Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis

Running title: Real-life study of lumacaftor-ivacaftor

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ABSTRACT

Rationale: Lumacaftor-ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) modulator combination recently approved for patients with cystic fibrosis (CF) homozygous for the Phe508del mutation.

Objectives: To evaluate the safety and effectiveness of lumacaftor-ivacaftor in adolescents (≥12 years) and adults (≥18 years) in a real-life post-approval setting.

Methods: The study was conducted in the 47 CF reference centers in France. All patients who initiated lumacaftor-ivacaftor from January 1st to December 31st 2016 were eligible. Patients were evaluated for lumacaftor-ivacaftor safety and effectiveness over the first year of treatment following the French CF learning society's recommendations.

Main Results: Among the 845 patients (292 adolescents, 553 adults) who initiated lumacaftor-ivacaftor, 18.2% (154 patients) discontinued treatment, often due to respiratory (48.1%, 74 patients) or non-respiratory (27.9%, 43 patients) adverse events. In multivariable logistic regression, factors associated with increased rates of discontinuation included adult age group, percent predicted forced expiratory volume in 1 sec ($ppFEV_1$)<40% and numbers of intravenous antibiotic courses during the year prior to lumacaftor-ivacaftor initiation. Patients with continuous exposure to lumacaftor-ivacaftor showed an absolute increase in $ppFEV_1$ (+3.67%), an increase in body mass index (+0.73 kg/m^2), and a decrease in intravenous antibiotic courses by 35%. Patients who discontinued treatment had significant decrease in $ppFEV_1$, without improvement in BMI or decrease in intravenous antibiotic courses.

Conclusions: Lumacaftor-ivacaftor was associated with improvement in lung disease and nutritional status in patients who tolerated treatment. Adults who discontinued lumacaftor-ivacaftor, often due to adverse events, were found at high risk of clinical deterioration.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which acts as a chloride and bicarbonate ion channel across many epithelia (1). Defective ion transport leads to multiple organ dysfunction, but airway involvement (related to mucus plugging and infection) and malnutrition are among the most important prognostic factors in patients with CF (2, 3). Over the past decades, symptomatic treatment, including inhaled and systemic antibiotics, nutritional support, pancreatic enzyme replacement, and specialized center care organization have led to major prognostic improvement (4, 5). More recently, mutation-specific small molecules targeting defective CFTR have been shown to partly restore ion transport in epithelia, which translated into clinical benefits (6, 7).

Phe508del is the most common *CFTR* mutation with approximately 70% of patients with CF carrying one Phe508del mutation and 40-50% of patients being homozygous for this mutation (8). Safety and efficacy of lumacaftor-ivacaftor have been reported in phase 3 clinical trials in patients 12 years of age or older who had CF and were homozygous for the Phe508del (7, 9). Improvement in lung function, reduction in pulmonary exacerbations and a trend towards an increase in body mass index (BMI) led to its approval by the Food and Drug Administration in February 2015 and by the European Medicines Agency in November 2015. However, the magnitude of effect on percent predicted forced expiratory volume in 1 sec ($ppFEV_1$), the small improvement in nutritional status and the limited use of concomitant treatment for reducing exacerbations have cast doubt on the clinical benefits associated with lumacaftor-ivacaftor (10, 11), which has not been approved in several countries. A recent real-life study in 41 adolescents and young adults homozygous for the Phe508del mutation has further highlighted the heterogeneity of the clinical response to treatment with lumacaftor-ivacaftor over 6 months (12). The safety profile of lumacaftor-ivacaftor seemed acceptable in phase 3 clinical trials (7,

9) and in extension studies (13), but small real-life studies have suggested that respiratory adverse events (AEs) could lead to increased rates of lumacaftor-ivacaftor discontinuation, especially in subjects with $ppFEV_1$ below 40% (14-16), who were not included in phase 3 clinical trials. Thus, it was suggested that evaluation of the clinical impact of lumacaftor-ivacaftor in real-life cohorts would be important, especially with regards to its high cost (10).

The present study sought to evaluate the effects of lumacaftor-ivacaftor in a real-life setting after its release in France in December 2015. An observational study of all patients who initiated lumacaftor-ivacaftor in 2016 in the French CF reference network, which comprises 47 pediatric and/or adult centers, was performed. Our goal was to examine its safety and effectiveness over the first year of treatment in a large, unselected, population of adolescents (≥12 years) and adults (≥18 years) with CF and Phe508del homozygous mutations. Some of the results of these studies have been previously reported in the form of an abstract (17).

METHODS

Study design

The present study was a multicenter (n=47 centers) observational study (NCT03475381) aimed at evaluating the effects of lumacaftor-ivacaftor treatment in a real-life setting in France. The study was approved by the Institutional Review Board of the French Society for Respiratory Medicine - *Société de Pneumologie de Langue Française*- (#2016-004). All patients received information about the study, but written consent was not necessary in accordance with French laws. Following the recommendations of the French CF learning Society, all patients who started lumacaftor-ivacaftor had systematic visits (with clinical assessment and pulmonary function test) at treatment initiation and at 1, 3, 6 and 12 months after starting treatment; respiratory and non-respiratory AEs were prospectively collected and recorded in patient charts by the caring physicians. At each visit, weight, height, BMI, and $ppFEV_1$ were recorded. Numbers of intravenous antibiotic courses and days were recorded in the 12 months before and the 12 months after lumacaftor-ivacaftor initiation. Recommended clinical laboratory assessment included alanine aminotransferase, aspartate aminotransferase (at each visit) and creatine phosphokinase (at 0, 1 and 12 months). All patients (including those who discontinued lumacaftor-ivacaftor) were followed for 12 months after lumacaftor-ivacaftor initiation.

Statistics

Data are presented as % (n), median [interquartile range, IQR] or mean ± standard deviation (SD). Probability of treatment discontinuation between groups (e.g., adults vs. adolescents, $ppFEV_1$<40% vs. ≥40%, patients with 0, 1 or 2+ IV antibiotic courses during the 12 months prior to lumacaftor-ivacaftor initiation) were analyzed using Kaplan-Meyer analysis and Log-Rank test. Intragroup (i.e., continuous treatment, intermittent treatment and discontinued treatment groups) comparison of changes of weight, BMI, and $ppFEV_1$ from baseline to 12

months of follow-up were performed using Wilcoxon's paired test. Difference in best $ppFEV_1$ observed in the 12 months before *vs*. the 12 months after lumacaftor-ivacaftor initiation were calculated. Comparisons of the number of IV antibiotics courses in the 12 months before vs. the 12 months after lumacaftor-ivacaftor initiation were performed using paired McNemar's test for nominal data and paired t-tests for quantitative data. Baseline variables associated with increased risk of treatment discontinuation from any cause or from respiratory AEs were analyzed by stepwise forward/backward logistic regression methods. Variables included in this latter analysis were those with a *P* value <0.10 in bivariate analysis. A *P* value<0.05 was considered statistically significant. All analyses were performed using SAS software version 9.4.

RESULTS

Patient population

Between January 1st and December 31st 2016, 845 patients (292 adolescents, 553 adults) initiated treatment with lumacaftor-ivacaftor in the 47 centers of the French CF Reference Network (see **online Figure S1** for additional information on numbers of F508del homozygous patients in France). Characteristics of patients at treatment initiation are presented in **Table 1**. Lumacaftor-ivacaftor was initiated at full dose (twice daily lumacaftor 400 mg/ivacaftor 250 mg therapy) in 88% of patients, with the remaining 12% of patients starting treatment at reduced doses due to suspected drug interactions (n=74) or miscellaneous reasons (n=26).

Treatment discontinuation

During the first year after lumacaftor-ivacaftor initiation, 641 patients (75.6%) received continuous treatment, 39 patients (4.6%) received intermittent treatment (i.e., discontinued and reintroduced during the study time) and 154 patients (18.2%) discontinued treatment (without

reintroduction during the study time) treatment. Follow-up data were missing in 11 patients (1.3%).

Treatment discontinuation (without reintroduction during the study time) occurred in 17.3% (129/745) of patients who started lumacaftor-ivacaftor at full dose *vs*. 25.0% (25/100) of patients who started lumacaftor-ivacaftor at reduced doses (*P*=0.062).

