ORIGINAL ARTICLE

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

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Abstract

Rationale: Lumacaftor–ivacaftor is a CFTR (cystic fibrosis transmembrane conductance regulator) 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 yr) and adults (≥18 yr) in a real-life postapproval setting.

Methods: The study was conducted in the 47 CF reference centers in France. All patients who initiated lumacaftor–ivacaftor from January 1 to December 31, 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.

Measurements and Main Results: Among the 845 patients (292 adolescents and 553 adults) who initiated lumacaftor–ivacaftor, 18.2% (154 patients) discontinued treatment, often owing to respiratory (48.1%, 74 patients) or nonrespiratory (27.9%, 43 patients) adverse events. In multivariable logistic regression, factors associated with increased rates of discontinuation included adult age group, percent predicted FEV_1 ($ppFEV_1$) less than 40%, and numbers of intravenous antibiotic courses during the year before 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 body mass index 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 owing to adverse events, were found at high risk of clinical deterioration.

Keywords: cystic fibrosis; lumacaftor–ivacaftor; postmarketing study

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A complete list of French Cystic Fibrosis Reference Network Study Group members may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: Phase 3 clinical trials have reported safety and efficacy of lumacaftor–ivacaftor in adolescents and adults with cystic fibrosis homozygous for Phe508del CFTR (cystic fibrosis transmembrane conductance regulator).

What This Study Adds to the Field: The present postmarketing 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 intravenous antibiotic courses in adolescents and adults with cystic fibrosis homozygous for Phe508del who tolerated the treatment. However, rates of treatment discontinuation, which were often due to adverse events, was more than three times increased compared with phase 3 trials. Risk of treatment discontinuation was increased in patients with low lung function or repeated exacerbations, and in adults versus adolescents.

Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene encoding for the CFTR (CF transmembrane conductance regulator) 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 1 Phe508del mutation and 40% to 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 mutation (7, 9). Improvement in lung function, reduction in pulmonary exacerbations, and a trend toward 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 FEV_1 ($ppFEV_1$), 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 regard 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 yr) and adults (≥18 yr) 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 nonrespiratory 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 (i.v.) 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 mo). All patients (including those who

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discontinued lumacaftor–ivacaftor) were followed for 12 months after lumacaftor–ivacaftor initiation.

Statistics

Data are presented as percentage and number [% (*n*)], median (interquartile range [IQR]), or mean ± SD. Probability of treatment discontinuation between groups (e.g., adults vs. adolescents, ppFEV$_1$ <40% vs. ⩾40%, and patients with 0, 1, or 2 or more i.v. antibiotic courses during the 12 months before 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 the Wilcoxon paired test. Difference in best ppFEV$_1$ observed in the 12 months before versus the 12 months after lumacaftor–ivacaftor initiation were calculated. Comparisons of the number of i.v. antibiotics courses in the 12 months before versus the 12 months after lumacaftor–ivacaftor initiation were performed using the paired McNemar 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 less than 0.10 in bivariate analysis. A *P* value less than 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc.).

Results

Patient Population

Between January 1 and December 31, 2016, 845 patients (292 adolescents and 553 adults) initiated treatment with lumacaftor–ivacaftor in the 47 centers of the French CF Reference Network (Figure E1 in the online supplement provides additional information on the 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). Follow-up data were missing in 11 patients (1.3%).

Treatment discontinuation (without reintroduction during the study time)

Table 1. Characteristics of Patients at the Time of Lumacaftor–Ivacaftor Initiation

	All Patients (*N = 845*)	Adolescents (12–17 yr) (*n = 292 [34.6%]*)	Adults (⩾18 yr) (*n = 553 [65.4%]*)	*P* Value
Age, yr	22.0 (16 to 30)	15.0 (13.3 to 16.3)	27.3 (22.8 to 33.0)	<0.0001
Sex, F	44.6 (377)	47.6 (139)	43.0 (238)	0.20
ppFEV$_1$	65 (47 to 80)	70 (59 to 81)	60 (43 to 80)	<0.0001
ppFEV$_1$ < 40%	14.8 (124)	5.2 (15)	19.9 (109)	<0.0001
BMI, kg/m^2	19 (17 to 21)	18 (16 to 19)	20 (18 to 21)	<0.0001
BMI, *z*-score	—	−0.60 (−1.22 to 0.11)	—	
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 i.v. antibiotic courses in the previous 12 mo	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

