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Original Article

Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators – an international survey ☆

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ABSTRACT

Background: As their long-term prognosis improves, women with CF are increasingly choosing to have children, but the safety of CFTR modulators in pregnancy and breastfeeding is currently unknown.

Methods: A survey was sent to lead clinicians of adult CF centres in Europe, the United Kingdom (UK), United States of America (USA), Australia and Israel requesting anonymised data on pregnancy outcomes in women using CFTR modulators before and during pregnancy and lactation.

Results: We identified 64 pregnancies in 61 women taking IVA ($n = 31$), LUM/IVA ($n = 26$) or TEZ/IVA ($n = 7$), resulting in 60 live births. In 44 pregnancies, CFTR modulators were either continued throughout pregnancy or temporarily stopped and then restarted. Two maternal complications were deemed related to CFTR modulator therapy; cessation of modulator therapy resulted in clinical decline in 9 women prompting resumption of therapy during pregnancy. No modulator-related complications were reported in infants exposed *in utero* and/or during breastfeeding.

Conclusions: CFTR modulators were reported to be generally well tolerated in pregnancy and breastfeeding, with only 2 maternal complications that were deemed related to CFTR modulator therapy. Women stopping CFTR modulators in pregnancy may experience a decline in clinical status and in the cases identified in this survey, restarting therapy led to a clinical improvement. Current experience remains limited and longer-term prospective follow-up is required to exclude delayed adverse effects.

1. Introduction

Survival of people with cystic fibrosis (CF) has dramatically improved over recent decades, such that the majority of people with CF are now adults [1]. Prognosis is likely to further improve with more widespread availability of small-molecule therapeutics that improve the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, termed CFTR modulators [2]. As outcomes improve, more women with CF are choosing to become pregnant [3,4] but currently it is unclear whether CFTR modulators are safe to use during pregnancy and lactation [5].

At the time of publication, the CFTR modulators that are currently licensed include (ivacaftor (IVA), dual combinations of lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), and the triple combination elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). These drugs have been tested in animal studies as individual components as part of their development and licensing [6–9]. Although placental transfer of CFTR modulators has been observed in these animal models, based on the lack

Abbreviations: AML, acute myeloid leukemia; BMI, body mass index; CF, cystic fibrosis; CFRD, CF-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; D&C, dilatation and curettage; E. coli, *Escherichia coli*; ELX, elexacaftor; ERS, European respiratory society; FDA, Food and drug administration; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastro-esophageal reflux disease; IQR, interquartile range; IVA, ivacaftor; LFTs, liver function tests; LUM, lumacaftor; *P. aeruginosa*, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation; pp, percent predicted; pwCF, people with CF; TEZ, tezacaftor; TGA, Therapeutic Goods Administration; TSANZ, Thoracic Society of Australia and New Zealand; UK, United Kingdom; USA, United States of America; VSD, ventricular septal defect.

☆ Part of this data was presented at the 2019 European CF Conference in Liverpool, UK (Taylor-Cousar J, Jain R, Brown AW, Nash EF. J Cyst Fibros 2019; 18 (Suppl 1), s22; Nash EF, Brokaar E, Casey R et al. J Cyst Fibros 2019; 18 (Suppl 1), s22.) and at the 2019 North American CF Conference in Nashville, TN, USA (Taylor-Cousar J and Nash EF. Ped Pulm 54 (Suppl 2: 364).

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of teratogenicity of these drugs at standard human dosing, IVA, and LUM/IVA were licensed with a Food and Drug Administration (FDA) & Therapeutic Goods Administration (TGA) pregnancy category B3, and TEZ/IVA and ELX/TEZ/IVA with the newer FDA designation which states that caution is advised during pregnancy because of the lack of human data available to assess risk (TGA category B3). The recent European Respiratory Society/Thoracic Society of Australia and New Zealand (TSANZ) statement on the management of women with airways diseases during pregnancy noted that "the clinician should compare the benefits and risks of each medication" [10].