Median [IQR] follow-up time in patients who received continuous treatment, intermittent treatment or who discontinued treatment were 369 [357; 385] days, 370 [349; 397] days and 363 [335; 391] days, respectively. Median [IQR] time under treatment was shorter in patients who discontinued treatment (90 [25; 179] days) and in those with intermittent treatment (322 [255; 349] days) than in patients with continuous treatment (369 [357; 385] days; all comparisons, *P*<0.01).

Reasons for treatment discontinuation in 154 patients are presented in **Table 2**. The two main reasons for treatment discontinuation were respiratory (48.1%) and non-respiratory AEs (27.9%). Median [IQR] time to treatment discontinuation due to respiratory AEs (n=74) was 42 [10-98] days *vs.* 127 [79-210] days for discontinuation due to other causes (n=80; *P*<0.0001). Rates of lumacaftor-ivacaftor discontinuation were significantly higher in adults than in adolescents (23.5% vs. 8.2%; *P*<0.0001, **Figure 1A**), in patients with $ppFEV_1$<40% vs. ≥40% (28.2% vs. 16.3%; *P*<0.0001, **Figure 1B**), and in patients with repeated IV courses in the previous year (**Figure 1C**). Baseline patient characteristics that were found to be associated with increased risk of treatment discontinuation from any cause or from respiratory AEs in multivariable logistic regressions are presented in **Table 3.** Preexisting CF liver disease (i.e., liver cirrhosis/portal hypertension or elevated liver enzymes) were not associated with increased risk of treatment discontinuation (see online Table S1).

Reasons for temporary discontinuation and reintroduction of lumacaftor-ivacaftor during the study time (intermittent treatment) included respiratory adverse events (n=16 patients), non-respiratory adverse events (8 patients), and miscellaneous reasons (n=11) including pregnancy, sperm aspiration procedure, and drug interaction.

Among 90 patients who discontinued lumacaftor-ivacaftor at least once during the study time for respiratory AEs, treatment reintroduction was attempted in 32 patients: 16 patients were able to continue lumacaftor-ivacaftor after reintroduction (and were assigned to the "intermittent treatment" group), whereas 16 patients had to discontinue lumacaftor-ivacaftor without restarting during the study (and were assigned to the "discontinued treatment" group).

Adverse events

AEs considered by treating physicians as possibly associated with lumacaftor-ivacaftor were reported in 59.4% (494 patients). AEs with a prevalence ≥2% were respiratory AEs (38%, n=316), digestive AEs (21.8%, n=181), menstrual abnormality (6.4%, n=53), fatigue (4.4%, n=37) and headache (3.3%, n=19). AEs, including respiratory and digestive AEs, were mostly observed in the first months of treatment and decreased gradually over time. Although these findings were due, in part, to decrease in the number of patients exposed to lumacaftor-ivacaftor secondary to treatment discontinuation (that occurred mostly in patients with adverse events), decrease in the occurrence of AEs over time was also observed in patients treated continuously over 12 months (n=641; **see online Figure S2**). AEs were more prevalent in patients with diabetes (65.4% vs. 56.8%; *P*=0.024; see online Table S3).

Only five patients had elevated liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) elevations greater than three times the upper limit of normal (ULN) at any time during the study period. Four of these latter patients had preexisting CF liver disease (2 with liver cirrhosis/portal hypertension, 2 with elevated liver enzyme before starting

lumacaftor/ivacaftor). Elevation of liver enzymes lead to lumacaftor-ivacaftor discontinuation in two patients (including one patient with a history of liver cirrhosis/portal hypertension) after 6 months and 12 months of treatment, respectively, due to elevations greater than six times the ULN. Detailed liver data for the five patients are shown in online Table S2.

Elevations of creatine phosphokinase (CPK) greater than five times the ULN occurred in twenty patients and lead to discontinuation of lumacaftor-ivacaftor in two patients with elevations greater than 10 times ULN and myalgia.

Effectiveness

Lung function

Improvement in $ppFEV_1$ from baseline was observed in the overall population as soon as one month after starting lumacaftor-ivacaftor and persisted over 12 months (**see online Figure S3)**. At 12 months post initiation, absolute change in $ppFEV_1$ from baseline was +2.7±8.86% (n=821 patients; Wilcoxon's paired test, $P<0.001$); improvement in $ppFEV_1$ was observed in patients with continuous (+3.67 ±8.62%; n=631 patients; $P<0.001$) and in those with intermittent treatment (+2.36±8.47%; n=45 patients; $P=0.09$), whereas patients who discontinued lumacaftor-ivacaftor had a decrease in $ppFEV_1$ (-1.36±9.03%; n=145 patients; Wilcoxon's paired test, $P=0.07$; see **Figure 2**). These effects were observed in both adolescents and adults (see **Figure 2**), although the decrease in FEV_1 in patients who discontinued lumacaftor-ivacaftor was mostly observed in adults. Note that the graphs in **Figure 2** were plotted using all available data, resulting in numerical differences with the data presented in the text, which were obtained using paired analysis (leading to the exclusion of a limited number of data).

To examine whether the magnitude of FEV_1 increase was greater in adolescents vs. adults, we first examined FEV_1 variations from baseline in each population. Because this analysis was

markedly biased by the differential rate of treatment discontinuation (that occurred mostly in adults), it was then limited to patients who received continuous treatment over 1 year: the absolute increase in $ppFEV_1$ was 4.76±8.17% and 2.91±8.85% in adolescents (n=258 patients) and adults (n=373 patients), respectively (P<0.001 in each group vs. baseline, and P=0.008 when comparing adolescents vs. adults).

Examining rates of patients with clinically significant changes in FEV_1, the difference in best $ppFEV_1$ between the 12 months before and the 12 months after initiation of lumacaftor-ivacaftor was following a Gaussian distribution (see **Figure S4**). Among patients who received continuous or intermittent treatment with lumacaftor-ivacaftor, approximately 40% and 20% experienced an absolute increase in $ppFEV_1$ of 5% and 10%, respectively (**Figure 3**).

Weight and body mass index

Weight gain (mean, +2.1 kg) and BMI (mean, +0.5 kg/m^2) increase were observed in the overall cohort over the 12 months after treatment initiation (see **online Figure S5**). Weight gain (see **online Figure S6**) and BMI increase (see **Figure 2**) were steady and regular in patients with continuous treatment but delayed in those with intermittent treatment; patients who discontinued lumacaftor-ivacaftor had no weight gain. Although weight gain (see **online Figure S6**) and increase in BMI z-scores (see **Figure 2**) were observed in all groups of adolescents, analyses performed in the adult population confirmed that weight gain and BMI increase occurred in adults who received continuous or intermittent treatment, but not in those who discontinued treatment (see **Figure 2**).

Intravenous antibiotic courses

Data on IV antibiotic courses in the 12 months before and/or the 12 months after lumacaftor-ivacaftor initiation was missing in 5.7% (48/845) of patients and analyses on IV antibiotic courses were therefore performed for 797 patients. Patients with continuous exposure to

lumacaftor-ivacaftor had 1.18±1.60 vs. 0.77±1.38 IV antibiotic courses/patient in the 12 months before vs. the 12 months after lumacaftor-ivacaftor initiation (n=626 patients, $P<0.001$, paired t-test), corresponding to a 35% reduction overall. Patients with intermittent exposure to lumacaftor-ivacaftor had 1.44±1.87 vs. 1.50±1.84 IV antibiotic courses/patient in the 12 months before vs. the 12 months after lumacaftor-ivacaftor initiation (n=36 patients, $P=0.98$). Patients with treatment discontinuation had 1.82±1.93 vs. 1.82±2.04 (n=136 patients; $P=0.18$). Distribution of the number of IV antibiotic courses in the 12 months before and the 12 months after lumacaftor-ivacaftor initiation by subgroups is presented in **Figure 4**.

Vitamins and HbA1C

Comparing serum levels of vitamin A, 25OHD, and vitamin E before the onset of treatment and one year after lumacaftor-ivacaftor initiation, we found no evidence of increase in vitamin serum level under lumacaftor-ivacaftor (see detailed data in Online Table S4). Surprisingly, serum levels of vitamin 250HD were significantly lower in patients treated continuously by lumacaftor-ivacaftor.

HbA1C levels were examined in patients with diabetes. No decrease in HbA1C levels were found during treatment with lumacaftor-ivacaftor (see online Table S4).