Definition of abbreviations: *B. cepacia* = *Burkholderia cepacia*; BMI = body mass index; *H. influenzae* = *Haemophilus influenzae*; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; *P. aeruginosa* = *Pseudomonas aeruginosa*; ppFEV$_1$ = percent predicted FEV$_1$.
Data are median (IQR), % (*n*), or mean ± SD.

occurred in 17.3% (129/745) of patients who started lumacaftor–ivacaftor at full dose versus 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 discontinued treatment was 369 (357–385) days, 370 (349–97) days, and 363 (335–391) days, respectively. Median (IQR) time under treatment was shorter in patients who discontinued treatment (90 [25–179] d) and in those with intermittent treatment (322 [255–349] d) than in patients with continuous treatment (369 [357–385] d) (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 nonrespiratory AEs (27.9%). Median (IQR) time to treatment discontinuation due to respiratory AEs ($n = 74$) was 42 (10–98) days versus 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 $ppFEV_1$ less than 40% versus greater than or equal to 40% (28.2% vs. 16.3%; $P < 0.0001$) (*see* Figure 1B), and in patients with repeated i.v. courses in the previous year (*see* 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 (Table E1).

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)
Nonrespiratory AE (all)	27.9 (43)
Gastrointestinal (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)
Nonadherence	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)

Definition of abbreviations: AE = adverse event; CPK = creatine phosphokinase; ULN = upper limit of normal.

Reasons for temporary discontinuation and reintroduction of lumacaftor–ivacaftor during the study time (intermittent treatment) included respiratory AEs ($n = 16$ patients), nonrespiratory AEs ($n = 8$ 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).

AEs

AEs considered by treating physicians as possibly associated with lumacaftor–ivacaftor were reported in 59.4% (494 patients). AEs with a prevalence of greater than or equal to 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 a decrease in the number of patients exposed to lumacaftor–ivacaftor secondary to treatment discontinuation (that occurred mostly in patients with AEs), decrease in the occurrence of AEs over time was also observed in patients treated continuously over 12 months ($n = 641$) (Figure E2). AEs were more prevalent in patients with diabetes (65.4% vs. 56.8%; $P = 0.024$) (Table E3).

Only five patients had elevated liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) greater than three times the upper limit of normal (ULN) at any time during the study period. Four of these patients had preexisting CF liver disease (two with liver cirrhosis/portal hypertension and two with elevated liver enzyme before starting lumacaftor–ivacaftor). Elevation of liver enzymes led to lumacaftor–ivacaftor discontinuation in two patients (including one patient with a history of liver cirrhosis/portal hypertension), one after 6 months and one after 12 months of treatment, due to elevations greater than six times the ULN. Detailed liver data for the five patients are shown in Table E2.

Elevations of creatine phosphokinase greater than 5 times the ULN occurred in 20 patients and led to discontinuation of lumacaftor–ivacaftor in 2 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 1 month after starting lumacaftor–ivacaftor and persisted over 12 months (Figure E3). At 12 months after initiation, absolute change in $ppFEV_1$ from baseline was $+2.7 \pm 8.86\%$ ($n = 821$ patients; $P < 0.001$; Wilcoxon paired test). Improvement in $ppFEV_1$ was observed in patients with continuous treatment ($+3.67 \pm 8.62\%$; $n = 631$ patients; $P < 0.001$) and in those with intermittent treatment ($+2.36 \pm 8.47\%$; $n = 45$ patients; $P = 0.09$), whereas patients who discontinued lumacaftor–ivacaftor had a decrease in $ppFEV_1$ ($-1.36 \pm 9.03\%$; $n = 145$ patients; $P = 0.07$; Wilcoxon paired test) (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,