While benefit to the woman with CF is known from phase III studies [11–14], the risk of discontinuation of modulators during pregnancy is less certain. Trimble and colleagues described three cases of dramatic decline following IVA withdrawal. [15]. Subsequently, Carpino and colleagues reported lung function decline and increased pulmonary exacerbations following discontinuation of study drug during short-term participation in a phase II study of triple combination therapy [16]. More recently, Vekaria and colleagues reported a case of rapid decline in lung function requiring hospitalization in a 29-year old pregnant woman following cessation of IVA during the first trimester of pregnancy [17]. These cases highlight the potential for women who discontinue CFTR modulators before or during pregnancy to experience sudden decline in pulmonary health.

The small number of individual case reports currently published for women who chose to continue or discontinue CFTR modulators during pregnancy [17–21] makes it difficult for health care providers and for women with CF to make evidence-based decisions when making the important choice to continue or interrupt therapy with CFTR modulators for pregnancy. In order to provide further evidence on the safety of CFTR modulators, we conducted a survey of CF clinicians in the USA, UK, Europe, Israel and Australia in order to identify and describe pregnancy outcomes for women with CF who became pregnant while taking CFTR modulators.

2. Methods and materials

We devised and sent a questionnaire (available in Supplementary materials) to lead clinicians in US, UK, Israeli, European and Australian adult CF centres in 2018–2019 requesting anonymised data on all pregnancies in women taking CFTR modulators at the time of conception. The questionnaire asked for relevant information on the demographics and CF-related comorbidities of the women, whether CFTR modulators were continued during part or all of pregnancy, complications of modulator therapy and the outcomes of the pregnancy. In the case of successful live births, we asked for details on any birth defects and whether modulators were continued (or restarted) following delivery and if so, whether they were continued during breast feeding. If adverse events were reported in pregnant women or infants, clinicians were asked if the events were CFTR-modulator-related and asked to provide a free-text explanation of their opinion of the relationship.

2.1. Statistical analysis

Descriptive statistics are expressed as median and interquartile range (IQR) for non-parametric data.

2.2. Ethics statement

The West Midlands (Solihull) Research Ethics Committee and National Jewish Health Institutional Review Board confirmed that the study did not require ethical approval and Western Sydney Local Health District approved this study as a Quality Assurance Project.

3. Results

We received data from 31 CF centres (17 USA, 5 Australia, 4 UK, 4 mainland Europe, 1 Israel) and from 1 woman with CF (list of contributing centres in supplement) on 64 pregnancies in 61 women resulting in 60* live births). CFTR modulators being taken included IVA (31 pregnancies), LUM/IVA (26 pregnancies) and TEZ/IVA (7 pregnancies). Data regarding pregnancy outcomes for each of these treatments are presented below and in Table 1.

3.1. Ivacaftor (IVA)

Thirty-one pregnancies were reported in 28 women (1 woman had 2 singleton births and 1 woman had 3 singleton births) and in 16 pregnancies IVA was continued throughout all trimesters of pregnancy (Fig. 1). In 15, IVA was stopped during the 1st, 2nd, and/or 3rd trimesters to avoid fetal exposure and in 6 pregnancies IVA was restarted later in pregnancy due to worsening CF-related comorbidities (pulmonary deterioration $n = 4$; recurrent pancreatitis $n = 2$). Two pregnancies resulted in miscarriage in the first trimester and 1 pregnancy was terminated due to maternal health concerns. There were no maternal deaths and 28 pregnancies resulted in live birth at median gestational age 38 weeks. Complications were reported in 16 pregnancies but none of these complications were reported to be IVA-related (gestational diabetes, $n = 4$; pulmonary deterioration, $n = 4$; pancreatitis, $n = 2$; sciatica, $n = 2$; hyperemesis, $n = 1$; GERD, $n = 1$; subchorionic placental hemorrhage, $n = 1$; placenta previa, $n = 1$; spinal fluid leak following epidural, $n = 1$). No cataracts were observed in infants (1 formal assessment) and there were 3 neonatal complications which were all deemed unrelated to IVA (respiratory distress syndrome/pneumothorax, $n = 1$; respiratory distress syndrome/pneumothorax/E. coli meningitis/hyperbilirubinemia, $n = 1$; pneumonia, $n = 1$). Thirteen infants were breastfed on IVA with no reported complications.

