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Early View

Original article

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Lumacaftor-ivacaftor-associated health stabilisation in adults with severe cystic fibrosis

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Clinical and body composition changes on lumacaftor-ivacaftor treatment for cystic fibrosis

Abstract (249 words)

Introduction: Lumacaftor-ivacaftor (LUM-IVA) has been shown to improve clinical outcomes in cystic fibrosis (CF) patients homozygous for Phe508del with ppFEV1>40%. We assessed the clinical utility of LUM-IVA in all eligible adult CF patients with ppFEV1<40% treated for at least one year under a single centre managed access program.

Methods: Following clinical optimisation eligible patients (n=40) with ppFEV1<40% were commenced on LUM-IVA and monitored for tolerance and clinical outcomes including health service utilisation, pulmonary function, weight and body composition. Twenty-four patients reached one year of treatment by the time of evaluation. Six discontinued due to adverse events (five for increased airways reactivity) and 3 underwent lung transplantation.

Results: In comparison to the year prior to LUM-IVA commencement, significant reductions (median/year) were observed in the treatment year in the number of pulmonary exacerbations requiring hospitalisation (3 to 1.5, p=0.002); hospitalisation days (27 to 17, p=0.0002) and intravenous antibiotic days (45 to 27, p=0.0007). Mean change in ppFEV$_1$ was -2.10(SE 1.18)% per year in the year prior, with the decline reversed in the year following (+1.45(SE 1.13)% per year, p=0.035) although there was significant heterogeneity in individual responses. Mean weight gain at one year was 2.5±4.1kg; p=0.0007), comprising mainly fat mass (mean 2.2kg). The proportion of patients with severe underweight (BMI<18.5kg/m^2) decreased from 33% at baseline to 13% at one year (p=0.003).

Conclusion: This real-world evaluation study demonstrated benefits over several clinical domains (infective exacerbations requiring hospitalisation, intravenous antibiotics, pulmonary function decline and nutritional parameters) in CF patients with severe lung disease.

Take home messages summary

In adults with severe cystic fibrosis lung disease one year of treatment with lumacaftor-ivacaftor was associated with reduced infective exacerbations, days of intravenous antibiotics and rate of pulmonary function decline, and improved nutritional status.

Introduction

Lumacaftor-ivacaftor (LUM-IVA) is a combination cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy proven to be useful in individuals with cystic fibrosis (CF) with two copies of the Phe508del mutation and was the first such agent available for this CF genotype.[1] In clinical trials involving patients with mild or moderate lung disease (percent predicted forced expiratory volume in one second [$ppFEV_1$] 40-90%), LUM-IVA was associated with modestly improved pulmonary function and weight, and reduced pulmonary exacerbation.[1-4]

However, LUM-IVA-eligible patients with severe lung disease ($ppFEV_1$<40%) were excluded from these clinical trials. Thus, our understanding of its impact in this group of patients is limited. Murer *et al* studied 20 CF adults and reported modest increases in $ppFEV_1$ of 2.5% from a mean baseline $ppFEV_1$ of 32% in the 10 patients that were able to tolerate the medication and remained on it for 6 months, as well as reduced pulmonary exacerbation rate and approximately 0.9kg/m^2 increase in body mass index (BMI).[5] Another observational study in 35 patients with severe lung disease ($ppFEV_1$<40%) completing 24 weeks on LUM-IVA reported reduction in hospitalisations and duration of intravenous antibiotic usage compared to the 24 weeks prior to commencement.[6] However, the use of these medications at the more severe end of the CF spectrum still needs to proceed with caution. This is pertinent given the not insignificant rates of adverse events and need for discontinuation, with all that this entails both clinically and psychologically regarding unmet expectations.[7]

LUM-IVA was not available in Australia until late 2018 outside a clinical trial setting, except via a compassionate use managed access program for individuals aged over 12 years, with $ppFEV_1$<40%, rapidly declining pulmonary function or lung transplant listing. The Alfred Adult CF Service is one of the largest adult CF centres in the southern hemisphere, caring for over

340 adults with CF. Severe lung disease ($ppFEV_1$<40%) is an indication for assessment and consideration of lung transplant[8]. In this setting, following care optimisation, LUM-IVA was able to be offered to patients with severe CF lung disease with two copies of the Phe508del mutation via the compassionate use program, undertaken in conjunction with referral to the lung transplant team and to help manage potential concerns of adverse drug reactions precipitating further respiratory decline. Importantly, low baseline pulmonary function and frequent pulmonary exacerbations requiring hospitalisation are major signals for increased mortality rates in CF and therefore for lung transplant consideration[8]. Hence the real-world implementation of LUM-IVA treatment in severe CF lung disease needed to proceed within this framework and with caution.[2,5]

Pulmonary function and nutritional status are strongly correlated in CF[9]. While it has long been appreciated that higher $ppFEV_1$ is associated with higher BMI and with indices of fat-free mass (FFM)[9-13], the significance of altered body composition is increasingly being recognised.[11,13-16]. FFM depletion is associated with more severe CF lung disease, increased pulmonary exacerbations rate and higher systemic inflammatory cytokines including IL-6[17-19]. Changes in weight, FFM and fat mass are not always aligned, underpinning the importance of body composition assessment in both routine clinical care and evaluating novel interventions such as CFTR modulator therapies[19-21]. However, to date there are no data reporting the effect of LUM-IVA on body composition.

