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Original Article

Effectiveness of lumacaftor/ivacaftor initiation in children with cystic fibrosis aged 2 through 5 years on disease progression: Interim results from an ongoing registry-based study☆,☆☆,☆☆☆

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ABSTRACT

Background: Lumacaftor/ivacaftor (LUM/IVA) has been shown to be safe and efficacious in people with cystic fibrosis (CF) ≥1 year of age. To assess the impact of early LUM/IVA initiation on CF disease progression, a 6-year observational study leveraging data from existing CF patient registries is being conducted in children with CF homozygous for *F508del* (*F/F* genotype) who were aged 2 through 5 years at treatment initiation. Here we present interim results from this study focusing on data from the European CF Society Patient Registry (ECFSPR).
Methods: The LUM/IVA cohort included children in the ECFSPR who started LUM/IVA between 15 January 2019 and 31 December 2020. Longitudinal trends in growth parameters, pulmonary exacerbations, hospitalizations, safety outcomes, and other effectiveness outcomes in the LUM/IVA cohort were compared to those in two modulator-naïve cohorts: (i) matched concurrent cohort heterozygous for *F508del* and a minimal function mutation (*F*/MF concurrent comparator cohort) and (ii) matched concurrent cohort with the *F/F* genotype from countries without commercial access to LUM/IVA as of 2020 (*F/F* concurrent comparator cohort).
Results: The LUM/IVA cohort matched to the *F*/MF concurrent comparator cohort had 681 children and the LUM/IVA cohort matched to the *F/F* concurrent comparator cohort had 183 children. LUM/IVA cohorts had increases in body mass index percentiles relative to the matched *F*/MF and *F/F* concurrent comparator cohorts (mean difference in change from baseline: 8.4 [95% CI: 5.5, 11.3] and 11.8 [95% CI: 5.9, 17.7], respectively). Increases in height and weight percentiles were also observed in the LUM/IVA cohort relative to the *F*/MF and *F/F* concurrent comparator cohorts. Reductions in pulmonary exacerbations and hospitalizations relative to baseline and the *F/F* concurrent comparator cohort were seen in 2021.
Conclusions: This interim analysis showed favorable trends in clinical outcomes, including growth parameters, pulmonary exacerbations, and hospitalizations, suggesting an early beneficial effect of LUM/IVA treatment in children aged 2 through 5 years at treatment initiation.

1. Introduction

Cystic fibrosis (CF), an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, affects an estimated 105,000 people worldwide, nearly half being children (under the age of 18 years) [1,2]. Clinical

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ECFSPR, European Cystic Fibrosis Society Patient Registry; *F/F*, homozygous for *F508del*; *F*/MF, heterozygous for *F508del* and a minimal function mutation; IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbations; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; RR, relative risk.

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manifestations of CF begin early in life and include progressive structural lung damage and pancreatic insufficiency [3–5]. In the lungs, mucus hyperconcentration and decreased mucociliary clearance can lead to air flow obstruction, infection, and inflammation and eventually the development of severe bronchiectasis and respiratory failure [6], while pancreatic damage caused by CF can result in nutrient malabsorption and poor weight gain [5]. More than 2000 *CFTR* variants have been identified [7]; however, the most common pathogenic variant is *F508del,* with nearly half of people with CF being homozygous for *F508del* (*F/F*) [8].

CFTR modulators, such as the CFTR corrector lumacaftor (LUM) and CFTR potentiator ivacaftor (IVA), are small molecule therapeutics designed to improve the function and trafficking of CFTR proteins in people with CF [9–11]. Phase 3 clinical trials showed treatment with a dual combination LUM/IVA led to long-term, sustained, multisystem clinical benefits, including improvements in lung function and growth parameters and reduced pulmonary exacerbation rates, in people with CF 6 years of age and older with the *F/F* genotype [12,13]. More recent clinical trials have shown LUM/IVA is also safe and efficacious in younger children, with participants as young as 1 year of age having reductions in sweat chloride concentration and improving trends in biomarkers of pancreatic function and intestinal inflammation following LUM/IVA initiation [14]. Given the early onset of CF disease manifestations, and the potential for children with CF to start LUM/IVA treatment early in life, it is important to understand the long-term clinical benefits, including changes in disease trajectory, associated with early initiation of LUM/IVA treatment.