DISCUSSION

The present study examined the 12-month safety and effectiveness of lumacaftor-ivacaftor in a large nationwide cohort of adolescents and adults with CF homozygous for Phe508del *CFTR*. Lumacaftor-ivacaftor was discontinued in 18.2% of patients, most due to respiratory AEs and, to a lesser extent, to non-respiratory AEs. Significant improvements in $ppFEV_1$ and in body weight and BMI, and reduction in the number of IV antibiotic courses were observed in the overall cohort. These results were driven by patients who received prolonged (continuous or intermittent) exposure to lumacaftor-ivacaftor, whereas patients in whom lumacaftor-ivacaftor

was discontinued had a significant decrease in $ppFEV_1$, no increase in body weight or BMI and no decrease in the use of IV antibiotics.

The proportion of patients (18.2%) who discontinued lumacaftor-ivacaftor was markedly higher in this study compared with pivotal clinical trials, where less than 5% of patients discontinued lumacaftor-ivacaftor (7, 9). These findings were likely related to a higher proportion of patients with severe respiratory disease (i.e., $ppFEV_1$<40% and several IV antibiotic courses in the previous year) compared with pivotal clinical trials. Thus, the rate of lumacaftor-ivacaftor discontinuation was 28.2% in patients with $ppFEV_1$<40% and $ppFEV_1$<40% was independently associated with treatment discontinuation, confirming previous studies (14, 16). However, the rates of discontinuation in patients with FEV_1≥40% (16.3%) were more than three times higher than in the phase 3 study. Our results extend previous results by showing that repeated exacerbations treated with IV antibiotics in the year prior to lumacaftor-ivacaftor initiation were also independently associated with treatment discontinuation. Rates of treatment discontinuation were markedly increased in adults vs. adolescents, independently of lung function and exacerbations, suggesting that other factors (e.g., comorbidities, which are more prevalent in adults than in adolescents) could have contributed to these findings. In support of these suggestions, bivariate analyses showed that rates of AEs and treatment discontinuation appeared increased in patients with diabetes. Finally, rather high rates (25%) in treatment discontinuation were found in patients in whom the caring physicians decided to start lumacaftor-ivacaftor at reduced doses before increasing to full doses. Although a recent study that suggested that starting lumacaftor-ivacaftor at reduced dose may be associated with a better safety profile in patients at high risk of adverse events (16), our data suggest that starting at low doses will not prevent treatment discontinuation in many patients.

The liver-related adverse event profile appeared encouraging, despite the inclusion of 5% of subjects with a previous history of liver cirrhosis/portal hypertension. Only 5 patients showed grade 3 and higher liver enzyme elevation and only two patients discontinued lumacaftor-ivacaftor due to liver-related adverse event. These data suggest that lumacaftor-ivacaftor could be well tolerated in most patients with CF-related liver disease, although the decision to treat or not to treat with lumacaftor-ivacaftor should consider the risk of liver-related AEs.

The present study also showed that patients receiving 12 months of lumacaftor-ivacaftor had significant improvement in $ppFEV_1$, weight and BMI, and reduction in the number of IV antibiotic courses compared with baseline. These data largely confirmed data obtained in more selected populations in pivotal clinical trials (9, 18) and goes further by (1) showing that approximately 40% and 20% of patients treated with lumacaftor-ivacaftor as an add-on to standard therapy show an absolute increase in $ppFEV_1$ by 5% and 10%, respectively (2) examining the number of exacerbations over 12 months as compared to 6 months in pivotal clinical trials and by comparing the number of IV courses with lumacaftor-ivacaftor according to the number of exacerbations in the previous year. Finally, we found no significant improvement in vitamin A, 25OHD and vitamin E serum levels in patients treated with lumacaftor-ivacaftor. HbA1C, a marker of diabetes control, was unchanged in diabetic patients treated with lumacaftor-ivacaftor. These data suggest that lumacaftor-ivacaftor is associated with clinically significant benefits in patients with CF who were able to tolerate this treatment regimen.

One-year treatment with lumacaftor-ivacaftor resulted in modest FEV_1 improvement, but also in a reduction by 35% of exacerbations and in a reduction of the proportion of patients with frequent exacerbations (≥2/patients/year). Patients with frequent exacerbations appear to experience an accelerated decline in lung function, and have an increased 3-year risk of death or lung transplant (19). A recent post-hoc analysis of phase 3 clinical trials suggested that a

reduction in exacerbation frequency occurs independently of change in lung function observed in the first 15 days of treatment (20). These data underscore the need for multiple criteria to evaluate the response to CFTR modulators.

The present nationwide academic study was conducted in the well-established French CF Reference Center network, which includes 47 centers from all parts of France. The study was performed and funded independently from lumacaftor-ivacaftor manufacturer. All centers followed recommendations of the French CF Learning Society on systematic assessment of patients under CFTR modulators, including the systematic collection of AEs and data necessary to assess effectiveness (e.g., spirometry, weight and BMI, and IV antibiotic courses), resulting in a limited amount of missing data. We also recognize limitations. Although the first cause of lumacaftor-ivacaftor discontinuation was respiratory adverse events, only limited data was available on the use of concomitant treatment (e.g., long acting bronchodilators) which have been proposed for limiting these adverse events (21, 22). Rates of use of DNAse, inhaled corticosteroids and inhaled antibiotics were comparable between our study and phase 3 clinical trials (7). However, lesser patients were treated with bronchodilators (75.7% vs. 92.2%) and hypertonic saline (12.5% vs. 59.9%) in the present study vs. phase 3 clinical trials, respectively. The potential impact of these differences in background therapy on efficacy and adverse events is unclear. Furthermore, no data was available on exacerbations treated with oral antibiotics, as these events are extremely difficult to capture in multicenter studies outside of clinical trials. The rate of elevated transaminases was lower in this observational study than in the phase 3 randomized control trial (7); this finding could be related to less frequent sampling and variability of transaminases in CF patients in general. Finally, although three subgroups of patients were identified according to treatment pattern (continuous, intermittent, discontinuation) no attempt was made to compare outcomes among these subgroups, which were not randomized, had different baseline characteristics and presumably, varying disease

trajectories. Further analysis evaluating FEV_1 decline over a longer period can be performed when the data become available.

Results nonetheless confirm that treatment discontinuation was less prevalent in adolescents than in adults and suggest that the magnitude of lung function improvement could be greater in adolescents. Importantly, the adolescent population in this study exceeds that from the phase 3 clinical trials (7) as both an absolute number and as a percentage of those studied. These findings concur with the concept that starting CFTR modulators earlier in life could be an important strategy. Recent clinical trials have provided reassuring data on the safety profile of lumacaftor-ivacaftor in children aged 6-11 years (23) and 2-5 years (24), but these findings will have to be confirmed in post-marketing real-life studies, in which effectiveness can be assessed further.

This study also showed that adult patients who discontinued lumacaftor-ivacaftor (often due to respiratory AEs) had rapid FEV_1 decline, a BMI decrease and multiple respiratory exacerbations. As highlighted by the multivariable analysis examining risk factors for treatment discontinuation, these patients had more severe disease presentation at baseline, leading to the conclusion that these patients belonged to a group of patients requiring special attention to prevent lung function and nutritional decline. Recent data suggest that tezacaftor-ivacaftor, another CFTR modulator combination therapy, could show a better safety profile with lower rates of respiratory AEs (16, 25). Results of studies that examine the efficacy and safety of tezacaftor-ivacaftor in patients who discontinued treatment with lumacaftor-ivacaftor secondary to respiratory symptoms (26) will be important to determine optimal treatment strategies in patients who did not tolerate lumacaftor-ivacaftor. It is also anticipated that the triple combinations of CFTR modulators, for which phase 2 clinical studies were recently published (27, 28), will reshuffle therapeutic landscape. We suggest that eligible patients with severe disease who cannot tolerate lumacaftor-ivacaftor should be granted faster access to

tezacaftor-ivacaftor (which is unavailable in France at this time) or to triple combination therapy (once it becomes available).

In conclusion, the present study showed that 12 months of treatment with lumacaftor-ivacaftor was associated with significant improvement in lung function and nutritional status, and with a reduction in IV antibiotic courses in adolescents and adults with CF homozygous for Phe508del who tolerated the treatment. It highlighted the importance of large real-life studies to assess the safety and effectiveness profile of novel therapies because patients treated in post-marketing studies often show reduced lung function and less stable disease characterized by higher rates of exacerbations than those included in clinical trials. These data further indicate that the benefits and risks of new therapies cannot be extrapolated to patients who are excluded from clinical trials. The anticipated availability of novel combination of CFTR modulators and the extension of indications to younger age groups warrant further real-life study that should be launched as soon as the drugs become available in eligible populations.