Systematically evaluating the effects of CFTR modulator therapy across multiple clinical domains in a single centre cohort of CF patients with severe lung disease therefore offers a unique opportunity to better understand the potential benefits of these new therapies. In this clinical evaluation study, we aimed to examine the clinical effects (hospitalisation for antibiotic treatment of pulmonary exacerbations, changes in pulmonary function, weight and body composition) of one year of treatment with compassionate access LUM-IVA in adult CF patients with severe lung disease ($ppFEV_1$<40% at baseline).

Methods

This clinical evaluation study reports on data from all adult patients (≥18 years) who received LUM-IVA under the care of the Alfred Adult Cystic Fibrosis Service, Melbourne, Australia, for at least one year, from January 2016 to July 2018 under the managed access program. This cut-off was chosen because LUM-IVA was approved for government subsidy in August 2018. All patients who became eligible during this period were identified and approached, and all accepted treatment. The study was approved by The Alfred Health Research and Ethics Committee (approval no. 464/18).

Following clinical evaluation of suitability to commence treatment [including homozygosity for the Phe508del mutation, ppFEV_1<40% and an absence of key contraindications, such as severe liver disease (Child-Pugh C, current severe infective exacerbation or bronchoconstriction], eligible CF patients were hospitalised and treatment regimens optimised prior to the first dose of LUM-IVA. This included pre-emptive management of airway sepsis and airways reactivity (if present) utilising parenteral antibiotic treatment as indicated and the use of inhaled ipratropium and inhaled/oral steroids as required, respectively. As is the usual practice at every admission, fluid and nutritional intake, and physiotherapy using airway clearance and exercise were optimised to ensure baseline functional levels as much as possible. LUM-IVA (supplied by Vertex Pharmaceuticals Inc) was initiated at half dose, and increased to full dose (two 200/125 mg tablets orally 12hrly) after a few days to one week as tolerated. Patients were educated on taking LUM-IVA 12 hourly with dietary fat. Patients were routinely monitored during inpatient stays and outpatient clinics for tolerance to LUM-IVA (including full clinical assessments, spirometry testing, routine biochemistry (including tests of liver function) and nutritional status). Identification and management of pulmonary exacerbations followed usual standard care practices. Any decision to cease treatment due to adverse events or tolerance issues was made by the treating team. LUM-IVA was ceased if patients underwent lung transplantation.

Where LUM-IVA treatment was ceased prior to one year of treatment, specific reasons for this decision were recorded.

For this clinical evaluation study, data were analysed for all adults who reached one year of LUM-IVA treatment. Demographic and clinical data at commencement of LUM-IVA (age, gender, $ppFEV_1$, use of supplementary oxygen, diagnosis of CF-related liver disease or CF-related diabetes mellitus and whether listed for lung transplant prior to commencement of LUM-IVA) were collected. Pulmonary function (post-bronchodilator spirometric data for FEV_1, $ppFEV_1$, forced vital capacity (FVC), ppFVC, mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$) and $ppFEF_{25-75\%}$) and weight measurements for the year prior to commencement of LUM-IVA and the year after commencement were extracted from clinical records (using data from all pulmonary function tests undertaken). At our centre, the predominant indication for intravenous antibiotics (IVAB) is pulmonary exacerbation, and these courses may be completed in hospital, or undertaken partly in hospital and partly at home. At our centre, continuation of IVAB courses at home is based on factors including clinical stability, patient ability to manage line care, IVAB delivery and other aspects of the CF care at home, social and geographic factors including patient preference, and for patients living outside the Melbourne region, availability of a local provider of hospital-in-the home nursing services and distance from their home to the CF centre. Access to home IVAB therapy is available across all FEV_1 ranges. All patients are trained in IVAB delivery and must complete a competency checklist prior to transfer to home care. Clinical criteria and practices for home IVAB therapy were consistent across the period of this study. The number of pulmonary exacerbations requiring hospitalisation, days in hospital and days of intravenous antibiotic (IVAB) usage during the year prior to commencement of LUM-IVA and during the year after commencement were recorded.

Body composition measurement was undertaken by trainer operators using multi-frequency bioelectrical impedance analysis (mBCA 515/514, SECA, Germany), a method with good reproducibility, and validity against reference methods.[22] Measurements were taken prior to commencement of LUM-IVA, and after one and six months and one year of treatment. Body composition variables collected included weight, fat-free mass (FFM), fat mass (FM), total body water (TBW), extra- and intracellular water (ECW, ICW), ECW as a percentage of TBW (ECW%TBW) and phase angle. Body mass index (BMI), fat-free mass index (FFMI) and fat mass index (FMI) were calculated by dividing weight, FFM and FM by the square of height in metres. FFM depletion was defined as FFMI<15kg/m^2 for females and <17kg/m^2 for males.[23] "Hidden" FFM depletion was defined as FFM depletion in patients with BMI<18.5kg/m^2.[11]

Statistical analysis

Statistical analyses were performed using Stata Software version15 (Stata Corporation, College Station, Texas, USA) or SAS software version 9.4 (SAS Institute, Cary, NC, USA). size calculation was not undertaken as data from all available patients were included. Continuous data were assessed for normality and reported as mean (standard deviation, SD) or median (interquartile range [IQR] or range) depending on underlying distribution. Differences in health service utilisation variables (number of exacerbations requiring hospitalisation, days in hospital and days of IVAB treatment) between the year prior to commencing LUM-IVA and the year following commencement were compared using Wilcoxon signed rank tests. For pulmonary function parameters and weight for the year prior to and the year following commencement of LUM-IVA, slope estimates and standard errors were derived for each patient using all measurements for each time period via linear regression modelling to determine annual rates of change pre- and post-LUM-IVA. Comparisons were made using weighted, linear-regression analyses with weights derived by the inverse variance method, in order to account for the number of measurements per