Here, we report results from the first interim analysis of a 6-year, post-authorization efficacy and safety study designed to evaluate disease progression in children with CF who initiate LUM/IVA treatment between the ages of 2 and 5 years in real-world settings.

2. Methods

2.1. Study design, population, and objectives

Study VX18–809–128 is a 6-year, observational, post-authorization efficacy study in children with CF who have the *F/F* genotype and were 2 through 5 years of age at LUM/IVA initiation. The source population for the study is children included in CF registries in the US and Europe. Here we report the first interim analysis results for the European CF Society Patient Registry (ECFSPR) population. US data are not reported because most of the study participants in the US initiated tezacaftor (TEZ)/IVA or elexacaftor (ELX)/TEZ/IVA during follow-up. The ECFSPR is a database containing over 54,000 consenting people with CF from 40 countries and represents, in most countries, ≥80% of people with CF [15].

In this study, we evaluated CF disease progression following LUM/IVA initiation through comparisons with two CFTR modulator–naïve matched concurrent comparator cohorts. Finding an appropriate treatment-naïve comparator is challenging when there is high uptake of the medicine of interest. In this study, a matched comparator cohort of children heterozygous for *F508del* and a minimal function mutation (*F*/MF genotypes) was used; these children are phenotypically similar to children with the *F/F* genotype and did not have an approved *CFTR* modulator therapy available at the time of study initiation. Additionally, the ECFSPR provides a unique opportunity to establish a matched comparator cohort of children with the *F/F* genotype who live in countries that do not have commercial access to LUM/IVA but have clinical outcomes comparable to those in countries with commercial access.

The LUM/IVA cohort included children with the *F/F* genotype who were 2 through 5 years of age at LUM/IVA initiation, initiated LUM/IVA treatment during the cohort entry period (15 January 2019–31 December 2020), and were from countries with commercial access to LUM/IVA (as of 31 December 2020: Austria, Denmark, France, Germany, Ireland, Luxembourg, the Netherlands, Slovenia, Sweden, Switzerland, and the UK).

The *F*/MF concurrent comparator cohort included children with *F*/MF genotypes who are from the same countries as the LUM/IVA cohort but have not received LUM/IVA (or any other CFTR modulator).

The *F/F* concurrent comparator cohort included children with the *F/F* genotype who live in countries with clinical outcomes similar to those in countries with commercial access but which did not have commercial access to LUM/IVA (as of 31 December 2020: Croatia, Czech Republic, Italy, Latvia, Norway, and Poland) and who have not received LUM/IVA (or other any CFTR modulator).

Children in the LUM/IVA cohort were matched 1:1 to children in the *F*/MF concurrent comparator and *F/F* concurrent comparator cohorts on age, sex, and body mass index (BMI)–for-age *z*-score at baseline. Age matches were based on the chronological year of age at baseline. BMI-for-age *z*-score matches were based on percentile brackets as follows: ≤25, >25 to ≤50, >50 to ≤75, and >75.

The start of the cohort entry period was the date of marketing authorization (15 January 2019) and the end was 31 December 2020. Follow-up will be through 31 December 2024 (the current interim analysis is based on data collected through 31 December 2021).

LUM/IVA exposure for each child was determined based on record of LUM/IVA treatment in the ECFSPR. Children were considered exposed to LUM/IVA until there was no evidence of treatment in the registry. If the registry data showed that a child was no longer exposed to LUM/IVA, the child was censored from the LUM/IVA cohort. If the registry data showed that a child from the concurrent comparator cohorts had a new record of CFTR modulator therapy initiation, the child was censored from the respective cohort.