3.2. Lumacaftor/Ivacaftor (LUM/IVA)

In 16/26 pregnancies, LUM/IVA was either continued throughout pregnancy or temporarily stopped then restarted. LUM/IVA was taken during the 1st trimester in 21/26 pregnancies (Fig. 1). In 10 pregnancies, LUM/IVA was stopped during the 1st, 2nd, and/or 3rd trimesters to avoid fetal exposure, but in 3 of these 10 pregnancies modulator therapy was restarted later in pregnancy due to pulmonary deterioration. In 2* pregnancies, LUM/IVA was stopped in the 1st trimester because of chest tightness and was not restarted. All 26 pregnancies resulted in live births, with 4 infants being delivered earlier than 37 weeks gestation (one pregnancy was induced because of oligohydramnios following maternal recovery from pericarditis). Complications occurred in 17/26 pregnancies but none of these complications were reported to be LUM/IVA-related (CFRD/gestational diabetes, $n = 8$; pulmonary exacerbation (PEx), $n = 6$; pericarditis, $n = 1$; sinusitis, $n = 1$; hemoptysis, $n = 2$; influenza A, $n = 2$; insufficient weight gain, $n = 1$; urinary tract infection, $n = 1$; hypoglycemia, $n = 1$). There were 2 additional maternal complications that were considered to be related to LUM/IVA [PEx during pregnancy, $n = 1$; post-partum diagnosis of acute myelocytic leukemia (AML), $n = 1$). Postpartum complications occurred in 4 women, but none were deemed to be LUM/IVA-related (decrease ppFEV$_1$, $n = 2$; PEx, $n = 2$; retained placental parts requiring D&C, $n = 1$). There were 8 reported complications in 7 infants, but all were deemed unrelated to LUM/IVA (mild increased LFTs, $n = 1$; hypospadias, $n = 1$; prematurity, $n = 1$; hypoglycemia, $n = 1$; meconium aspiration, $n = 1$; chromosome 17 abnormality of unknown significance). No cataracts were observed

Table 1
Characteristics of women with CF included in the case series.

Pregnancies with CFTR modulator exposure (N)	Age (y)	ppFEV$_{1\ (\%)}$	BMI (kg/m2)	Presence of CFRD prior to pregnancy	Pre-conception CFTR modulator exposure (months)
IVA $N = 31$[#]	25 (22–27)	90 (65.8–106)	22 (22–24)	7/31 (23%)	15 (12.8–26)
LUM/IVA $N = 26$	30 (25–34)	59 (48–86)	22 (20.5–24.7)	12/26 (46%)	17[@] (12–25)
TEZ/IVA $N = 7$	26 (21–31)	65 (50–85)	20.7 (19.3–28.7)	1/7 (14%)	3 (0–6)

Median (lower and upper quartile range).
[#] 31 pregnancies in 28 women.
[@] $n = 22$, data missing on 3 women.