person in each time period. Changes in body composition variables in the year following LUM-IVA were assessed. To account for repeat measures, these data were analysed using linear, mixed-effects regression modelling, fitting main effect for time with patients treated as random effects. Post-hoc comparisons of time points were performed with Bonferroni correction for multiple comparisons. McNemar's test of paired proportions was used to compare BMI distribution at baseline and one-year follow-up. Correlations between variables were assessed using Pearson's or Spearman rank correlation wherever appropriate. A formal power calculation was not undertaken as data from all available patients were included. However, a retrospective sample size calculation was performed for FFM change. Based on a clinically important mean change of 5% and the standard deviation of change in FFM at one year at power of 80% and alpha of 0.05, a sample size of 7 would have been sufficient to detect this effect size, suggesting the lack of significant change in mean FFM is not due to a type II error. A two-sided p value of less than 0.05 indicated statistical significance.

Results

Between January 2016 and July 2018, 40 adults with severe CF lung disease commenced LUM-IVA treatment under the managed access program. All were homozygous for the Phe508del mutation. Of these, 24 had reached one year of treatment by July 2018. Six ceased due to not tolerating LUM-IVA (five: airway reactivity, one: deterioration in liver function tests)*;* three underwent lung transplantation; while seven had not yet reached one year of treatment. These 16 patients had similar means age (31.8±9.2 years, p=0.78) and ppFEV$_1$ (34.3±7.9%, p=0.87) to the 24 adults who reached one year of treatment, on whom this report is based. Data acquisition was complete other than for 3/96 missing body composition data points (unanalysable data for one patient at baseline and one month, one patient missed the 6-month measurement). Table 1 shows demographic and clinical characteristics at commencement of LUM-IVA. Whilst no one was on the waitlist for lung transplant at commencement, two patients were listed during the first year of LUM-IVA treatment (but not yet transplanted by one year). No patients were diagnosed with APBA requiring anti-fungal treatment and no substrates of CYP3A4 were required. Of the 6 patients who did not tolerate LUM-IVA, their baseline clinical characteristics were similar to the cohort of 24 patients who completed one year of treatment (mean±SD ppFEV$_1$ 31.7±7.0, p=0.38; BMI 22.1±1.9, p=0.14; with 50% having CFRD and 33% having CFLD and none on supplemental oxygen).

Table 2 shows hospitalisation and IVAB usage data for the year prior to and the year following commencement on LUM-IVA. The median numbers of pulmonary exacerbations requiring hospitalisation, total days in hospital and days of IVAB usage all decreased significantly (Table 2 , Figure 1). Eleven patients had more than 14 days fewer hospital days in the first year on LUM-IVA, compared to the previous year. For IVAB usage, 21 patients had fewer days on IVAB in the first year on LUM-IVA (range 1-247 fewer days, Figure 1). There were no significant gender differences in hospitalisation or IVAB days.

Significant differences in the rates of change in $ppFEV_1$ and weight were seen in the year following LUM-IVA treatment, compared with the year prior to commencement, with reversal of the patterns of decline for both $ppFEV_1$ and weight (Table 2)., A waterfall plot of the linear regression line slopes for change in $ppFEV_1$ in the year following the commencement of LUM-IVA reveals the individual patient response heterogeneity and three of 15 positive responders having a response of ≥10% (Figure 1). Sensitivity analyses were performed excluding the outlier for each of FEV_1% change, change in IVAB days and change in hospital days and the significance of each result was retained, showing that the overall results were not driven by single patient responses.

In keeping with the severity of lung disease in this cohort, one third of patients were underweight (BMI<18.5kg/m^2) at commencement of LUM-IVA treatment. However, half of the patients had FFM depletion at baseline, in five (42%) of whom the FFM depletion was hidden (ie low FFMI with BMI≥18.5kg/m^2).

No changes were observed in weight or body composition in the first month on LUM-IVA treatment. Increase in mean weight was observed during the first six months, plateauing by one year (Table 3, Figure 2). At one year, mean weight gain was 2.5±4.1kg (p=0.0007), or a mean percentage increase from baseline of 4.9±7.3% (p=0.0002). Half of the patients gained more than 5% of baseline weight, but only one lost >5% of baseline weight. Similarly, BMI increased significantly at one year (0.90±1.40kg/m^2, p=0.001, Table 3). Fat mass increased significantly in the first six months, plateauing by one year (mean total gain: 2.2kg, Table 3, Figure 2). In contrast, there was no overall change in FFM or FFMI, indicating preservation of FFM stores over the first year of treatment (Table 3, Figure 2); however, 20% of patients gained more than 5% of baseline FFM in the year of treatment.

The proportion of patients with severe underweight (BMI <18.5kg/m^2) decreased from 33% at baseline to 13% at one year of treatment (p=0.003 using McNemar's test). In contrast, there was no reduction in the proportion with FFM depletion between baseline and one year (50% at both timepoints). One patient had a BMI>25kg/m^2 throughout the observational period, but no new cases of overweight emerged. Baseline BMI was inversely correlated with change in weight (r = -0.54, p=0.006); % change in weight (r = -0.56, p=0.005) and change in FFM (r = -0.57, p=0.005), but not change in fat mass (-0.32, p=0.14); indicating that those with the poorest baseline nutritional status experienced the greatest gains in weight and FFM. No gender differences in patterns of change in body composition were observed. Neither age nor pulmonary function correlated with changes in body composition (data not shown). However, change in FFM by one year correlated with greater reduction in the number of both hospitalisation days and IVAB days in the year post-commencement of LUM-IVA compared to the year prior (rho= -0.50, p=0.001 and rho= -0.43, p=0.04 respectively). Change in weight in the year post-commencement was correlated with greater reduction in hospitalisation days (rho= -0.48, p=0.02), whilst changes in fat mass showed no correlation.