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Legends of Figures

Figure 1. Probabilities of pursuing lumacaftor-ivacaftor over 1 year according to patient characteristics at baseline. 1A. Comparison of adults (≥18 years, n=553) vs. adolescents (12-17 years, n=292); discontinuation rates were 23.5% *vs*. 8.2% in adults and adolescents, respectively, *P*<0.001. 1B. Comparison of patients with $ppFEV_1$<40% (n=124) vs. ≥40% (n=714); discontinuation rates were 28.2% vs. 16.3% in subjects with $ppFEV_1$<40% vs. those with $ppFEV_1$≥40%, respectively, *P*<0.001. Missing values for $ppFEV_1$ at baseline (n=7). 1C. Comparison according to the number of IV antibiotic courses during the 12 months prior to lumacaftor-ivacaftor initiation. Rates of treatment discontinuation were 12.9% (46/347) in patients with no IV antibiotic course, 17.6% (33/188) in patients with 1 antibiotic course and 25.5% (69/271) in patients with 2 or more antibiotic courses; *P*=0.0002. Data were analyzed using Kaplan-Meier and Log-Rank test.

Figure 2. Change from baseline in percentage of predicted FEV_1 ($ppFEV_1$, left column) and in body mass index (BMI, right column).

Results are presented for all patients (12 years and older, upper panels), adults (18 years and older, middle panels) and adolescents (12-17 years, lower panels). In each figure, patients are grouped according to pattern of lumacaftor-ivacaftor exposure (continuous treatment, intermittent treatment and treatment discontinuation). Data are plotted at each time point using all available data, resulting in numerical differences between the absolute values presented in the graphs and the numbers shown in the text, which were obtained by paired analysis.

Figure 3. Distribution of the difference between the best $ppFEV_1$ in the 12 months after vs. the 12 months before lumacaftor-ivacaftor initiation in all patients. Data are presented by subgroup of treatment exposure: continuous treatment (top panel), intermittent treatment (middle panel), treatment discontinuation (lower panel). Numbers of patients are indicated on top of the bars.

Figure 4. Exacerbations requiring intravenous antibiotics in the 12 months before and the 12 months after lumacaftor-ivacaftor initiation by treatment exposure pattern.

The bars at the left show the proportions of patients with no exacerbation, one exacerbation, or two or more exacerbations in year prior to lumacaftor-ivacaftor initiation. The bars at the right show the proportion of patients with no exacerbation, one exacerbation or two or more exacerbations in the year after lumacaftor-ivacaftor initiation. Patients are grouped according to treatment exposure pattern (continuous treatment; intermittent treatment, treatment discontinuation). The number of patients with exacerbations was reduced only in patients with continuous treatment (paired analysis by McNemar test, $P<0.001$; n=618 patients), whereas no significant difference was observed in patients with intermittent treatment ($P=0.48$; n=36 patients) and in patients who discontinued treatment ($P=0.72$; n=137 patients). Data are presented as % (n) patients within each group.

Table 1. Characteristics of patients at the time of lumacaftor-ivacaftor initiation

	All patients n=845	**Adolescents (12-17 years) n=292 (34.6%)**	**Adults (≥18 years) n=553 (65.4%)**	***P* values**
Age, years	22.0 [16; 30]	15.0 [13.3 ; 16.3]	27.3 [22.8 ; 33.0]	<0.0001
Female sex	44.6% (377)	47.6% (139)	43.0% (238)	0.20
ppFEV$_1$	65 [47; 80]	70 [59; 81]	60 [43 ; 80]	<0.0001
ppFEV$_1$<40%	14.8% (124)	5.2% (15)	19.9% (109)	<0.0001
BMI, kg/m^2 **BMI, Z score**	19 [17 ; 21]	18 [16 ; 19] -0.60 [-1.22 ; -0.11]	20 [18; 21] -	<0.0001
P. aeruginosa				
None	39.0% (330)	55.1% (161)	30.6% (169)	<0.0001
Intermittent	12.0 (101)	18.5% (54)	8.5% (47)	
Chronic	48.5% (410)	26.0% (76)	60.4% (334)	
Missing	0.5% (4)	0.3% (1)	0.5% (3)	
B. cepacia	2.7% (23)	2.1% (6)	3.1% (17)	0.39
MSSA	67.1% (567)	76.0% (222)	62% (345)	<0.0001
MRSA	15.7 (133)	13.4% (39)	17.0% (94)	0.15
H. influenzae	13.7 (116)	16.4 (48)	12.3% (68)	0.10
Diabetes mellitus	28.4 (240)	15.8% (46)	35.1 (194)	<0.0001
Cirrhosis/portal hypertension	5.0 (42)	4.1 (12)	5.4% (30)	0.40
Elevated liver enzymes	12.1 (102)	12.0 (35)	12.1 (67)	0.96
≥1 IV antibiotic courses in the previous 12 months	54.6% (461)	37.3% (109)	63.7% (352)	<0.0001
Maintenance pulmonary medications at baseline				
Azithromycin	60.2% (509)	50.2% (146)	65.4% (355)	<0.0001
Inhaled antibiotics	61.1% (516)	53.6% (156)	65.2% (354)	0.001
Dornase alfa	68.8% (581)	81.8% (238)	61.7% (335)	<0.0001
Inhaled hypertonic saline	12.5% (106)	19.9% (58)	8.5% (46)	<0.0001
Inhaled bronchodilators	75.7% (640)	71.8% (209)	77.7% (422)	0.06
Inhaled corticosteroids	55.5% (469)	58.1% (169)	54.0% (293)	0.25
Oral corticosteroids	8.8% (74)	7.2% (21)	9.2% (50)	0.33

Data are median [IQR], % (n) or mean ± SD

ppFEV$_1$: percent predicted forced expiratory volume in 1 sec; BMI : body mass index ; MSSA : methicillin-susceptible *S. aureus* ; MRSA : methicillin-resistant *S. aureus*

Table 2. Reasons for lumacaftor-ivacaftor discontinuation in 154 patients

Reasons	% (n)
Respiratory AE	**48.1% (74)**
-Abnormal respiration (chest tightness/dyspnea)	24.7% (38)
-Bronchospasm	15.6% (24)
-Increase in cough and sputum	5.8% (9)
-Hemoptysis	1.3% (2)
-Pneumothorax	0.7% (1)
Non-respiratory AE (all)	**27.9% (43)**
-Gastro-intestinal (diarrhea, abdominal pain)	11.7% (18)
-Myalgia with increase in CPK>10 ULN	3.2% (5)
-Fatigue	3.2% (5)
-Headache	2.6% (4)
-Depression	2.6% (4)
-Metrorrhagia	1.9% (3)
-High liver function tests	1.3% (2)
-Tachycardia	0.7% (1)
-Cutaneous rash	0.7% (1)
Non adherence	**4.6% (7)**
Perceived lack of effectiveness	**4.6% (7)**
Procreation related (all)	**3.9% (6)**
-Pregnancy	2.6% (4)
-Sperm aspiration	1.3% (2)
Lung transplantation	**3.3% (5)**
Miscellaneous	**2.6% (4)**
Unknown	**1.9% (3)**
Drug interaction	**1.9% (3)**
Death	**1.3% (2)**

Table 3. Baseline characteristics of patients associated with lumacaftor-ivacaftor discontinuation in multivariable logistic regression.