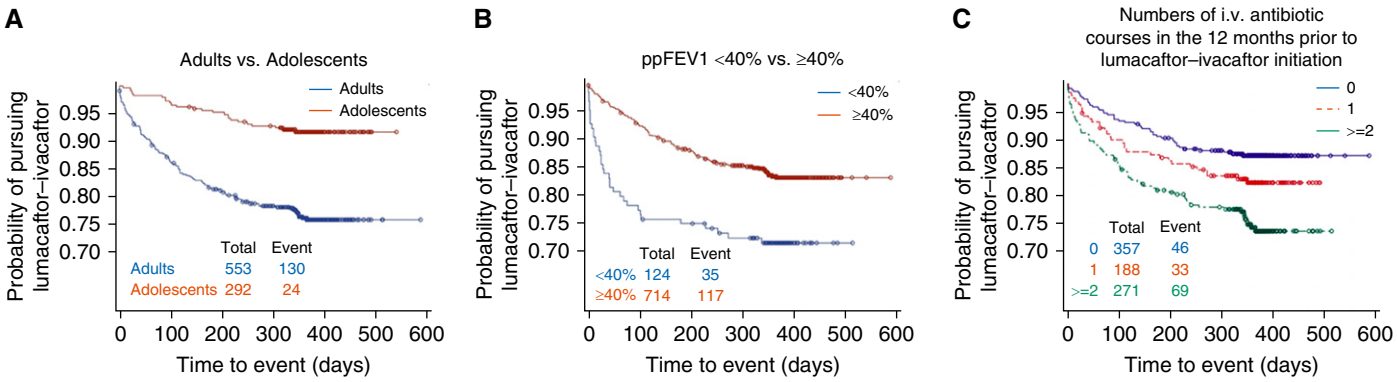

Figure 1. Probabilities of pursuing lumacaftor–ivacaftor over 1 year according to patient characteristics at baseline. (*A*) Comparison of adults (⩾18 yr, $n = 553$) versus adolescents (12–17 yr, $n = 292$); discontinuation rates were 23.5% versus 8.2% in adults and adolescents, respectively ($P < 0.001$). (*B*) Comparison of patients with percent predicted FEV_1 ($ppFEV_1$) less than 40% ($n = 124$) versus greater than or equal to 40% ($n = 714$); discontinuation rates were 28.2% versus 16.3% in subjects with $ppFEV_1$ less than 40% versus those with $ppFEV_1$ greater than or equal to 40%, respectively ($P < 0.001$). Some values for $ppFEV_1$ at baseline are missing ($n = 7$). (*C*) Comparison according to the number of intravenous antibiotic courses during the 12 months before lumacaftor–ivacaftor initiation. Rates of treatment discontinuation were 12.9% (46/347) in patients with no intravenous antibiotic course, 17.6% (33/188) in patients with one antibiotic course, and 25.5% (69/271) in patients with two or more antibiotic courses ($P = 0.0002$). Data were analyzed using Kaplan-Meier and log-rank test.

resulting in numerical differences from 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 versus 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 $4.76 \pm 8.17\%$ and $2.91 \pm 8.85\%$ in adolescents ($n = 258$ patients) and adults ($n = 373$ patients), respectively ($P < 0.001$ in each group vs. baseline; $P = 0.008$ 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 (Figure E4). 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 BMI. Weight gain (mean, +2.1 kg) and BMI increase (mean, +0.5 kg/m^2) were observed in the overall cohort over the 12 months after treatment initiation (Figure E5). Weight gain (Figure E6) 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* Figure E6) 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 i.v. 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 i.v. antibiotic courses were therefore performed for 797 patients. Patients with continuous exposure to lumacaftor–ivacaftor had 1.18 ± 1.60 versus 0.77 ± 1.38 i.v. antibiotic courses per patient in the 12 months before versus 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

Table 3. Baseline Characteristics of Patients Associated with Lumacaftor–Ivacaftor Discontinuation in Multivariable Logistic Regression

Variable	Odds Ratio	95% CI	*P* Value
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
i.v. 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
i.v. antibiotic course†	1.14	0.99–1.30	0.06

Definition of abbreviations: BMI = body mass index; CI = confidence interval; $ppFEV_1$ = percent predicted FEV_1.
*Odds ratio per 10% decrease in $ppFEV_1$.
†Odds ratio per each additional intravenous antibiotic course.
‡Odds ratio per 1 kg/m^2 decrease.