2.2. Study outcomes

Outcomes assessed in the study include growth parameters (BMI percentile, height percentile, weight percentile, BMI-for-age *z*-score, height-for-age *z*-score, and weight-for-age *z*-score), pulmonary exacerbations (PEx) leading to hospitalization (≥1 day of IV antibiotics in hospital), hospitalizations (≥1 day hospitalized for any reason), CF medications (inhaled antibiotics and oral corticosteroids), CF complications (distal intestinal obstruction syndrome and CF-related diabetes), pulmonary microorganisms (*Pseudomonas aeruginosa, Haemophilus influenzae*, and *Staphylococcus aureus* [including methicillin-resistant]), organ transplant, and death.

2.3. Statistical analyses

Continuous variables were summarized using descriptive summary statistics: number of observations, mean, SD, SE, median, range, and 95% CI for the mean, as appropriate. Categorical variables were summarized using counts and percentages, as appropriate.

Descriptive statistics were used to summarize age at baseline, age at cohort entry, age at initiation of LUM/IVA treatment (as applicable), and measures of growth parameters. Age categories, sex (male versus female), CF medication use (inhaled antibiotics and oral corticosteroids), pulmonary microorganisms, PEx, and hospitalizations were summarized using counts and percentages. Baseline was defined as the 2018 calendar year for all cohorts. The ECFSPR collects data annually (based on calendar year), and 2018 was the most recent year in which no one in the LUM/IVA cohort was exposed to LUM/IVA.

Statistical assessments were performed to compare children in the LUM/IVA cohort to children in the concurrent comparator cohorts, using descriptive summary statistics, relative risks (RRs), and 95% CIs. RR is calculated relative to the comparator as: Risk in LUM/IVA Cohort/Risk in Comparator Cohort. Summary statistics of study outcomes in the LUM/IVA and concurrent comparator cohorts during the baseline period and in each year of follow-up were provided. In addition, change from baseline was estimated for the growth parameters, and 95% CIs were obtained from two-sample *t*-tests for differences. Growth parameters

were calculated using World Health Organization child growth standards for all children aged <2 years (during the pre-treatment baseline period) and Centers for Disease Control and Prevention standards for children aged ≥2 years. Missing values were not imputed.

3. Results

3.1. Cohort characteristics

A total of 1014 children were identified as being 2 through 5 years of age at LUM/IVA treatment initiation at the end of the cohort entry period (31 December 2020). During this same period, 793 children were eligible for inclusion in the *F*/MF concurrent comparator cohort and 195 for inclusion in the *F/F* concurrent comparator cohort.

Following individual 1:1 matching based on age, sex, and BMI-for-age *z*-score, 681 matched pairs were formed between the LUM/IVA cohort and *F*/MF concurrent comparator cohort and 183 matched pairs between the LUM/IVA cohort and *F/F* concurrent comparator cohort (Fig. 1; Figure S1). Matched cohorts were generally well balanced on pretreatment baseline values of age, sex, and BMI-for-age *z*-score (Table 1). At the time of this interim analysis, mean exposure to LUM/IVA was 23.0 (SD: 5.43) months in the LUM/IVA cohort matched to the *F*/MF concurrent comparator cohort and 23.3 (SD: 5.57) months in the LUM/IVA cohort matched to the *F/F* concurrent comparator cohort.

3.2. Growth parameters

3.2.1. BMI percentiles

At pretreatment baseline (2018), BMI percentiles were similar between the LUM/IVA cohort and matched *F*/MF concurrent comparator cohort (mean [SD]: 48.5 [30.38] and 48.7 [30.20], respectively) and between the LUM/IVA cohort and matched *F/F* concurrent comparator cohort (42.2 [32.10] and 42.0 [32.94], respectively) (Table 1). During follow-up, BMI percentiles increased from baseline in the LUM/IVA cohorts, while they decreased in both concurrent comparator cohorts (Fig. 2; Table S1). The mean difference in absolute change from baseline was 8.4 (95% CI: 5.5, 11.3) between the LUM/IVA cohort and the *F*/MF concurrent comparator cohort and 11.8 (95% CI: 5.9, 17.7) between the LUM/IVA cohort and the *F/F* concurrent comparator cohort.

