis transmembrane conductance regulator; FEV1, forced expiratory volume in 1 second; N/A, not available

References

[1] Lommatzsch ST, Taylor-Cousar JL. 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;13 1753466619844424.
[2] UK Cystic Fibrosis Registry Annual Data Report 2018. Published by the Cystic Fibrosis Trust; August 2019 www.cysticfibrosis.org.uk/registry.
[3] Cystic Fibrosis Foundation Patient Registry. 2016 Annual Data Report. Bethesda, Maryland. 2017. (Accessed 04 January 2018, at https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf.)
[4] Center for Drug Evaluation and Research. CDER Clinical Review of SYMDEKO (tezacaftor/ivacaftor). Stacy Chin, MD. NDA 210491. Edition 1. Maryland: Food and Drug Administration; Bethesda; 2015. Version date: November 5.
[5] Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015;373:220–31.
[6] Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377:2013–23.
[7] VanDevanter DR, Mayer-Hamblett N, Boyle M. Feasibility of placebo-controlled trial designs for new CFTR modulator evaluation. J Cyst Fibros 2017;16:496–8.

Damian G. Downey
Centre for Experimental Medicine, Queen's University Belfast, N. Ireland, UK

Jennifer Taylor-Cousar*
Departments of Medicine and Pediatrics, National Jewish Health, Denver, CO 80206, USA

*Corresponding author: Internal Medicine and Pediatrics, 1400 Jackson Street, Denver, CO 80206, USA.
E-mail address: Taylor-CousarJ@NJHealth.org (J. Taylor-Cousar)

Received 19 September 2019
Revised 1 October 2019
Accepted 2 October 2019