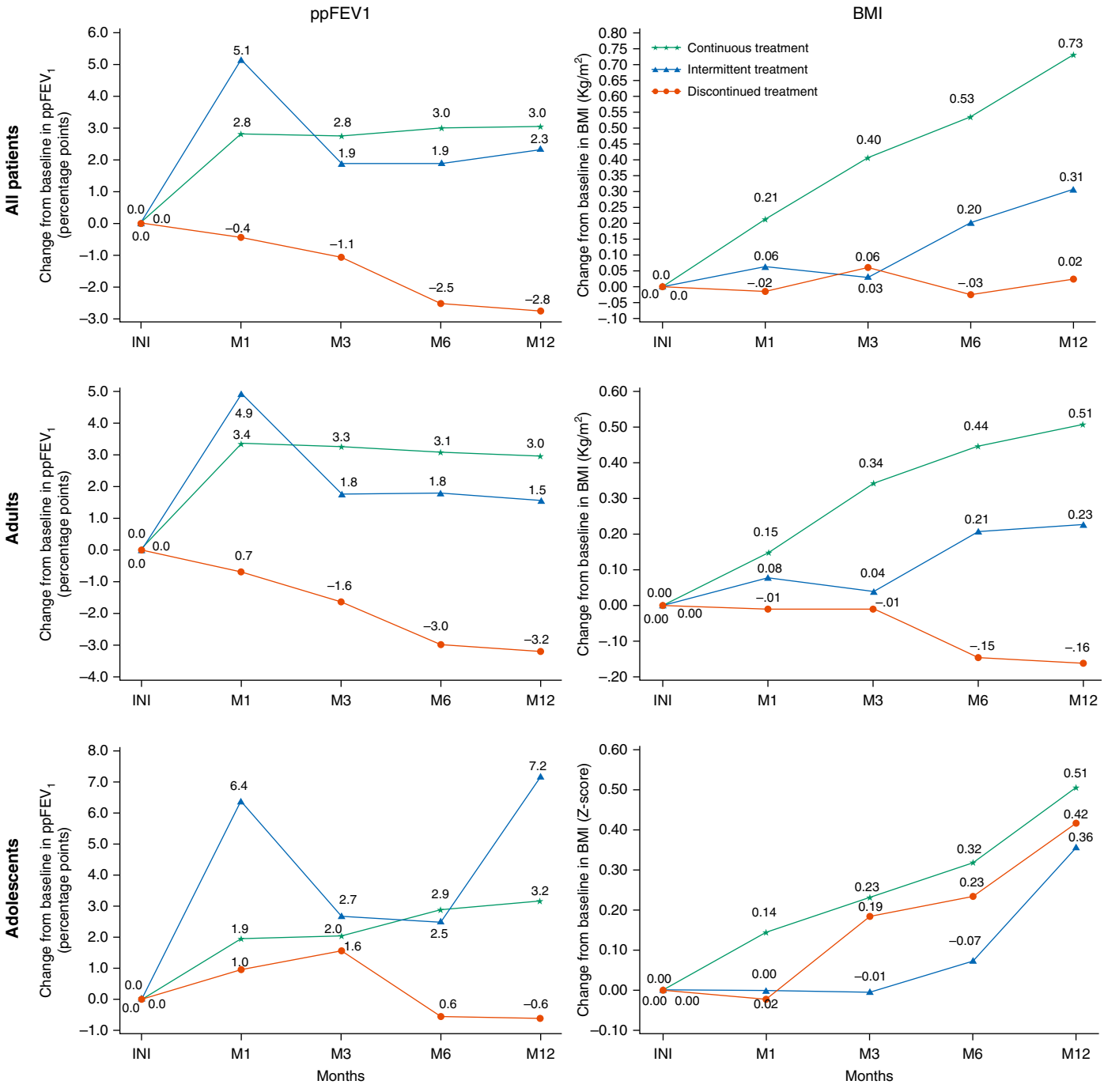

Figure 2. Change from baseline in percent predicted FEV_1 (left column) and in body mass index (right column). Results are presented for all patients (≥12 yr, upper panels), adults (≥18 yr, middle panels), and adolescents (12–17 yr, lower panels). In each figure, patients are grouped according to pattern of lumacaftor–ivacaftor exposure (continuous treatment, intermittent treatment, or treatment discontinuation). Data are plotted at each timepoint 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. BMI = body mass index; INI = initiation of lumacaftor–ivacaftor; $ppFEV_1$ = percent predicted FEV_1.

lumacaftor–ivacaftor had 1.44 ± 1.87 versus 1.50 ± 1.84 i.v. antibiotic courses per patient in the 12 months before versus the 12 months after lumacaftor–ivacaftor initiation ($n = 36$ patients; $P = 0.98$). Patients with treatment discontinuation had 1.82 ± 1.93 versus 1.82 ± 2.04 ($n = 136$ patients; $P = 0.18$). Distribution of the number of i.v. 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, 25-hydroxycholecalciferol (25OHD), and vitamin E before the onset of treatment and 1 year after lumacaftor–ivacaftor initiation, we found no evidence of increase in vitamin