3.2.2. Height percentiles

Baseline height percentile was lower in the LUM/IVA cohort versus the *F*/MF concurrent comparator cohort (mean [SD]: 44.2 [28.60] and 47.9 [29.24], respectively), and in the LUM/IVA cohort versus the *F/F* concurrent comparator cohort (mean [SD] 41.3 [28.22] and 51.5 [30.77], respectively) (Table 1). During follow-up, height percentiles increased from baseline in the LUM/IVA cohorts and the magnitude of increase was greater than the increases seen in both concurrent comparator cohorts (Fig. 2; Table S1). The mean difference in absolute change from baseline was 3.6 (95% CI: 1.5, 5.8) between the LUM/IVA cohort and the *F*/MF concurrent comparator cohort and 5.5 (95% CI: 1.2, 9.9) between the LUM/IVA cohort and the *F/F* concurrent comparator cohort (Fig. 2; Table S1).

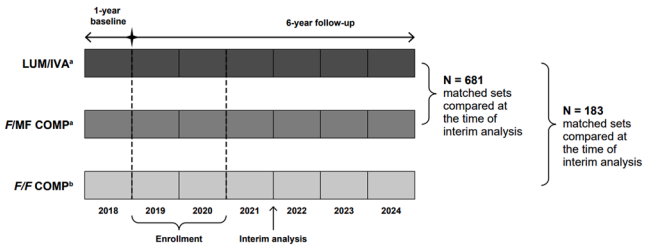

Fig. 1. Study Design.
CFTR: cystic fibrosis transmembrane conductance regulator; COMP: comparator; *F/F*: homozygous for *F508del-CFTR; F*/MF: heterozygous for *F508del* and a minimal function mutation; LUM/IVA: lumacaftor/ivacaftor.
[a]Data from 11 countries with LUM/IVA access in 2020: Austria, Denmark, France, Germany, Ireland, Luxembourg, the Netherlands, Slovenia, Sweden, Switzerland, and the UK.
[b]Data from six countries without LUM/IVA access in 2020 with clinical outcomes comparable to those in countries with LUM/IVA access: Croatia, Czech Republic, Italy, Latvia, Norway, and Poland.

Table 1
Baseline (2018) Characteristics and Demographics.

Characteristic[b]	Matched to *F*/MF COMP[a] LUM/IVA *N* = 681	*F*/MF COMP *N* = 681	Matched to *F/F* COMP[a] LUM/IVA *N* = 183	*F/F* COMP *N* = 183
Age at baseline, years, mean (SD)[c]	2.9 (1.36)	2.9 (1.37)	2.9 (1.59)	3.0 (1.61)
Female, n (%)	317 (46.5)	317 (46.5)	88 (48.1)	88 (48.1)
BMI-for-age *z*-score at baseline, mean (SD)	−0.1 (1.18)	−0.1 (1.18)	−0.3 (1.26)	−0.4 (1.33)
BMI percentile at baseline, mean (SD)	48.5 (30.38)	48.7 (30.20)	42.2 (32.10)	42.0 (32.94)
Height-for-age *z*-score at baseline, mean (SD)	−0.2 (1.07)	−0.1 (1.11)	−0.3 (1.07)	0 (1.22)
Height percentile at baseline, mean (SD)	44.2 (28.60)	47.9 (29.24)	41.3 (28.22)	51.5 (30.77)
Weight-for-age *z*-score at baseline, mean (SD)	−0.4 (1.14)	−0.2 (1.05)	−0.6 (1.09)	−0.4 (1.35)
Weight percentile at baseline, mean (SD)	41.2 (29.19)	43.7 (28.49)	33.3 (26.90)	41.3 (31.12)
Pulmonary exacerbations leading to hospitalization at baseline, n/N1 (%)	127/680 (18.7)	101/679 (14.9)	40/182 (22.0)	39/181 (21.5)

BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; COMP: comparator; *F/F*: homozygous for *F508del-CFTR; F*/MF: heterozygous for *F508del* and a minimal function mutation; LUM/IVA: lumacaftor/ivacaftor.
[a] The LUM/IVA cohort was matched 1:1 to the comparator cohorts on age, sex, and BMI-for-age *z*-score.
[b] n is the number of children with an event; N is the total cohort size; N1 is the number of children with a non-missing measurement of the outcome. Denominators for percentages are the total cohort size (i.e., N, N1).
[c] Age as of 31 December 2018.