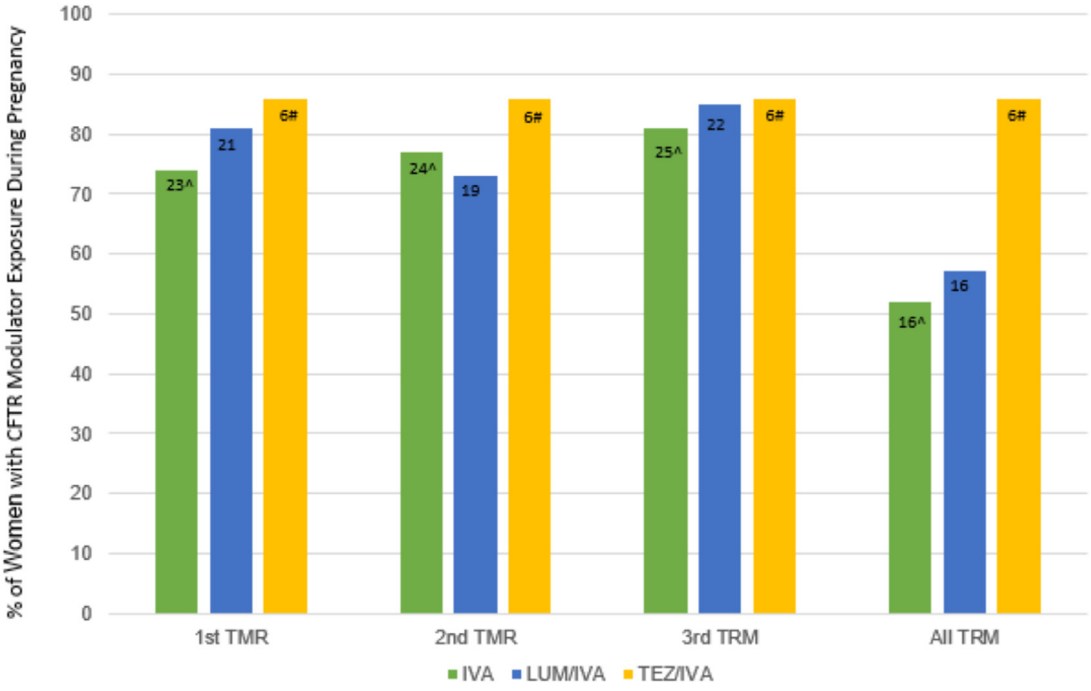

Fig. 1. CFTR modulator exposure by trimester.
^2 pregnancies resulted in 1st trimester miscarriage and 1 pregnancy was terminated for health reasons; # one pregnancy resulted in 1st trimester miscarriage and one pregnancy resulted in twins.

in infants (4 formal assessments) and 9 infants were breastfed on LUM/IVA with no reported complications.

3.3. Tezacaftor/Ivacaftor (TEZ/IVA)

In 5/7 pregnancies, TEZ/IVA was taken during all trimesters and in 1 pregnancy TEZ/IVA was withheld during the 1st trimester to avoid fetal exposure (Fig. 1). Complications during pregnancy occurred in 5 women and all were deemed unrelated to TEZ/IVA (abdominal pain related to previous caesarian-section, $n = 1$; sinusitis, $n = 1$; caesarian-section, $n = 2$; fetal decelerations, $n = 1$; premature birth at 34 weeks). Six pregnancies resulted in live births, with one miscarriage at 9 weeks, which was deemed unrelated to TEZ/IVA. There was one pair of twins. There were two reported complications in infants; both were deemed unrelated to TEZ/IVA [fetal decelerations leading to Caesarian-section, $n = 1$; ventricular septal defect (VSD), $n = 1$]. No cataracts were observed in infants (1 formal assessment) and 5 infants were breastfed on TEZ/IVA with no reported complications.

4. Discussion

We present the first and largest case series of the outcomes of pregnancy in women with CF taking CFTR modulators throughout part or the entirety of their pregnancy. We are aware of 5 previously published case reports of pregnancies in women with CF taking CFTR modulators [17–21]. In the first case, a 25-year old woman with G551D/3272–26A>*G* CF and normal lung function conceived while taking IVA and therapy was continued throughout pregnancy [18]. There was no evidence of adverse effects in the mother and a healthy infant was delivered at 39 weeks gestation. IVA was not continued during breast feeding in this case due to personal reasons. In the second case, a 20-year old woman with G551D/c.1585–2A>*G* CF became pregnant having taken IVA for 5 months prior to conception, however the patient stopped IVA after her positive pregnancy test and did not restart it [19]. There was no evidence of adverse effects on mother or infant and the woman chose to restart IVA 5 weeks post-delivery. In the third case, a 23-year old woman with F508del homozygous CF became pregnant while taking LUM/IVA, but modulator therapy was discontinued at 13 weeks gestation at the advice of her CF provider [20]. However, due to worsening respiratory function, the woman self-initiated LUM/IVA 2 weeks later and remained on treatment during the remaining pregnancy and while breastfeeding. There were no adverse effects in the mother, but in the infant there were noted to be transient increases in serum aspartate transaminase and bilirubin. Despite these transaminase elevations, the infant was breastfed for 267 days with no evidence of further transaminase abnormalities. In this case report, measurements of drug levels of LUM/IVA in maternal plasma, cord blood, breast milk, and infant