Variable	Odds ratio	95% CI	P values
Discontinuation from all causes (n=154 patients)			
Adult vs. adolescent	2.65	1.57-4.48	0.0003
$ppFEV_1$*	1.13	1.02-1.25	0.02
IV antibiotic course**	1.13	1.01-1.26	0.03
Discontinuation related to respiratory adverse events (n=74 patients)			
Adult vs. adolescent	4.36	1.65-11.49	0.003
Diabetes	1.71	1.03-2.85	0.04
$ppFEV_1$*	1.32	1.14-1.51	0.0001
BMI***	1.11	1.00-1.23	0.03
IV antibiotic course**	1.14	0.99-1.30	0.06

*** OR per 10% decrease in $ppFEV_1$**
**** OR per each additional IV antibiotic course**
***** OR per 1 kg/m^2 decrease**

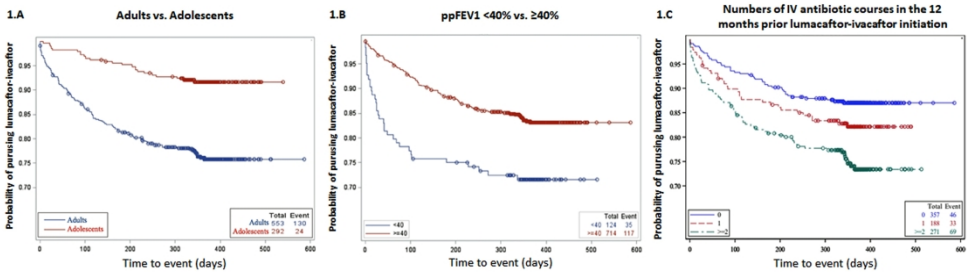

Figure 1. Probabilities of pursuing lumacaftor-ivacaftor over 1 year according to patient characteristics at baseline. 1A. Comparison of adults (≥18 years, n=553) vs. adolescents (12-17 years, n=292); discontinuation rates were 23.5% vs. 8.2% in adults and adolescents, respectively, P<0.001. 1B. Comparison of patients with ppFEV1<40% (n=124) vs. ≥40% (n=714); discontinuation rates were 28.2% vs. 16.3% in subjects with ppFEV1<40% vs. those with ppFEV1≥40%, respectively, P<0.001. Missing values for ppFEV1 at baseline (n=7). 1C. Comparison according to the number of IV antibiotic courses during the 12 months prior to lumacaftor-ivacaftor initiation. Rates of treatment discontinuation were 12.9% (46/347) in patients with no IV antibiotic course, 17.6% (33/188) in patients with 1 antibiotic course and 25.5% (69/271) in patients with 2 or more antibiotic courses; P=0.0002. Data were analyzed using Kaplan-Meier and Log-Rank test.

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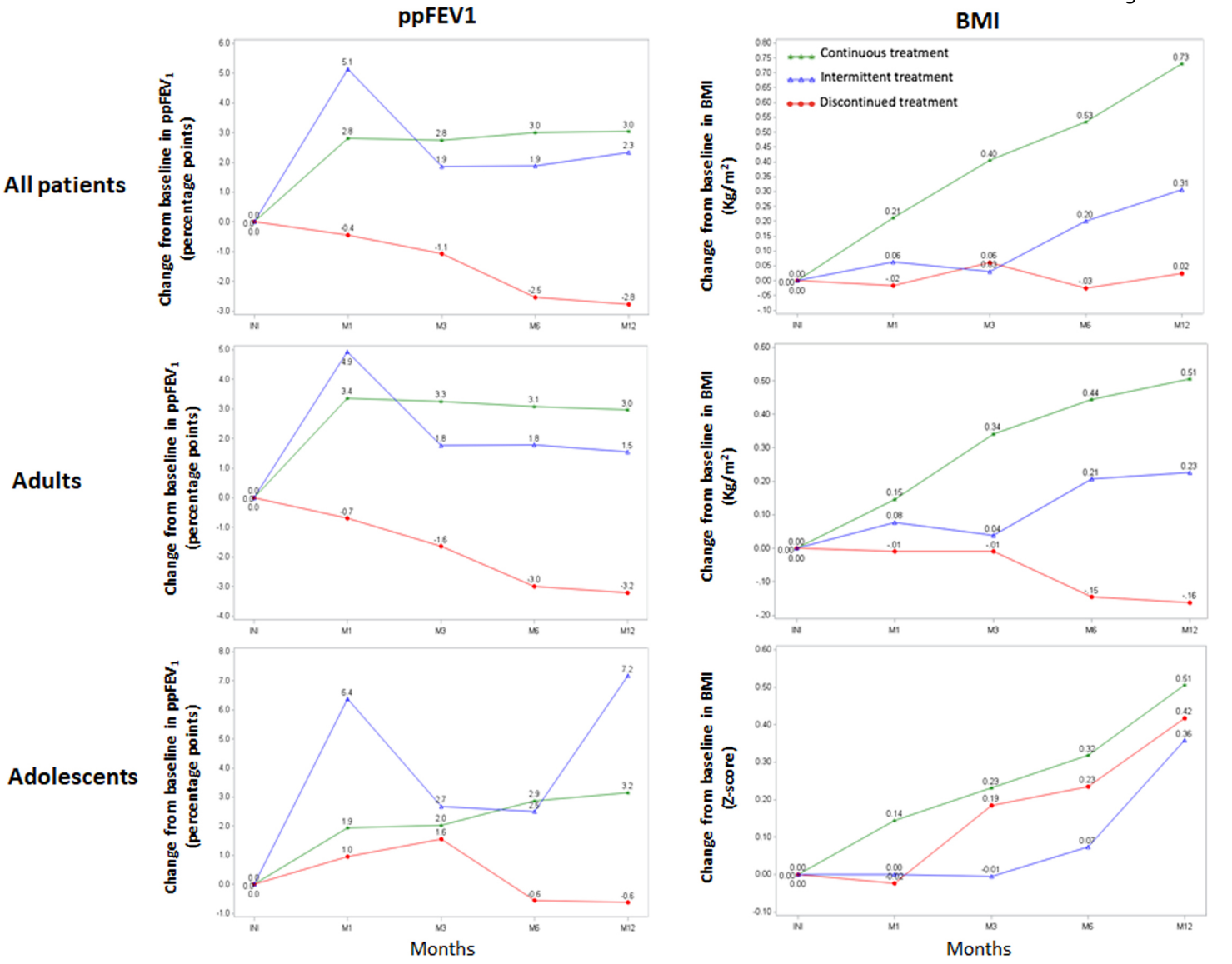
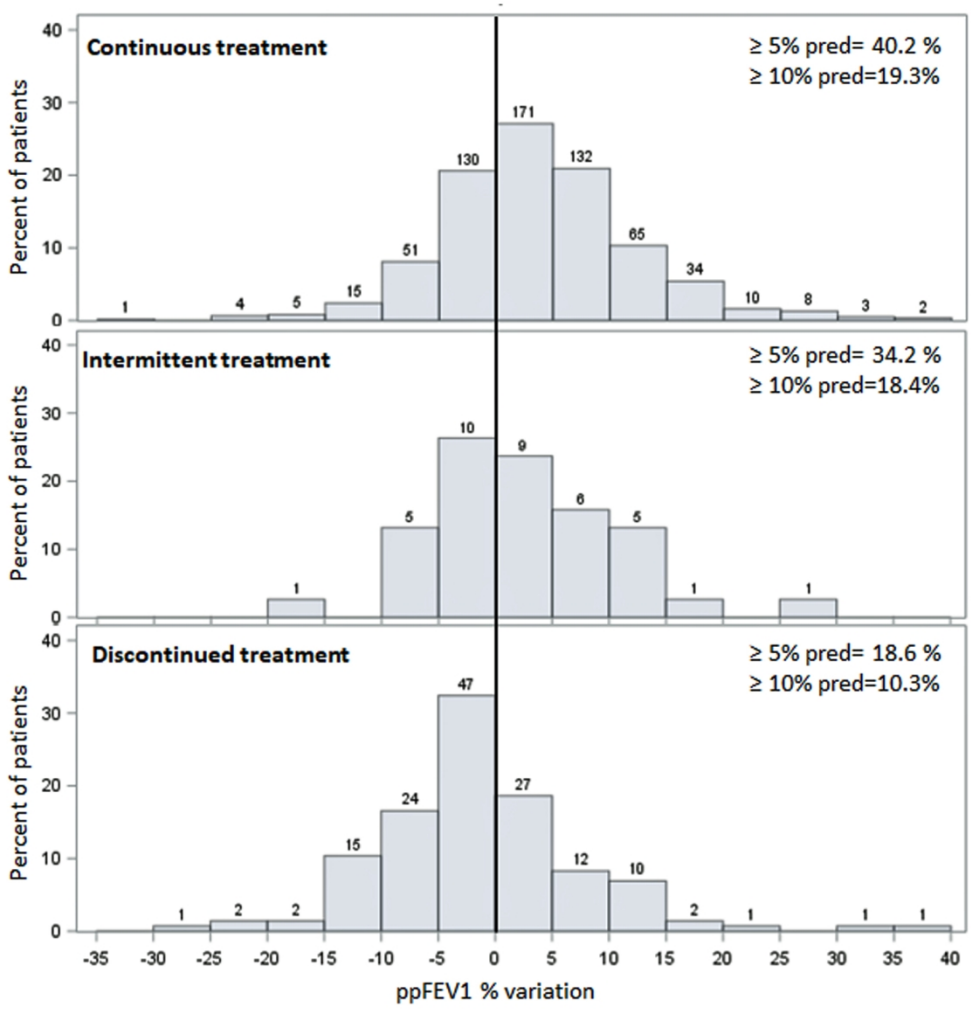

ppFEV1
BMI
All patients
Adults
Adolescents
Change from baseline in ppFEV1 (percentage points)
Change from baseline in BMI (Kg/m²)
Change from baseline in BMI (Z-score)
Continuous treatment
Intermittent treatment
Discontinued treatment
INI
M1
M3
M6
M12
Months