The reduction in hospitalisation days and IVAB usage between the years prior to and post-LUM-IVA were strongly correlated (rho=0.72, p=0.0001) in our patient cohort. However, no significant correlations were seen between changes in IVAB usage and changes in the slopes for pulmonary function parameters, nor for age or gender, indicating no clearly detectable clustering in the health status improvements following commencement of LUM-IVA (Figure 3). Similar patterns were observed for changes in hospitalisation days (data not shown).

Discussion

In the present study we describe our real-world clinical experience with LUM-IVA treatment in a cohort of CF adults homozygous for the Phe508del mutation with severe lung disease. Although 31 adults were still on compassionate use LUM-IVA at the time of study assessment, only 24 had reached one year of LUM-IVA treatment and therefore were the focus of this report. Of the remaining nine patients who ceased LUM-IVA treatment, six (15%) had ceased because of adverse events / intolerance (five: airway reactivity, one: significant deterioration in liver function tests); whereas three (7.5%) ceased due to undergoing lung transplantation. The discontinuation rates for LUM-IVA in our cohort were therefore similar to, if not lower than, those quoted in the literature for patients with severe lung disease.[5,6,24-26] Whilst the reasons for this cannot be conclusively identified, we believe that the model of care we established, including initiating LUM-IVA in the inpatient setting and regular outpatient review, maximised clinical stability, facilitated early identification and pre-emptive management of adverse effects and supported adherence to LUM-IVA.

In our cohort of 24 patients who received LUM-IVA treatment for one year we report health stabilisation with significant improvements in CF-related clinical measures (frequency and severity of exacerbations in pulmonary sepsis requiring hospitalisation and IV antibiotic treatment, relative stabilisation in pulmonary function decline), significant improvements in weight and fat mass; and a reduction in the prevalence of severe underweight. These results both confirm and extend the findings from previous studies involving patients mild-moderate lung disease[1,2,4,26] as well as those with severe lung disease[5,6,25]. Moreover, the overall reduction in pulmonary exacerbation rate post LUM-IVA in our cohort of severe lung disease patients ($ppFEV_1$ <40%) and the improvement in average rate of decline in $ppFEV_1$ at an individual level, were not dissimilar to those found in larger studies of patients with $ppFEV_1$ >40%[1,2].

On the other hand, at the individual patient level, there was no clear clustering of improvement across clinically relevant domains. Hence, the subset of patients with the greatest reduction in health service utilisation were not consistently those with the greatest stabilisation in ppFEV$_1$ decline, nor were they necessarily associated with the greatest improvements in weight. These findings of improvements in various clinical domains as well patient-focused and health service-related outcomes, underscores the importance of including these measures in both clinical trials and in the post-trial clinical evaluation setting where possible. Given the progressive rollout of CFTR modulator therapies including LUM-IVA, tezacaftor-ivacaftor (TEZ-IVA) and elexacaftor-tezacaftor-ivacaftor ("Trikafta"), it can be argued that this will need to be matched with a parallel real-world evaluation. This will best inform the continuous evolution of clinical models of care for adults with CF, especially as care shifts away from inpatient care and acute exacerbations to requiring a higher proportion of their hospital visits in the outpatient setting. Given that patients with ppFEV$_1$ <40% were also excluded from clinical trials of triple combination therapy for CF patients, real-world evaluation of its clinical effects in severe lung disease are also critical. Our data reporting on body composition changes on LUM-IVA will also provide comparative data for interpretation of the greater weight gain seen with triple combination therapy[27,28], which is particularly relevant given that excess adiposity is associated with normal weight obesity.[14]

Although our data indicated an expected positive correlation between the reduction in hospitalisation days and IVAB usage, changes in health service utilisation and pulmonary function were not correlated, nor were improvements in nutritional parameters and pulmonary function status. The latter two findings suggest that the improvement in physiological measures following the commencement of LUM-IVA is relatively discordant in severe lung disease. This may have significant mechanistic implications. Specifically, pathobiological drivers for exacerbations in airway infection, ongoing inflammation and catabolic processes at the very least are not completely overlapping and appear to be

variably responsive to CFTR modulator intervention at the individual patient level. A recent biomarker study suggested heterogeneity in the response to CFTR modulator treatment[29]. As “real-world” experience with CFTR modulators accumulates, emerging information on variability in clinical responses will help guide clinical decision making.

The reversal of previous weight loss and stability of FFM signals in our CF cohort with more severe lung disease treated with compassionate use LUM-IVA for one year is an important finding. Given that malnutrition is associated with poor outcomes both pre- and post-lung transplantation, interventions to maintain and improve nutritional status are key components of the management of patients with severe lung disease (reference to be added CFF consensus guidelines on management of CF patients with end-stage lung disease.[30] Our findings suggest that FFM change was associated with reduced requirement for hospitalisation and parenteral antibiotics, although not necessarily associated with improvements in rates of pulmonary function decline. Although our real-world evaluation study was not designed to examine the mechanisms underpinning our observations and therefore cannot delineate the potential contribution of improvements in the anorectic/catabolic state to improvements in nutritional parameters, it does nevertheless suggest that these and other factors are likely to be important. These factors may include: improvements in gastro-intestinal absorption of nutrients; increased nutrient intake, improvements in neuro-hormonal stress metabolism; reduction in resting energy expenditure and improvements in intracellular energetics and metabolic efficiencies, with most of the evidence in support of mechanisms underlying nutritional improvements coming from studies on ivacaftor.[31-33] There was relatively minimal change seen in extracellular water as a percentage of total body water across the cohort throughout the one-year period, whereas the weight and fat mass gains generally plateaued between 6 months and one year.