blood were obtained. This data showed that both LUM and IVA traversed the placenta and that LUM concentrations in the cord plasma sample were higher than in maternal plasma. In the fourth case, a 29-year old with F508del homozygous CF became pregnant having taken LUM/IVA for 10 months and the combination treatment was discontinued at 10 weeks gestation due to potential concerns regarding safety of CFTR modulators in pregnancy [21]. However, LUM/IVA was restarted at 15 weeks gestation due to deterioration of the mother's clinical status and was continued during the remaining pregnancy, with no evidence of adverse effects. A healthy infant was delivered at 35 weeks gestation, with no evidence of fetal malformation or cataracts. The mother chose not to breastfeed in this case. In the fifth case (to which was already alluded), a 29-year old with F508del/G551D CF became pregnant having taken IVA for 12 months and then stopped IVA at 5 weeks gestation due to limited safety data [17]. This discontinuation coincided with a rapid decline in lung function requiring hospitalization. Despite inconclusive safety data of IVA in pregnancy, the woman made an informed decision to restart IVA at 10 weeks gestation and her health subsequently improved. A healthy infant was delivered at 36.4 weeks and the mother chose to continue with IVA throughout a subsequent pregnancy with no deterioration in her health. Both babies were born without evidence of congenital malformations or cataracts and maternal health was good postpartum. The second child is being investigated for asthma, but otherwise both children are healthy and continue to meet developmental milestones. We are not aware of any previously reported cases of pregnancy in women taking TEZ/IVA nor in ELX/TEZ/IVA. While pregnancies have occurred during the phase III trials of CFTR modulators [22], women who became pregnant were withdrawn from the studies per the protocol, and no information has been published.

IVA, LUM/IVA and TEZ/IVA, and ELX/TEZ/IVA have been extensively studied in preclinical animal studies [6-9]. This testing of the individual agents failed to reveal evidence of teratogenicity in animals when the drugs were used at high human doses. When used in animal studies at doses above the maximum recommended human dose (MRHD), IVA [6] and TEZ [7] treatment resulted in decreased fetal body weights in rats, and TEZ treatment resulted in early developmental delays in pinna detachment, eye opening, and righting reflex [7]. IVA also was related to the development of lens opacities in 7–35 day old rats when dosed at 0.1–0.8 times the MRHD. LUM treatment resulted in a slight increase in incidence of minor skeletal abnormalities in rabbits at doses above the MRHD [8].

Orally administered IVA and LUM are known to be expressed in human breast milk [20] and TEZ is present in the breast milk of lactating rats [7]. Levels of IVA and TEZ are higher in the breast milk of lactating rats than plasma levels (IVA 1.5 times; TEZ 3 times higher) [6,7] whereas breast milk levels of LUM were 40% of plasma levels [8]. When considering whether to take CFTR modulators during breastfeeding, the proven benefits of breastfeeding need to be considered along with the mother's clinical need for treatment and any potential adverse effects for the breastfed child.