3.2.3. Weight percentiles

Baseline weight percentile was lower in the LUM/IVA cohort versus the *F*/MF concurrent comparator cohort (mean [SD]: 41.2 [29.19] and 43.7 [28.49], respectively) and in the LUM/IVA cohort versus the *F/F* concurrent comparator cohort (mean [SD] 33.3 [26.90] and 41.3 [31.12], respectively) (Table 1). The mean difference in absolute change from baseline was 8.0 (95% CI: 5.7, 10.3) between the LUM/IVA cohort and the *F*/MF concurrent comparator cohort and 11.8 (95% CI: 7.3, 16.4) between the LUM/IVA cohort and the *F/F* concurrent comparator cohort (Fig. 2; Table S1).

Changes in BMI-for-age, height-for-age, and weight-for-age *z*-scores were consistent with changes in growth percentiles (Table S2).

3.3. PEx

The proportion of children who experienced ≥1 PEx leading to hospitalization during the pre-treatment baseline year (2018) was higher in the LUM/IVA cohort (18.7%) than in the *F*/MF concurrent comparator cohort (14.9%), but the proportions were similar between the matched LUM/IVA cohort (22.0%) and the *F/F* comparator cohort (21.5%) (Fig. 3; Tables 1 and S3). From baseline to 2021, the proportion of children experiencing PEx leading to hospitalization declined in the LUM/IVA cohorts and the *F*/MF concurrent comparator cohort, whereas it remained stable in the *F*/F concurrent comparator cohort. The percent