A major strength of this study is the real-world evaluative aspects of compassionate use LUM-IVA in a cohort of severe lung disease patients followed for a year in a large, single adult CF centre. By its very nature, this study's clear trade-off is that it was not prospectively designed, randomised and fully protocol driven and not feasible to have a control (no treatment) group. Thus, we cannot rule out that for this group of patients with severe lung disease the hope and opportunity offered by access to LUM-IVA may have contributed to improvements in motivation of adherence to usual treatment regimens. However the relatively tight regulation associated with gaining access to compassionate use LUM-IVA and monitoring its use as well as the single centre approach significantly helped reduce, but not eliminate, the possibility of health care decision-related biases. Furthermore, a single centre study allowed inclusion of body composition data for sequential monitoring, available at our centre, but not routinely in all CF centres. With this in mind, our report included complete follow-up and data acquisition for all patients except for only 3 of 96 body composition data points missing. Additionally, the potential for biasing pulmonary function testing by having more measurements in the sicker patients was statistically accounted for in our analysis, thereby minimising any potential impact on this result.

Another strength is inclusion of body composition monitoring, which is infrequently reported in clinical trials. Therefore our data extend knowledge beyond the predominantly weight-based nutritional outcomes for CFTR modulator therapies available to date. The lack of further systematic assessment of nutritional and energy parameters as well as sweat chloride testing throughout the study period is a limitation to our final analysis. Whereas the use of BIA proved to be practical and feasible (no recurrent cost, no exposure to radiation, available on demand at our centre) in our study and has high precision, it was not feasible to perform more detailed metabolic testing such as indirect calorimetry or sweat chloride testing nor obtain repeated food records for dietary intake analysis[32] in a busy clinical setting. The impact of CFTR modulators on quality of life, physical functioning and social participation are

important patient-centred outcomes, but which were outside the scope of the current report; and therefore, we are unable to comment on any correlations between clinical or nutritional findings and these parameters.

In conclusion, our real-world evaluation study confirmed the feasibility and benefits of LUM-IVA in a significant proportion of CF patients with severe lung disease. Moreover, these benefits occurred over several clinical domains (infective exacerbations requiring hospitalisation for parenteral antibiotic treatment, rates of pulmonary function decline and nutritional parameters) that were not necessarily clustered in individual CF patients. Whether these findings will be similar with the newer CFTR modulator therapies applicable to this cohort of patients will be of major interest, as will the question of whether patients who did not tolerate LUM-IVA will be able to tolerate and achieve clinical benefit from these newer agents. To this end, our data support a case for completing real world evaluations of these new medications to maximise understanding and insights that may be associated with their prolonged use. Such evaluations at the very least should include a systematic clinical framework within which a range of investigative assessments that have a relatively high index of capturing important signals can be readily performed in an outpatient setting at an acceptable cost.

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Declarations

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Table 1: Demographics and CF therapies at baseline: 24 adults with cystic fibrosis (prior to commencement of LUM-IVA)

Variable	Mean±SD or %
Male gender	54%
Age (years)	32.6±8.6
Height (cm)	169.0±10.4
BMI (kg/m^2)	20.3±2.7
FEV_1 (litres)	1.30±0.41
FEV_1 % predicted	34.7±7.4
FVC (litres)	2.65±0.81
FVC % predicted	57.8±10.0
$FEF_{25-75\%}$ (litres)	0.51±0.19
$FEF_{25-75\%}$ % predicted	13.3±4.2
Diagnosis of Cystic-fibrosis-related diabetes mellitus	33%
Diagnosis of Cystic-fibrosis-related liver disease	33%
Use of supplementary oxygen therapy	0%
Azithromycin	87.5%
rhDNase	58.3%
Hypertonic saline	58.3%
Inhaled antibiotics	41.4%
Oral antibiotics	33.3%
Inhaled corticosteroids	87.5%
Oral corticosteroids	4.2%
Long-acting beta agonists	91.7%
Long-acting muscarinic antagonists	4.2%

BMI: Body mass index; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; $FEF_{25-75\%}$: mean forced expiratory flow between 25% and 75% of FVC

Table 2: Health service utilisation data, and rates of change of pulmonary function and weight in the year prior to and the year following commencement of lumacaftor-ivacaftor in 24 adults with CF

Variable	During the year prior to commencement	During the year following commencement	P value
Health Service utilisation data			
Number of pulmonary exacerbations requiring hospitalisation	3 [2,4]	1.5 [1-2]	0.0002
Days in hospital (on ward)	27 [18,58] (range 10-103)	17 [10,25] (range 1-70)	0.0002
Days of IVAB usage	45 [21, 75] (range 10-280)	27 [11,52] (range 1-167)	0.0007
Annual rates of change in pulmonary function and weight (Slope [SE])			
FEV_1 (litres)	-0.084 [0.046]	0.027 [0.041]	0.077
FVC (litres)	-0.04 [0.10]	0.00 [0.06]	0.75
$FEF_{25-75\%}$ (litres)	-0.07 [0.02]	0.02 [0.02]	0.007
FEV_1 %predicted	-2.10 [1.18]	1.45 [1.13]	0.035
FVC %predicted	-0.69 [2.11]	1.27 [1.51]	0.46
$FEF_{25-75\%}$ %predicted	0.07 [0.20]	0.07 [0.05]	0.97
Weight (kg)	-0.62 [0.89]	2.60 [0.88]	0.013

FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; $FEF_{25-75\%}$: mean forced expiratory flow between 25% and 75% of FVC

Health service utilisation data show median [IQR]. IVAB: intravenous antibiotic usage

Pulmonary function and weight data show mean change per year [Slope (SE)] using linear regression modelling of all clinical measurements in each year-long period. SE: Standard Error

P value for difference between year prior and year following commencement (Wilcoxon signed rank test for health service utilisation data and weighted linear regression analyses for pulmonary function and weight data

Table 3: Body composition during treatment with lumacaftor-ivacaftor in 24 adults with CF

	Baseline	1 month	6 months	One year	P value for overall effect of time
Weight (kg)	58.4±12.1	59.0±11.3	60.6±10.9**	60.8±11.1	0.0007
FFM (kg)	46.1±11.2	45.8±10.9	46.7±11.0	46.2±10.7	0.49
Fat mass (kg)	12.5±6.7	13.5±6.4	14.0±5.8**	14.7±6.3***	<0.0001
BMI (kg/m^2)	20.3±2.7	20.5±2.4	21.1±2.1*	21.2±2.3**	0.0003
FFMI (kg/m^2)	15.9±2.5	15.8±2.4	16.1±2.4	16.0±2.3	0.48
Fat mass index (kg/m^2)	4.4±2.4	4.8±2.4	4.9±2.2**	5.2±2.4***	<0.0001
TBW (L)	33.7±8.1	33.6±7.7	34.2±7.9	33.9±7.8	0.46
ICW (L)	19.2±5.5	19.2±5.5	19.7±5.3	19.5±5.2	0.27
ECW (L)	14.5±2.8	14.4±2.7	14.5±2.8	14.4±2.8	0.84
ECW as %TBW	43.6±3.9	43.3±3.4	42.8±3.8	43.0±3.5	0.29
Phase angle	4.8±0.9	4.8±0.9	4.7±1.4	4.8±0.9	0.08

Data show mean ± SD. N=23 for all body composition measurements and phase angle and baseline, 1 month and 6 month timepoints (For one patient, useable BIA could not be obtained at baseline and 1 month, one patient missed the 6 month measurement).

FFM: fat-free mass, BMI: body mass index, FFMI: Fat-free mass index, TBW: total body water, ICW: intracellular water, ECW: extracellular water

Overall p value is for Linear mixed effects regression model for effect of time on variables.

*Asterisks indicate individual p values for change between baseline and that timepoint (derived from the regression model, with Bonferroni correction): *p<0.05; **p<0.005; ***p<0.0001*

Figure legends

Figure 1 Waterfall plots

Figure 1a Waterfall plot for the slope of percentage predicted FEV_1 ($ppFEV_1$) in the year following starting LUM-IVA.
Data show the individual patient changes in absolute $ppFEV_1$ points in the year following LUM-IVA commencement, determined by linear regression of all pulmonary function from commencement to one-year post. Mean change [Slope (SE)]: 1.45% per year

Figure 1b Waterfall plot for changes in number of days of intravenous antibiotics in the year following commencement of LUM-IVA, compared to the year prior. Data show individual patient changes in IVAB days: post-days - pre-days. Median reduction: 13 [IQR 4-30] days.

Figure 1c Waterfall plot for changes in number of days in hospital in the year following commencement of LUM-IVA, compared to the year prior. Data show individual patient changes in hospitalisation days: post-days - pre-days. Median reduction: 12 [IQR 3-30] days.

Figure 2: Body composition changes in 24 adults receiving LUM-IVA for one year

a) Change in weight
b) Change in fat-free mass
c) Change in fat mass

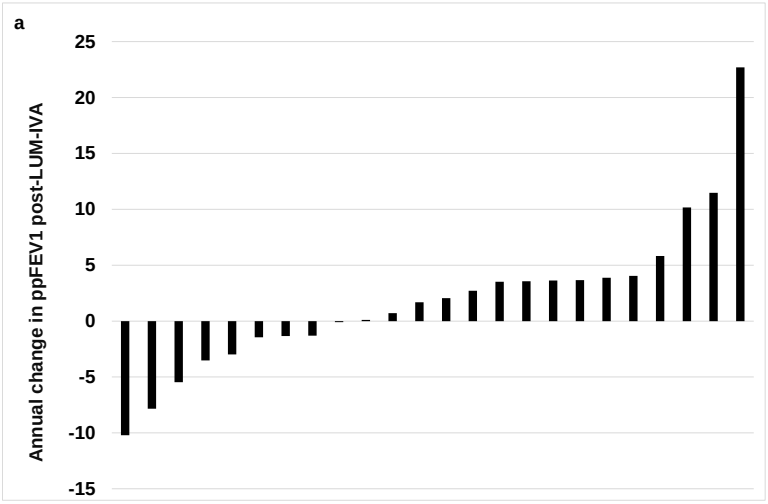
Data show each individual measurement. Solid lines show mean change from baseline at each timepoint. p-values indicate differences in mean values between timepoints using linear mixed effects modelling with Bonferroni correction for multiple comparisons. FFM: Fat-free mass

Figure 3: Venn diagram showing lack of clustering of clinical response domains for changes on lumacaftor-ivacaftor in 24 adults with CF

Data have taken the median response for each domain (Days intravenous antibiotics (IVAB); Change in annual rate of change in $ppFEV_1$; and change in rate of weight change).

