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## Clinical response to lumacaftor-ivacaftor in patients with cystic fibrosis according to baseline lung function

Pierre-Régis Burgel, Isabelle Durieu, Raphaël Chiron, Laurent Mely, Anne Prevotat, Marlene Murriss-Espin, Michele Porzio, Michel Abely, Philippe Reix, Christophe Marguet, et al.

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**Title :** Clinical response to lumacaftor-ivacaftor in patients with cystic fibrosis according to baseline lung function.

**Author list:** Pierre-Régis BURGEL MD<sup>1,2,3</sup>, Isabelle DURIEU MD<sup>3,4,5</sup>, Raphaël CHIRON MD<sup>6</sup>, Laurent MELY MD<sup>7</sup>, Anne PREVOTAT MD<sup>8</sup>, Marlene MURRIS-ESPIN MD<sup>9</sup>, Michele PORZIO MD<sup>10</sup>, Michel ABELY MD<sup>11</sup>, Philippe REIX MD<sup>12</sup>, Christophe MARGUET MD<sup>13</sup>, Julie MACEY MD<sup>14</sup>, Isabelle SERMET-GAUDELUS MD<sup>3,15,16</sup>, Harriet CORVOL MD<sup>17</sup>, Stéphanie BUI MD<sup>18</sup>, Tiphaine BIOUHEE MD<sup>19</sup>, Dominique HUBERT MD<sup>2,3</sup>, Anne MUNCK MD<sup>20</sup>, Lydie LEMONNIER PhD<sup>21</sup>, Clémence DEHILLOTTE PhD<sup>21</sup>, Jennifer DA SILVA BS<sup>1,3,22</sup>, Jean-Louis PAILLASSEUR PhD<sup>23</sup>, Clémence MARTIN MD<sup>1,2,3</sup> for the **French Cystic Fibrosis Reference Network study group**

**Author's affiliations:**

<sup>1</sup> Université de Paris, Institut Cochin, Paris, France

<sup>2</sup> Respiratory Medicine and National Reference Cystic Fibrosis Reference Center; Cochin Hospital; Assistance Publique Hôpitaux de Paris (AP-HP), Paris, France

<sup>3</sup> ERN-Lung CF network

<sup>4</sup> Centre de référence Adulte de la Mucoviscidose, Service de médecine interne, Hospices civils de Lyon, F-69495, Pierre Bénite, France

<sup>5</sup> Université de Lyon, Équipe d'Accueil Health Services and Performance Research (*HESPER*) 7425, F-69003 Lyon, France

<sup>6</sup> Cystic Fibrosis Center, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire de Montpellier, Univ Montpellier, France

<sup>7</sup> Hôpital Renée Sabran, Cystic Fibrosis Center, Giens, France

<sup>8</sup> CHU-Lille, Cystic Fibrosis Center, Service de Pneumologie et Immuno-allergologie, Hôpital Calmette and Univ. Lille, Lille, France

<sup>9</sup> Cystic Fibrosis Center, Service de Pneumologie, Pôle des Voies Respiratoires, Hôpital Larrey, CHU de Toulouse, Toulouse, France

<sup>10</sup> Department of Respiratory Medicine and Cystic Fibrosis Center, Federation of Translational Medicine of Strasbourg (FMTS), University Hospitals, Strasbourg, France

<sup>11</sup> Department of Pediatrics A and Cystic Fibrosis Center, American Memorial Hospital, Reims, France.

<sup>12</sup> UMR 5558 CNRS, Equipe EMET, Université Claude Bernard Lyon 1, Lyon, France; Cystic Fibrosis Center, Hospices Civils de Lyon, Lyon, France.

<sup>13</sup> Pediatric Respiratory Disease and Cystic Fibrosis Center, Hospital, UNIROUEN, Inserm EA 2656, Rouen University Hospital, Normandie Univ, Rouen, France.

<sup>14</sup> Respiratory Medicine and Cystic Fibrosis Center, CHU de Bordeaux, Bordeaux, France.

<sup>15</sup> Pediatric Respiratory Disease and Cystic Fibrosis Center, National Reference Cystic Fibrosis Reference Center, Hôpital Necker Enfants Malades, Paris France

<sup>16</sup> INSERM U 1151, Institut Necker Enfants Malades, Paris, France

<sup>17</sup> Sorbonne Université, Centre de Recherche Saint-Antoine (CRSA), Paris, France ; Pediatric Respiratory Disease and Cystic Fibrosis Center, Hôpital Trousseau, APHP, Paris, France

<sup>18</sup> Pediatric Respiratory Disease and Cystic Fibrosis Center and CIC 1401, CHU de Bordeaux, Bordeaux, France.

<sup>19</sup> Pediatric CF Center, Nantes University Hospital, Nantes, France.

<sup>20</sup> Hôpital Robert Debré, AP-HP, Paris, France.