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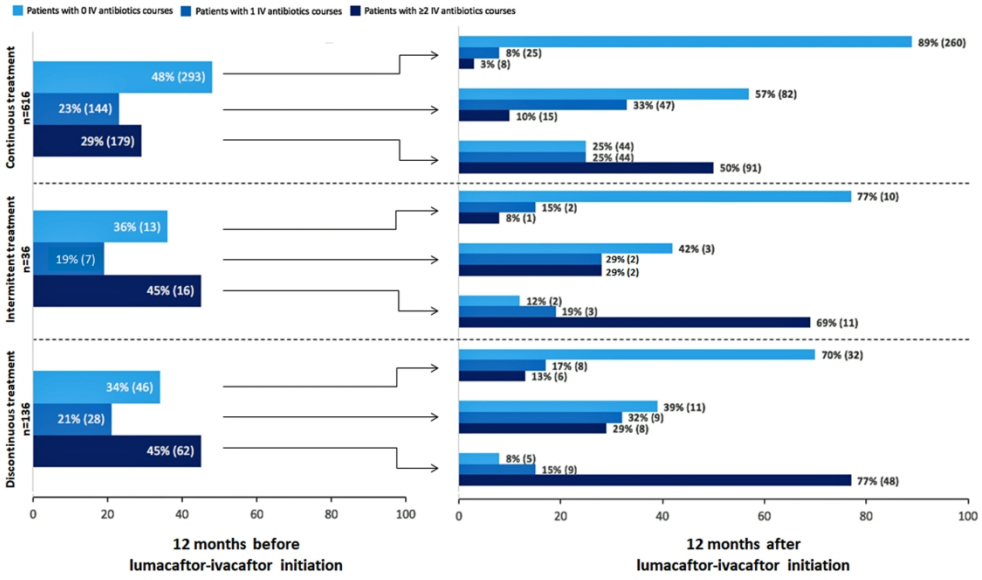

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Online Data Supplement

Study population

Physicians were asked to recruit all patients with CF aged 12 years and older homozygous for the F508del CFTR mutations who started lumacaftor-ivacaftor between January 1st and December 31st 2016, outside of an interventional research study. This resulted in the inclusion of 853 patients in the study. Of these, 5 patients were excluded due to insufficient data, one patient was <12 years and 2 patients had started treatment at unknown dates. These 8 patients were excluded from our analyses and the final studied population comprised 845 patients.

Because our study database was nested as a specific observational study within the French CF Registry database, we were able to gain better knowledge of the national picture of lumacaftor-ivacaftor treatment in France at the end of 2016.

The Flow chart below (Figure S1) depicts the study population as compared to the overall CF population in France in 2016.

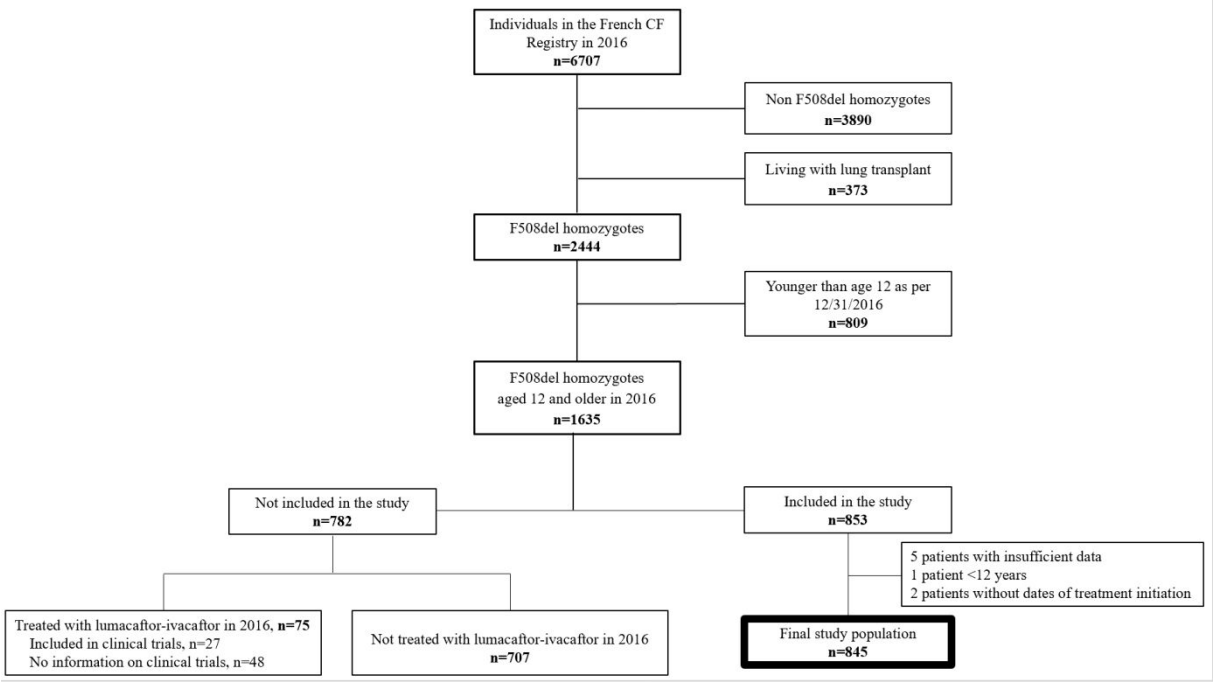
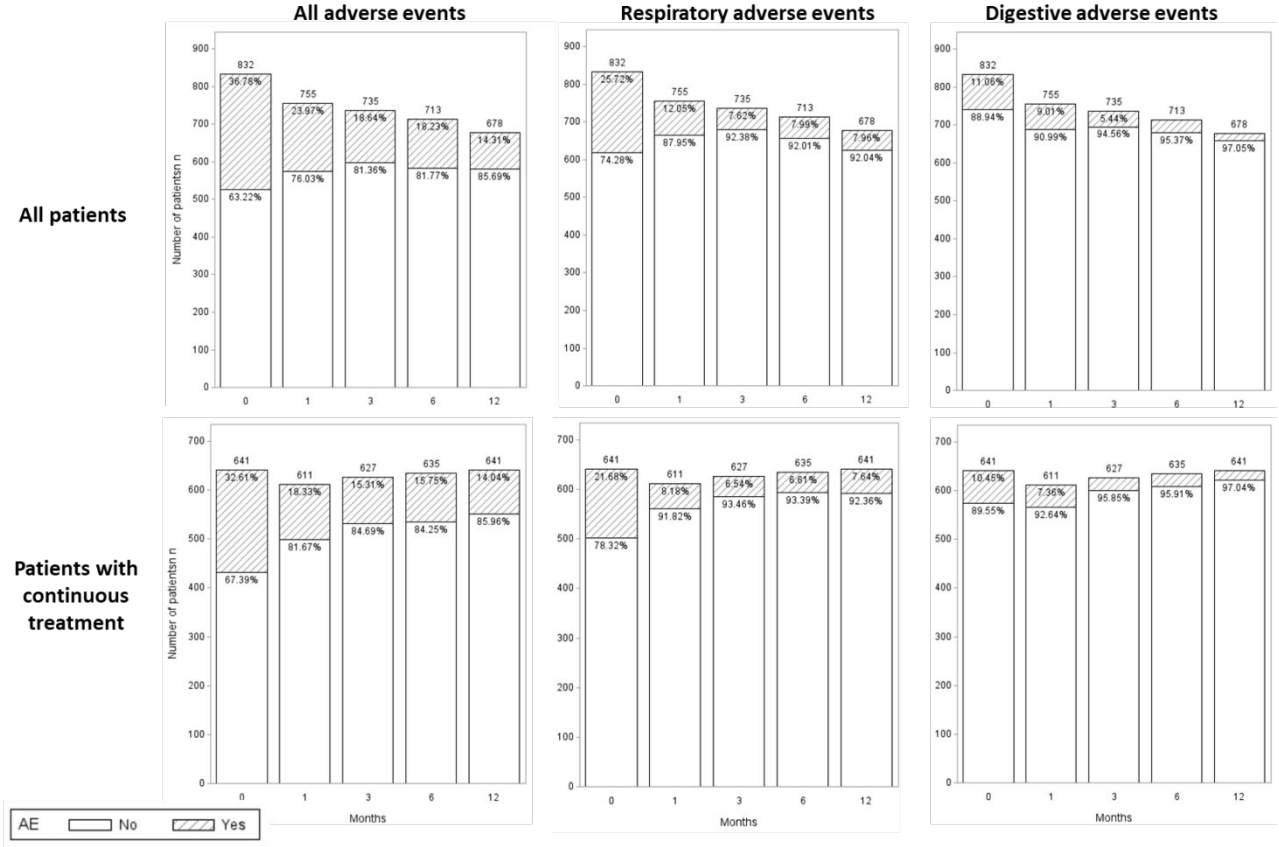