Numbers in the circles show patients with a response greater than the median change (where "response" is the change in rate between the year prior to starting lumacaftor-ivacaftor and the year following commencement

Figure 1 Waterfall plots



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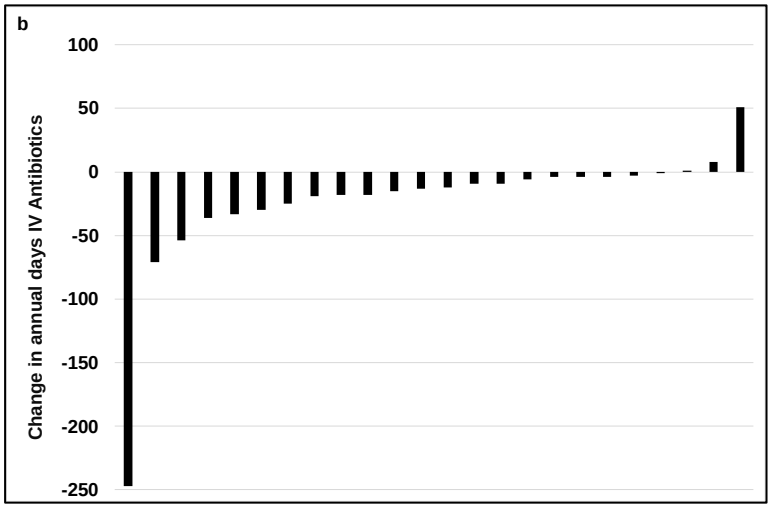

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Data show individual patient changes in IVAB days: post-days - pre-days. Median reduction: 13 [IQR 4-30] days.

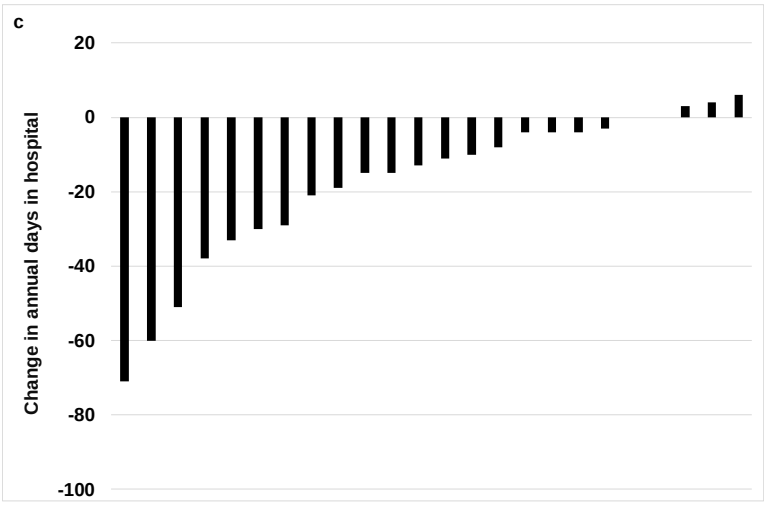

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Figure 2: Body composition changes in 24 adults receiving LUM-IVA for one year

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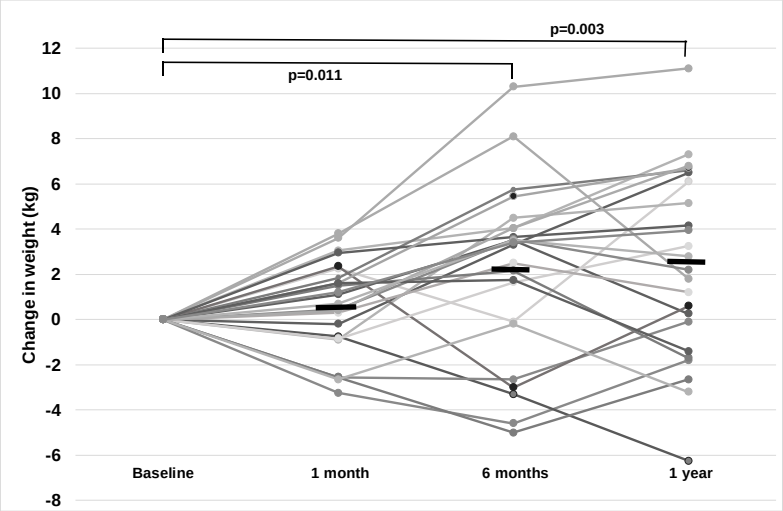
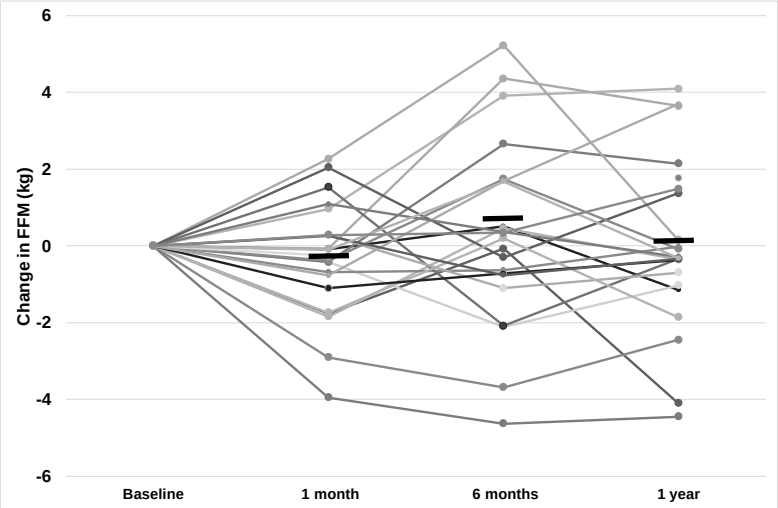
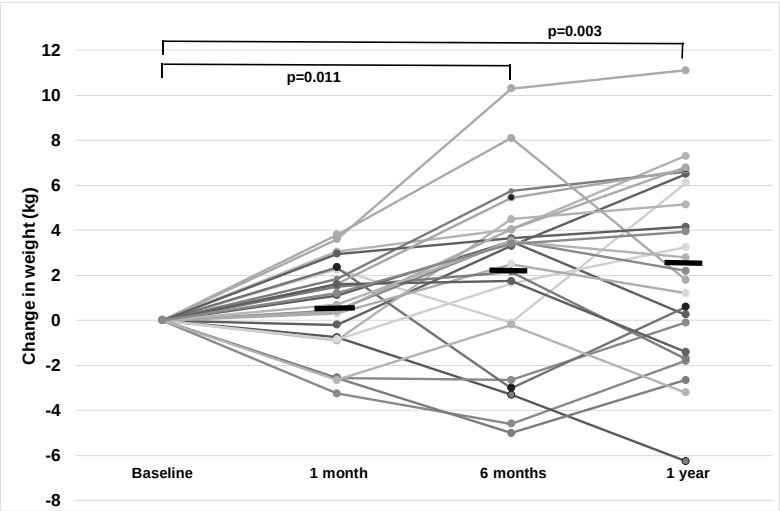