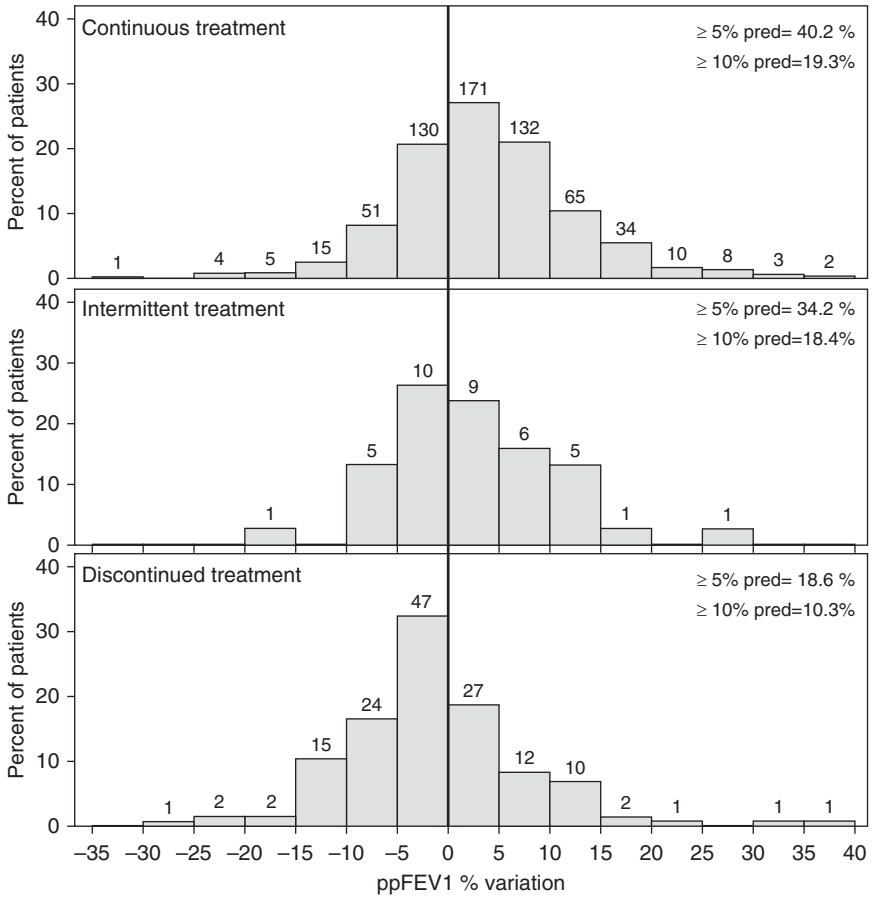

Figure 3. Distribution of the difference between the best percent predicted FEV_1 in the 12 months after versus the 12 months before lumacaftor–ivacaftor initiation in all patients. Data are presented by subgroup of treatment exposure: continuous treatment (top panels), intermittent treatment (middle panels), and treatment discontinuation (lower panels). Numbers of patients are indicated on top of the bars. $ppFEV_1$ = percent predicted FEV_1; pred = predicted.

serum level under lumacaftor–ivacaftor (detailed data are provided in Table E4). Surprisingly, serum levels of vitamin 25OHD were significantly lower in patients treated continuously by lumacaftor–ivacaftor.

HbA1C levels were examined in patients with diabetes. No decrease in HbA1C levels was found during treatment with lumacaftor–ivacaftor (Table E4).

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, mostly due to respiratory AEs and, to a lesser extent, to nonrespiratory AEs. Significant improvements in $ppFEV_1$, body weight, and BMI, and reduction in the number of i.v. 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 i.v. antibiotics.

The proportion of patients (18.2%) who discontinued lumacaftor–ivacaftor was markedly higher in this study compared with pivotal clinical trials in which 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 i.v. antibiotic courses in the previous year) compared with pivotal clinical trials. Thus, the rate of lumacaftor–ivacaftor discontinuation was 28.2% in patients with $ppFEV_1$ less than 40%, which was independently associated with treatment discontinuation, confirming previous studies (14, 16). However, the rates of discontinuation in patients with FEV_1 greater than or equal to 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 i.v. antibiotics in the year before lumacaftor–ivacaftor initiation were also independently associated with treatment discontinuation. Rates of treatment discontinuation were markedly increased in adults versus 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 suggested that starting lumacaftor–ivacaftor at reduced dose may be associated with a better safety profile in patients at high risk of AEs (16), our data suggest that starting at low doses will not prevent treatment discontinuation in many patients.

The liver-related AE profile appeared encouraging, despite the inclusion of 5% of subjects with a previous history of liver cirrhosis/portal hypertension. Only five patients showed grade 3 and higher liver enzyme elevation and only two patients discontinued lumacaftor–ivacaftor due to liver-related AE. 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 i.v.