Figure S1. Flow chart depicting the study population as compared to the overall population in the French CF Registry in 2016

These data show that 1635 patients with CF were eligible to lumacaftor-ivacaftor as per 2016 label in Europe (F508del homozygotes, 12 years and older, and not living with lung transplant). Among these patients, 57% (928 patients) received lumacaftor-ivacaftor in 2016, whereas 44% (707 patients) did not receive lumacaftor-ivacaftor at that time. Our study included 92% (853 patients) of all patients treated with lumacaftor-ivacaftor in France in 2016. Among the 8% (75 patients) who received lumacaftor-ivacaftor in 2016 and were not included in our study, at least 27 patients received lumacaftor-ivacaftor in clinical trials (and thus were not eligible to the present study); registry data were not sufficiently precise to establish whether the remaining 48 patients received lumacaftor-ivacaftor as part of clinical trials or as real-life prescription.

Adverse effects

Figure S2. Prevalence of all (left), respiratory (middle) or digestive (right) adverse events (AEs) in all patients (upper panel) and in patients who received continuous treatment over 12 months. AE reported in this figure were considered by treating physicians as possibly associated with lumacaftor-ivacaftor. Numbers of available data at each time point are shown on top of the bars.



Effectiveness

Figure S3. Evolution of ppFEV1 over 12 months after initiation of lumacaftor-ivacaftor in all patients (left, n=834 patients), adults only (middle, n=543) and adolescents only (right, n=291) with available data.

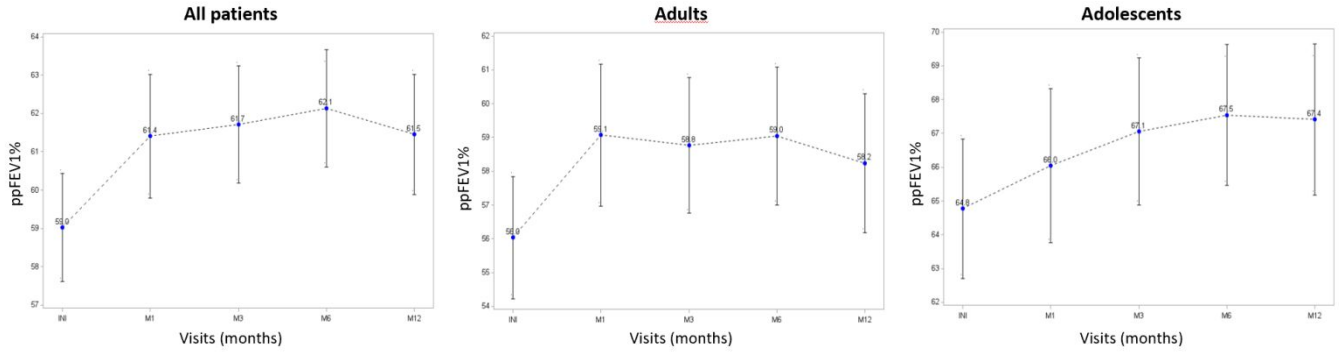


Figure S4. Distribution of the difference between the best ppFEV1 in the 12 months after vs. the 12 months before lumacaftor-ivacaftor initiation in all patients. Numbers of patients are shown on top of each bar. % of patients with an increase in ppFEV1 ≥5% and ≥10% are also indicated in the figure.

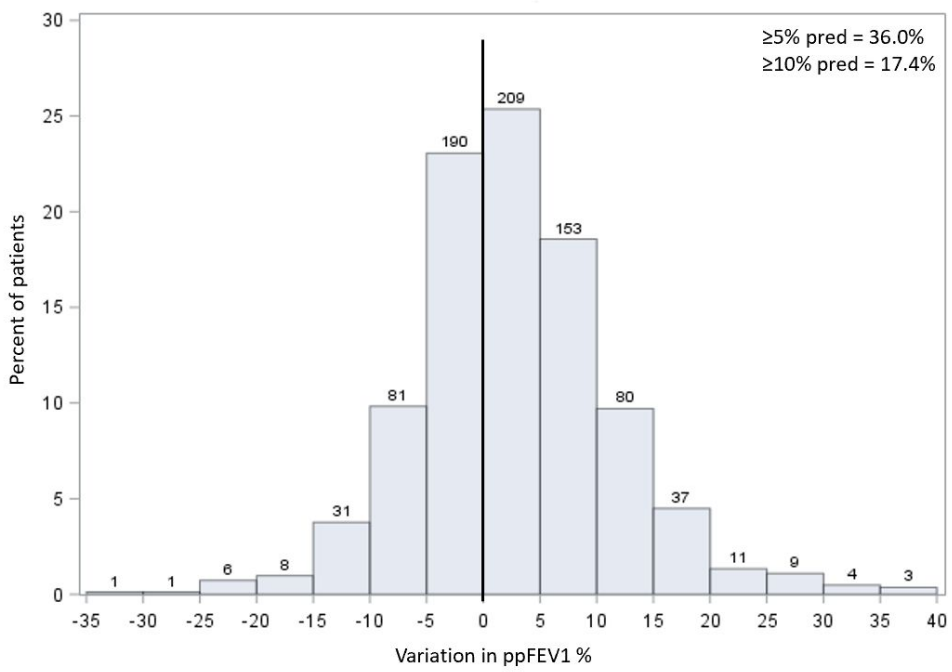


Figure S5. Evolution of weight and body mass index (BMI) over 12 months after initiation of lumacaftor-ivacaftor in all patients (n=834 patients), adults only (n=543) and adolescents only (n=291).