b) **Change in fat-free mass**



c) Change in fat mass



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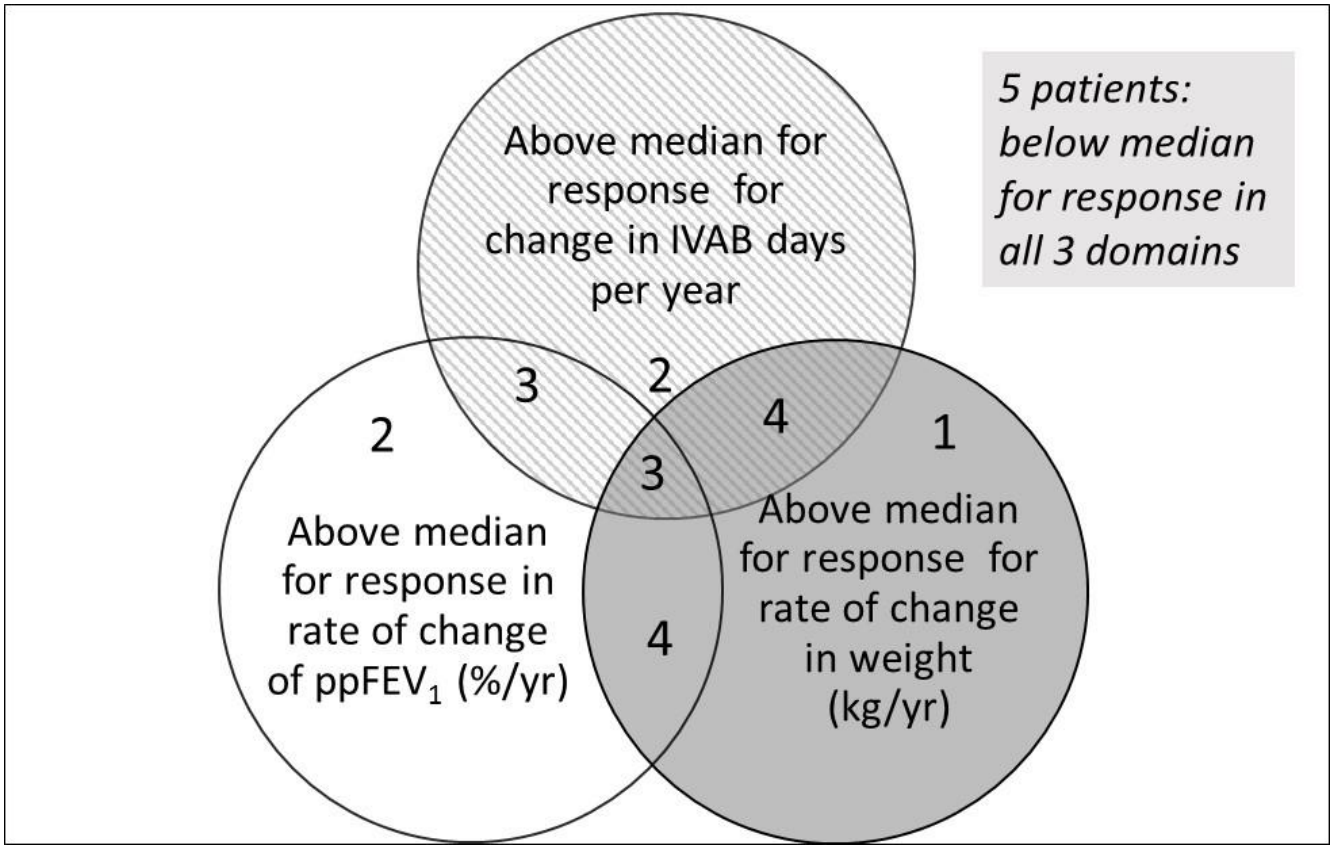
Clinical and body composition changes on lumacaftor-ivacaftor treatment for CF, King et al Fig 2

Figure 3: Venn diagram showing lack of clustering of clinical response domains for changes on lumacaftor-ivacaftor in 24 adults with CF



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