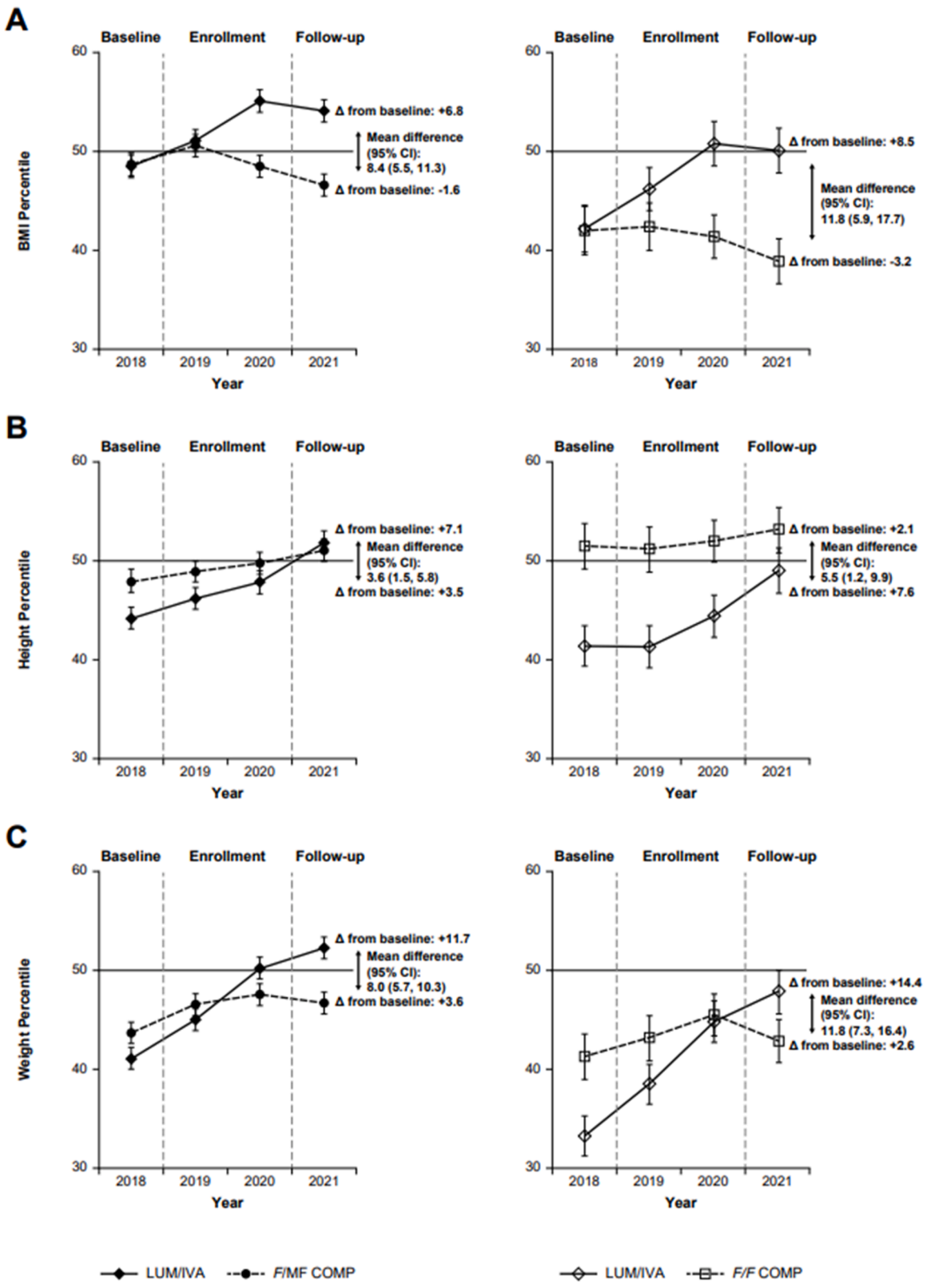

Fig. 2. Changes in A) BMI, B) Height, and C) Weight Growth Parameter Percentiles in the Matched LUM/IVA and *F*/MF and *F/F* Concurrent Comparator Cohorts From Baseline.
BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; *F/F*: homozygous for *F508del-CFTR; F*/MF: heterozygous for *F508del* and a minimal function mutation; LUM/IVA: lumacaftor/ivacaftor.

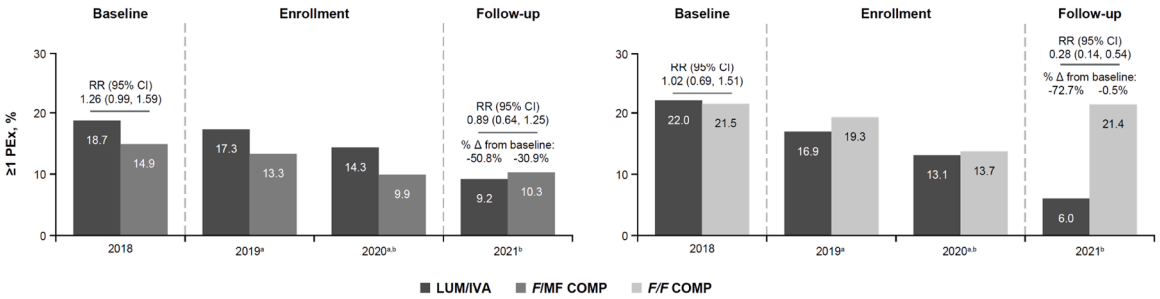

Fig. 3. Proportion of Children who Experienced ≥1 PEx Leading to Hospitalization in the Matched LUM/IVA and *F*/MF and *F/F* Concurrent Comparator Cohorts. The vertical dotted lines delineate the baseline/enrollment and post-enrollment follow-up periods. RR is calculated relative to the comparator as: Risk in LUM/IVA Cohort/Risk in Comparator Cohort. The percent change from baseline is calculated as: (Proportion with ≥1 PEx in 2021 – Proportion with ≥1 PEx in 2018) / Proportion with ≥1 PEx in 2018 × 100.

CFTR: cystic fibrosis transmembrane conductance regulator; COMP: comparator; *F/F*: homozygous for *F508del-CFTR;* *F*/MF: heterozygous for *F508del* and a minimal function mutation; LUM/IVA: lumacaftor/ivacaftor; PEx: pulmonary exacerbations; RR: relative risk.