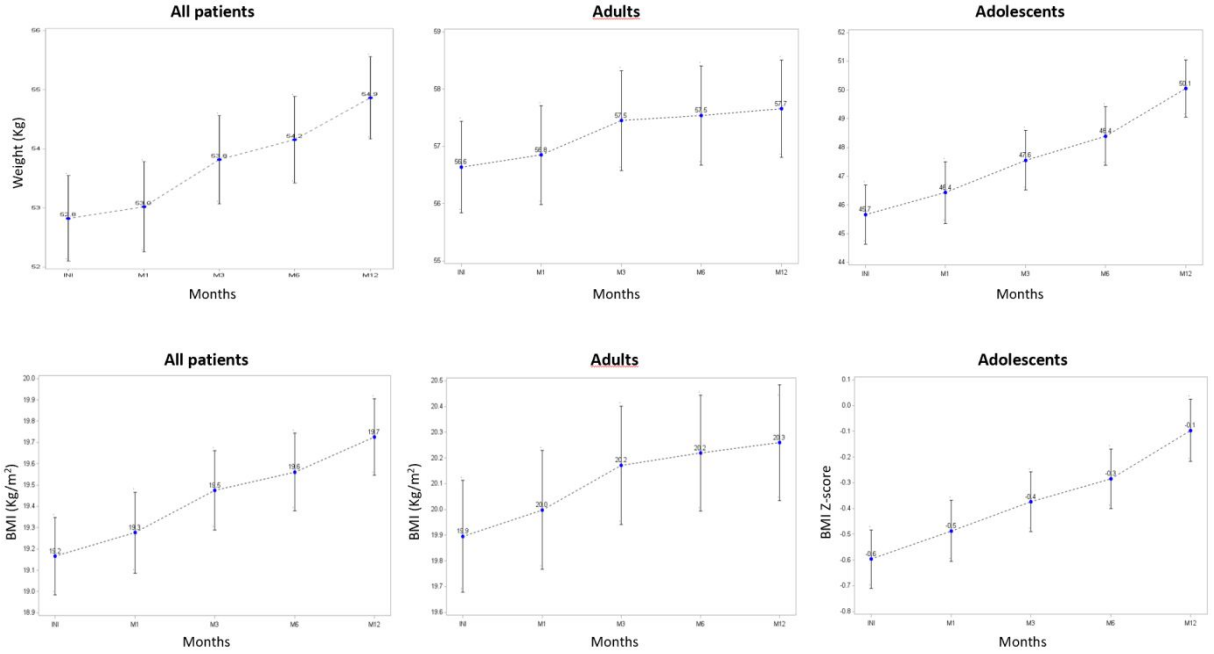


Figure S6. Evolution of weight according to treatment pattern (continuous, intermittent, discontinued treatment) in all patients, in adults only and in adolescents only

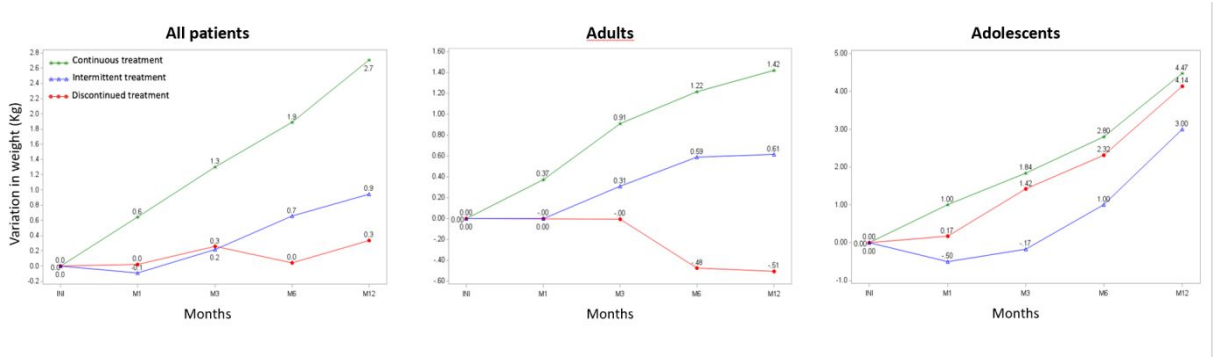


Table S1. Prevalence of cirrhosis/portal hypertension or elevated liver enzyme according to the pattern of treatment with lumacaftor-ivacaftor.

Variable	Continuous or intermittent treatment n=680	Discontinued treatment n=154	P values (Chi square)
Cirrhosis/Portal hypertension, % (n)	5.0% (34)	5.2% (8)	0.92
Elevated liver enzymes, % (n)	12.4% (84)	11.7% (18)	0.82

Data are provided for 834 patients (11 patients were lost to follow-up).

Table S2. Liver disease prior to lumacaftor-ivacaftor initiation and liver enzyme follow-up over 12 months in the 5 patients with elevated values greater than three times the upper limit of normal at any time during the study.

		Year prior to lumacaftor-ivacaftor initiation		Year after lumacaftor-ivacaftor initiation									
Patient	Pattern of Lumacaftor-Ivacaftor treatment	Cirrhosis/portal hypertension	Elevated liver enzymes	Liver enzyme grade (times normal)									
				Baseline		Month 1		Month 3		Month 6		Month 12	
				AST	ALT	AST	ALT	AST	ALT	AST	ALT	AST	ALT
1	***Continuous***	No	No	N/A	N/A	0	0	N/A	N/A	**3 (6N)**	**3 (6N)**	N/A	N/A.
2	***Continuous***	Yes	Yes	1	2	1	2	2	**3 (6N)**	N/A	N/A	1	1
3	***Continuous***	No	Yes	0	0	0	**3 (6N)**	0	0	1	1	0	1
4	***Discontinued****	Yes	Yes	1	1	1	1	1	1	1	1	**3 (7N)**	**3 (9N)**
5	***Discontinued*** **	No	Yes	0	1	0	0	0	1	**3 (8N)**	**3 (11N)**	0	1

* Discontinued at 12 months due to elevated liver enzyme

** Discontinued at 6 months due to elevated liver enzyme

N/A: not available. Grade 0: Normal (N); Grade 1 = 1 to 3 N; Grade 2 = 4 to 5 N; Grade 3 = 6 to 20 N; Grade 4 > 20 N

Table S3 Rates of all AEs, respiratory AEs and digestive AEs according to the presence of diabetes at study entry.

Variable	Patients without diabetes n=600	Patients with diabetes n=234	P values (Chi-square)
Any AEs	56.8% (341)	65.4% (153)	0.024
Any respiratory AEs	36.5% (219)	41.5% (97)	0.185
Any digestive AEs	21.7% (130)	21.8% (51)	0.968

Table S4. Differences between serum levels of Vitamins A, D and E and HbA1C between 12 months (M12) after initiation of lumacaftor-ivacaftor and baseline (Month 0, M0) according to treatment pattern.

		Baseline (M0)		12 months (M12)		Difference (M12-M0)		P values
		n	value	n	value	n	value	
Vitamin A µmol/l	**All patients**	606	1.39 [1.07; 1.72]	569	1.50 [1.20; 1.81]	468	0.14 [-0.14; 0.44]	<0.0001
	Continuous treatment	481	1.39 [1.09; 1.70]	490	1.52 [1.22; 1.83]	402	0.15 [-0.13; 0.46]	<0.0001
	Intermittent treatment	27	1.54 [1.0.2.0]	23	1.50 [1.12; 1.76]	20	0.12 [-0.26; 0.44]	0.68
	Treatment discontinuation	98	1.35 [1.00; 1.73]	56	1.32 [1.00; 1.59]	46	0.10 [-0.31; 0.25]]	0.41
Vitamin D (25OHD) nanomol/l	**All patients**	644	60.3 [44.8; 78.0]	594	51.0 [34.0; 67.2]	491	-11.1 [-9.7; 4.3]	<0.0001
	Continuous treatment	511	60.3 [46.4; 77.0]	509	49.0 [32.5; 65.0]	424	-12.0 [-24.0; 2.3]	<0.0001
	Intermittent treatment	24	66.8 [41.8; 83.5]	25	60.3 [41.3; 67.3]	20	-4.8 [-17.6; 10.6]	0.37
	Treatment discontinuation	109	61.0 [39.4; 78.0]	60	60.9 [40.6; 81.2]	47	-2.3 [-16.2; 20.9]	0.95
Vitamin E µmol/l	**All patients**	600	19.6 [14.9; 24.6]	571	16.7 [12.7; 21.8]	464	-2.4 [-2.9; 0.7]	<0.0001
	Continuous treatment	477	19.6 [14.9; 24.3]	492	16.7 [12.7; 21.5]	400	-2.6 [-6.0; 0.7]	<0.0001
	Intermittent treatment	26	18.2 [15.3; 24.7]	23	17.2 [11.5; 22.7]	19	-1.8 [-5.9; 2.0]	0.19
	Treatment discontinuation	97	20.7 [14.0; 25.7]	56	19.4 [14.9; 24.1]	45	-1.3 [-5.9; 0.5]	<0.001
HbA1C* %	**All patients**	176	6.4 [6.0; 6.9]	173	6.3 [5.8; 7.0]	136	0 [-0.3; 0.3]	0.50
	Continuous treatment	128	6.3 [6.0; 6.9]	135	6.3 [5.8; 6.9]	110	0 [-0.3; 0.3]	0.56
	Intermittent treatment	11	6.3 [5.4; 7.0]	16	6.3 [5.7; 7.2]	10	0.1 [-0.2; 0.3]	0.50
	Treatment discontinuation	37	6.6 [6.2; 6.9]	22	6.8 [6.0; 7.2]	16	-0.2 [-0.5; 0.6]	0.63

*in patients with diabetes at baseline