There were 2 reported maternal complications in the current case series that were considered to be related to LUM/IVA therapy by the responding clinician. The first was a pulmonary exacerbation during pregnancy, but it is not clear to the authors whether this was related to LUM/IVA or was in fact due to the mother's underlying CF lung disease. The initiation of LUM/IVA is reported to be associated with chest discomfort, dyspnea and 'respiration abnormal' which could potentially explain why the respondent felt that the mother's symptoms were LUM/IVA-related [8]. The second adverse event that was considered to be LUM/IVA-related was a post-partum diagnosis of AML. The authors are not aware of any other previously-reported association between LUM/IVA and hematological malignancies and the authors feel that the development of AML could have been an unfortunate coincidence rather than directly related to LUM/IVA. Equally, this case should be considered when assessing the safety of CFTR modulators over the coming years.

These considerations are particularly relevant given that in a recent survey 78% of young women expressed a desire to have children in future [23]. There are also several mechanisms by which CFTR modulators could increase the fertility of women with CF. Women with CF are usually fertile despite changes in the cervical mucous becoming thickened and relatively acidic as result of CFTR dysfunction [24]. It has been suggested that CFTR modulators may make a woman with CF more fecund directly by decreasing cervical mucus thickness or improving cervical mucus pH, by altering hormonal response, improving nutritional status and by regulating female menses [24,25]. In addition, LUM may decrease the exposure of hormonal contraceptives by induction of the 3A isoenzyme of cytochrome P450 (CYP3A) and UDP-glucuronosyltransferase (UGT), which may reduce their efficacy [8]. Women taking LUM/IVA are therefore advised not to rely on hormonal contraceptives to prevent pregnancy. This interaction is not seen with IVA, TEZ or ELX and therefore TEZ/IVA and ELX/TEZ/IVA are not expected to interact with hormonal contraceptives [6–9].

We acknowledge several limitations of this study. Firstly, although the only case series to date, we have only received retrospective data regarding a relatively small number of pregnancies in women taking CFTR modulators. The questionnaire was widely distributed but despite this fact, there are likely additional pregnancies that have occurred in women taking CFTR modulators that have not been included in this case series and their absence could feasibly bias the findings. For instance, clinicians may have been more likely to submit data on pregnancies for which the infant was delivered at the same hospital as the CF center, with potential better CF care for the mother around the time of delivery. Alternatively, if the infant was delivered at a hospital separate from the CF center with better access to specialists in maternal-fetal medicine, this factor could potentially have resulted in improved maternal and infant outcomes. In these scenarios, data on maternal and fetal complications may also have been missed because we only sent the questionnaire to CF specialists. Finally, in relation to early miscarriages, it is possible that the women with CF or their clinicians did not report these cases to this current study.

It is also important to note that the data from infants born to women included in this study represents a limited and variable amount of post-partum time. It is possible that adverse health outcomes resulting from fetal CFTR modulator exposure could become apparent later in infancy or in early childhood.

In conclusion, the evidence from this case series suggests that the previously available CFTR modulators (IVA, LUM/IVA and TEZ/IVA) are generally well tolerated in pregnancy. There were 3 reported first-trimester miscarriages in the 64 included pregnancies, a rate which compares favourably with the expected first-trimester miscarriage rate in women of this age range of approximately 10%. There were two reported maternal complications that were deemed by the clinician to be related to LUM/IVA therapy, although as explained above, it is debatable whether these complications were indeed modulator-related. The majority of complications observed during pregnancy occurred in the 9 women that chose to stop IVA or LUM/IVA during pregnancy and subsequently experienced a decline in their CF-related health. Those women that decided to restart therapy later in the pregnancy experienced an improvement in clinical status and no obvious complications. Given the relative clinical impact of the different CFTR modulators in eligible patients, choosing to stop IVA or ELX/TEZ/IVA treatment could potentially be associated with a greater clinical decline than stopping either LUM/IVA or TEZ/IVA, although 3 of the women

who experienced decline in our study did so after discontinuation of LUM/IVA. Importantly, a proportion of patients experience dramatic clinical benefits from LUM/IVA or TEZ/IVA and discontinuing therapy, particularly in those with lower health status, could cause significant clinical decline. It is well known that women with lower lung function experience worse pregnancy outcomes [10].