[a]Treatment effect is not expected to be notable during enrollment years and some PEx could have occurred prior to enrollment.

[b]Outcome patterns in 2020 and 2021 are potentially affected by the COVID-19 pandemic.

change was −50.8% in the LUM/IVA cohort versus −30.9% in the *F*/MF concurrent comparator cohort and −72.7% in the LUM/IVA cohort versus −0.5% in the *F*/F concurrent comparator cohort. In 2021, the LUM/IVA cohort matched to the *F*/MF concurrent comparator cohort had a comparable (numerically lower but not significant) risk of PEx leading to hospitalization (RR: 0.89; 95% CI: 0.64, 1.25), and that matched to the *F/F* concurrent comparator cohort had a lower risk (RR: 0.28; 95% CI: 0.14, 0.54).

3.4. Hospitalizations

The proportion of children who experienced any hospitalizations during the pre-treatment baseline year (2018) was higher in the LUM/IVA cohort (36.9%) than in its *F*/MF concurrent comparator cohort (29.7%), whereas the opposite was seen when comparing the LUM/IVA cohort (38.7%) to the *F/F* concurrent comparator cohort (55.2%) (Figure S2; Table S3). From baseline to 2021, the proportion of children experiencing any hospitalization declined in all cohorts. The percent change was −50.9% in the LUM/IVA cohort versus −41.1% in the *F*/MF concurrent comparator cohort and −60.2% in the LUM/IVA cohort versus −35.5% in the *F*/F concurrent comparator cohort. In 2021, the LUM/IVA cohort and the *F*/MF concurrent comparator cohort had a comparable annual risk of hospitalizations (RR: 1.03; 95% CI: 0.82, 1.31), while the LUM/IVA cohort had a lower annual risk of hospitalizations compared to the *F/F* concurrent comparator cohort (RR: 0.43; 95% CI: 0.29, 0.65).

3.5. Death and organ transplant

No deaths or organ transplants occurred in the LUM/IVA cohorts or the *F/F* concurrent comparator cohort; one death and no organ transplants occurred in the *F*/MF concurrent comparator cohort.

3.6. CF medications, CF complications, and pulmonary microbiology

No clear trends were observed in the proportion of children using CF medications across cohorts (Table S4), and no discernable patterns in CF complications (Table S5) or pulmonary microbiology were found (Table S6).

4. Discussion

For this ongoing post-authorization study, we identified children in the ECFSPR who were aged 2 through 5 years at LUM/IVA initiation, as well as matched *F*/MF and *F/F* concurrent comparator cohorts. Children in the LUM/IVA cohort had improved growth parameters (BMI-for-age, height-for-age, and weight-for-age *z*-scores and percentiles) compared with the modulator-naïve *F*/MF and *F/F* comparator cohorts. Reductions in PEx and hospitalizations were also seen in the LUM/IVA cohort relative to baseline and the *F/F* comparator cohort. There were no discernible trends or differences relative to the comparators in CF medication use, CF complications, and pulmonary microbiology.

At baseline, children in all cohorts were either slightly below or at the 50th BMI percentile (i.e., median). During the interim analysis period, mean BMI percentile increased in the LUM/IVA cohorts but decreased in the modulator-naïve comparator cohorts. Improvements in growth parameters following LUM/IVA initiation have also been seen in other real-world studies, including a 24-month observational cohort study of LUM/IVA in older children (aged 6 through 11 years) with CF conducted in Ireland, which found improvements from baseline in weight-for-age, height-for-age, and BMI-for-age *z*-scores with LUM/IVA treatment [16]. Furthermore, in a recent phase 2, placebo-controlled, 48-week trial in children aged 2 through 5 years with CF, LUM/IVA treatment also led to improvements in growth parameters compared with placebo [17]. These results demonstrate that early initiation of LUM/IVA treatment has the potential to provide clinically meaningful growth benefits to children with CF.