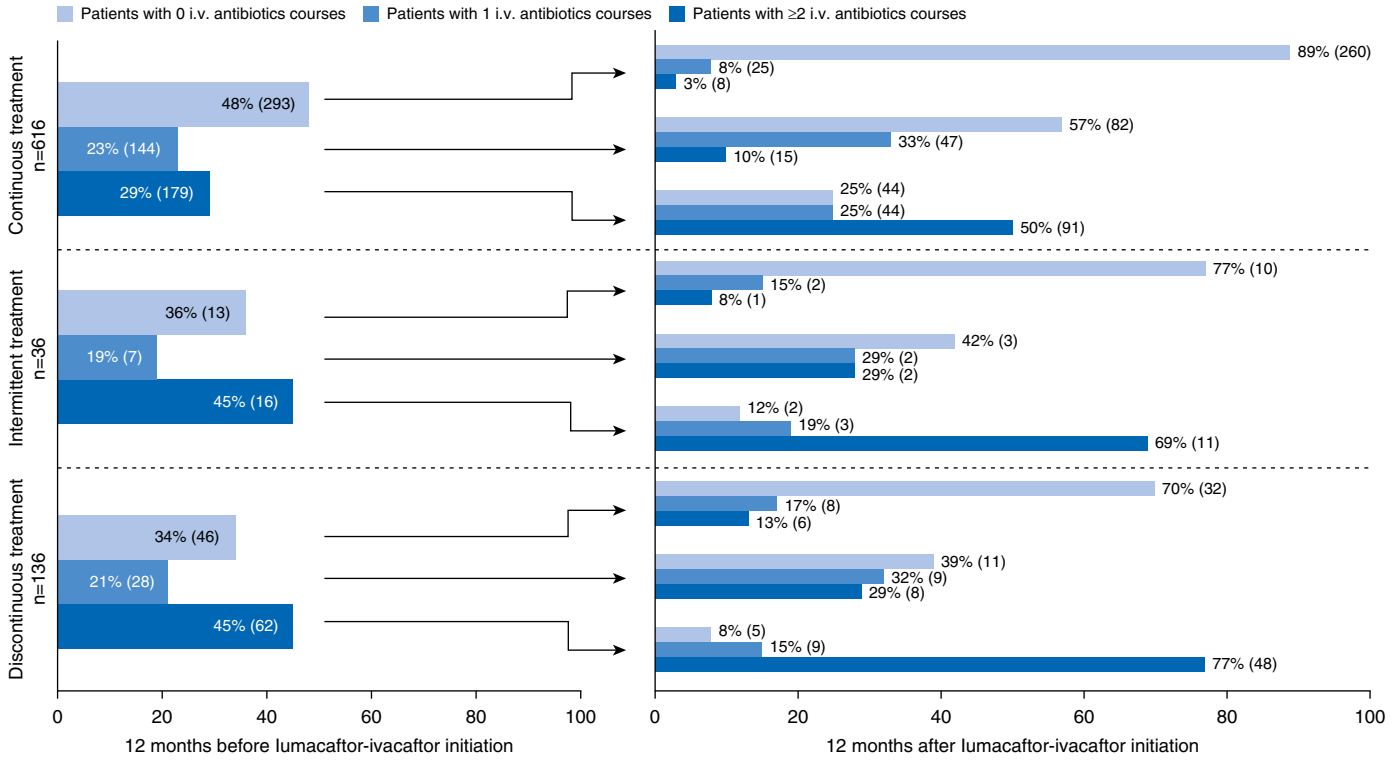

Figure 4. Exacerbations requiring intravenous antibiotics in the 12 months before and the 12 months after lumacaftor–ivacaftor initiation by treatment exposure pattern. The bars at the left show the proportions of patients with no exacerbation, one exacerbation, or two or more exacerbations in the year before 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, or treatment discontinuation). The number of patients with exacerbations was reduced only in patients with continuous treatment ($n = 618$ patients; $P < 0.001$; paired analysis by the McNemar test), whereas no significant difference was observed in patients with intermittent treatment ($n = 36$ patients; $P = 0.48$) and in patients who discontinued treatment ($n = 137$ patients; $P = 0.72$). Data are presented as percentage and number [% (*n*)] of patients within each group.

antibiotic courses, compared with baseline. These data largely confirmed data obtained in more selected populations in pivotal clinical trials (9, 18) and go 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 with 6 months in pivotal clinical trials; and *3*) comparing the number of i.v. 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/patient/yr). 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 i.v. antibiotic courses), resulting in a limited amount of missing data. We also recognize limitations. Although the first cause of lumacaftor–ivacaftor discontinuation was respiratory AEs, only limited data were available on the use of concomitant treatment (e.g., long-acting bronchodilators), which have been proposed for limiting these AEs (21, 22). Rates of use of DNase, inhaled corticosteroids, and inhaled antibiotics were comparable between our study and

phase 3 clinical trials (7). However, fewer patients were treated with bronchodilators (75.7% vs. 92.2%) and hypertonic saline (12.5% vs. 59.9%) in the present study versus phase 3 clinical trials, respectively. The potential impact of these differences in background therapy on efficacy and AEs is unclear. Furthermore, no data were available on exacerbations treated with oral antibiotics because 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 had 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 to 11 years (23) and 2 to 5 years (24), but these findings will have to be confirmed in postmarketing 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 i.v. 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 postmarketing 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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