Particularly in light of the recent FDA approval of ELX/TEZ/IVA, for which up to 90% of women with CF will ultimately be eligible [26], we strongly recommend prospective data collection of the outcomes of future pregnancies on CFTR modulators. Based on the relatively recent U.S. approval of TEZ/IVA in February 2018, we were only able to include data on 7 pregnancies on TEZ/IVA; because this combination is included in ELX/TEZ/IVA, it is particularly important to collect data on future pregnancies on these drugs. We suggest that these studies should include longer-term follow up to assess for delayed adverse effects in the woman but also in the infants exposed to CFTR modulators in utero and/or during lactation. When being counselled by healthcare providers, women with CF and their families need to be advised to consider the unknown effects of these medications on the fetus/breast-feeding infant against the potential clinical deterioration if CFTR modulators are stopped either before or during pregnancy and lactation. Some recent recommendations have suggested that CFTR modulators should be avoided during pregnancy and breast-feeding due to limited human safety data [27], whilst others recommend an individualised approach [10]. We hope that the data presented in this case series provides data to guide and support women with CF, their families and caregivers regarding the safety of continuing CFTR modulator treatment during pregnancy and lactation.

Authorship

All authors were involved in the writing or editing of the manuscript and approved the article for submission.

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Declaration of competing interest

Edward Nash

- Personal financial relationships with commercial interests relevant to medicine within the past 3 years:
  - As a consultant in an institution that is part of the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN), I have been site PI on studies for Vertex.
  - I have been on an advisory board for Vertex.
  - I have received grant funding from Mologic Ltd.
- Personal financial support from a non-commercial source relevant to medicine within the past 3 years:
  - I have received grant funding from NIHR.
- Personal relationships with tobacco industry entities within the last 3 years:
  - No relationships to disclose.
  - Professional Memberships
  - ECFS

Peter Middleton

- Personal financial relationships with commercial interests relevant to medicine within the past 3 years:
  - As a center Director of the CF Clinic, I have been site PI on studies for Vertex, Algipharma, Proteostasis and Zambon. Author on the recent Phase III trial of ELEX/TEZ/IVA.
  - I have provided Consulting and Advisory board input for Vertex.
- Personal financial support from a non-commercial source relevant to medicine within the past 3 years:
  - I have received grant funding Rebecca Cooper Foundation, Westmead Medical Research Foundation.
  - Personal relationships with tobacco industry entities within the last 3 years:
  - No relationships to disclose.
  - Professional Memberships
  - Member, Steering Committee, Australian CF Data Registry
  - Member, ECFS, ERS, TSANZ
  - Co-Chair, CF center Directors Group and CF Special Interest Group, TSANZ

Jennifer Taylor–Cousar

- Personal financial relationships with commercial interests relevant to medicine within the past 3 years:
  - As faculty in an institution that is part of the CF TDN, I have been site PI on studies for Vertex, Bayer, Celtaxys, Nivalis and Proteostasis.
  - I have received a career award from Gilead Pharmaceuticals.
  - I have been on advisory boards for Genentech, Gilead, Novartis, Proteostasis, Protalix, and Vertex.
  - I have done consulting/provided clinical trial design advice for Vertex, Celtaxys, Proteostasis and Santhera.
- Personal financial support from a non-commercial source relevant to medicine within the past 3 years:
  - I have received grant funding from NIH and CFF.
- Personal relationships with tobacco industry entities within the last 3 years:
  - No relationships to disclose.
  - Professional Memberships
  - CFF Clinical Research Executive Committee
  - ATS Clinical Problems Programming and Scientific Advisory Committees

CRediT authorship contribution statement

Edward F Nash: Conceptualization, Methodology, Writing - original draft, Validation. **Peter G Middleton:** Writing - review & editing, Validation. **Jennifer L Taylor-Cousar:** Methodology, Writing - review & editing, Data curation, Validation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2020.02.018.

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