In adults, the occurrence of PEx has been shown to be associated with reductions in lung function, decreases in quality of life, and increased mortality [1]. During the first interim analysis period of this study, the proportion of children who experienced at least one PEx leading to hospitalization decreased to < 10% in the LUM/IVA cohort. This finding is consistent with those of other studies, which have also observed decreases in PEx rates in both children and adults following LUM/IVA initiation [16,18], and suggests the potential for early initiation of LUM/IVA to also have a beneficial impact on pulmonary function in people with CF.

The current study has limitations. Because this is the first interim analysis of an ongoing study, results should be interpreted with caution due to the relatively short follow-up. Longer follow-up may reveal additional information on trends in CF medication use, CF complications, and pulmonary microbiology following the initiation of LUM/IVA treatment, as well as lung function trends as children age and accumulate reliable spirometry data. The LUM/IVA cohort matched to the *F/F* comparator cohort was limited in size due to the relatively small number of children eligible to be included in the *F/F* comparator cohort, and may have been subject to selection bias. Although the LUM/IVA cohorts were matched to comparator cohorts based on age, sex, and BMI-for-age *z*-score, residual confounding by other factors is also possible. For example, there may be systematic differences in the standard of care between countries with and without commercial access to LUM/IVA. Furthermore, young patients with CF initiating LUM/IVA may have been

followed up more closely than untreated patients with CF, leading to differences in ascertainment of outcomes. Even though the LUM/IVA cohorts and the comparator cohorts were matched on BMI-for-age z-score, imbalances in height and weight *z*-scores were observed at baseline.

Data collected by registries may have missing information, which could introduce misclassification of exposure and outcomes. Although evidence of structural lung damage is present early in life, prominent loss of pulmonary function as measured by FEV_1 is not expected before children reach adolescence; in the current study, FEV_1 data were limited due to the patients' young age, and no children had spirometry data at baseline since all were aged <6 years at baseline. Finally, the precise dates of the development of CF complications in patients contributing data to the registries were not available. Since dates were available for LUM/IVA treatment initiation, but not for the start of complications, the temporal relationship between LUM/IVA treatment initiation and development of CF complication cannot be determined.

This interim analysis period overlapped with the COVID-19 pandemic, and implementation of social distancing measures, restrictions on social interactions, and the use of masks might have impacted some of the outcomes evaluated in this study, including PEx and hospitalizations [19]. However, it is important to note that any potential impact of the COVID-19 pandemic would have likely had the same effect across the concurrent cohorts.

The availability of new CFTR modulator therapies is likely to impact the assessment of long-term outcomes in this study. During the follow-up period of this interim analysis, some children aged into the 6 years and older age group, thereby becoming eligible to initiate TEZ/IVA and ELX/TEZ/IVA. As a result of recent regulatory approvals, people with CF ages 2 years and older who have at least one *F508del* mutation now have access to ELX/TEZ/IVA in the US and some European countries. Although it is expected that many of the children in this study will be censored following their initiation of ELX/TEZ/IVA, those children whose treatment status remains unchanged will continue to be followed up through the end of 2024. The findings from the present analysis will still be relevant for guiding treatment decisions for children with CF, especially for those who only have access to LUM/IVA.

5. Conclusion

The results of this first interim analysis of an ongoing 6-year, real-world, observational study showed early favorable trends in clinical outcomes, including growth parameters, PEx, and hospitalizations, in children with CF who initiated LUM/IVA treatment between the ages of 2 and 5 years in the ECFSPR. Overall, these data suggest an early beneficial effect on CF disease progression with LUM/IVA treatment in children aged 2 through 5 years at initiation.

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CRediT authorship contribution statement

Claire Kim: Investigation, Writing – original draft, Writing – review & editing. **Mark Higgins:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Lingyun Liu:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Nataliya Volkova:** Writing – review & editing. **Anna Zolin:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Lutz Naehrlich:** Investigation, Writing – review & editing.

Declaration of competing interest

CK, MH, LL, NV: employees of Vertex Pharmaceuticals and may own stock or stock options in Vertex Pharmaceuticals. AZ: acting as statistician for the ECFSPR. LN: acting pharmacovigilance study manager of the ECFSPR; institutional fees for study participation from Vertex Pharmaceuticals and the German Center for Lung Research.

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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.2024.02.004.

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