<sup>21</sup> Association Vaincre la Mucoviscidose, Paris, France

<sup>22</sup> URC-CIC Paris Descartes Necker Cochin, AP-HP, Hôpital Cochin, Paris, France

<sup>23</sup> Effi-stat, Paris, France

**Corresponding author:** Prof Pierre-Régis Burgel  
French National Reference Center for Cystic Fibrosis  
Cochin Hospital  
27 rue du Faubourg Saint Jacques  
75014 Paris, France  
Email : pierre-regis.burgel@aphp.fr

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## ABSTRACT

**Background:** Phase 3 trials have demonstrated the safety and efficacy of lumacaftor-ivacaftor (LUMA-IVA) in patients with cystic fibrosis (CF) homozygous for the Phe508del CFTR mutation and percent predicted forced expiratory volume in 1 sec (ppFEV<sub>1</sub>) between 40 and 90. Marketing authorizations have been granted for patients at all levels of ppFEV<sub>1</sub>.

**Methods** To evaluate the safety and effectiveness of LUMA-IVA over the first year of treatment in patients with ppFEV<sub>1</sub><40 or ppFEV<sub>1</sub>≥90 in comparison with those with ppFEV<sub>1</sub> [40-90[. Analysis of data collected during a real world study, which included all patients aged ≥12 years who started LUMA-IVA in 2016 across all 47 French CF centers.

**Results:** 827 patients were classified into 3 subgroups according to ppFEV<sub>1</sub> at treatment initiation (ppFEV<sub>1</sub><40, n=121; ppFEV<sub>1</sub> [40-90[, n=609; ppFEV<sub>1</sub>≥90, n=97). Treatment discontinuation rate was higher in ppFEV<sub>1</sub><40 patients (28.9%) than in those with ppFEV<sub>1</sub> [40-90[ (16.4%) or ppFEV<sub>1</sub>≥90 (17.5%). In patients with uninterrupted treatment, significant increase in ppFEV<sub>1</sub> occurred in the ppFEV<sub>1</sub> [40-90[ subgroup (+2.9%, *P*<0.001), and in those ppFEV<sub>1</sub><40 (+0.5%, *P*=0.03) but not in those with ppFEV<sub>1</sub>≥90 (*P*=0.46). Compared with the year prior to initiation, the number of days of intravenous antibiotics were reduced in all subgroups, although 72% of patients with ppFEV<sub>1</sub><40 still experienced at least one exacerbation/year under LUMA-IVA. Comparable increase in body mass index was seen in the three subgroups.

**Conclusion:** Phe508del homozygous CF patients benefit from LUMA-IVA at all levels of baseline lung function, but the characteristics and magnitude of the response vary depending on ppFEV<sub>1</sub> at baseline.

## INTRODUCTION

Cystic fibrosis (CF) is a genetic autosomal recessive disease involving mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein [1-3]. CFTR dysfunction is responsible for a multisystem disease dominated by respiratory manifestations with chronic airway infection, accelerated decline in lung function and frequent respiratory exacerbations, and by impaired nutritional status [1, 2]. Over the past decades, CF management has consisted in symptomatic treatment, which includes airway clearance techniques, systemic and inhaled antibiotics, pancreatic enzyme replacement and high fat-high calorie diet [2, 4]. More recently, small molecules that enable partial correction of CFTR dysfunction and lead to the partial restoration of chloride transport in epithelia have been discovered [5]. These molecules, called CFTR modulators, target the underlying cause of CF and have been associated with clinical improvement in patients with eligible *CFTR* genotypes [5].

Lumacaftor-ivacaftor (LUMA-IVA), a combination of CFTR modulators, is now licensed in many countries for patients homozygous for the Phe508del CFTR mutation, who represent 40-50% of patients with CF worldwide [6]. Initial phase 3 clinical trials were undertaken in patients aged 12 years and older with a percent predicted forced expiratory volume in one second (ppFEV<sub>1</sub>) between 40 and 90 [7]. Reasons for these criteria included the fear of adverse effects in patients with more severe respiratory disease (ppFEV<sub>1</sub><40) and the general belief that, in patients with ppFEV<sub>1</sub>≥90, an increase in ppFEV<sub>1</sub> would be very unlikely. Nonetheless, LUMA-IVA was approved for Phe508del homozygous patients at all levels of ppFEV<sub>1</sub> by regulatory agencies in the US and in Europe. Several post-marketing studies have reported safety issues, mostly related to respiratory adverse events, in patients with ppFEV<sub>1</sub><40 [8-10]. However, few studies have examined the safety profile of LUMA-IVA in patients with ppFEV<sub>1</sub>≥90 or its benefits for those with ppFEV<sub>1</sub><40 [11, 12] or ppFEV<sub>1</sub> ≥90 [13]. Furthermore these studies generally included a limited number of patients from a small

number of centers, who were not compared to patients with FEV<sub>1</sub> [40-90] in terms of effect magnitude.

The present study used data collected during a previously published real world study conducted in France, which followed a large cohort of patients aged 12 years and older who started LUMA-IVA in 2016[14], in order to examine its safety and effectiveness at different levels of baseline ppFEV<sub>1</sub> over the first year of treatment. Our goal was to gain knowledge on the safety and effectiveness profile of LUMA-IVA in patients whose lung function at baseline was considered too low (ppFEV<sub>1</sub><40) or too high (ppFEV<sub>1</sub>≥90) for them to be eligible to participate in clinical trials. The magnitude of improvement in ppFEV<sub>1</sub> and body mass index (BMI), and the reduction in exacerbation frequency in these patients was compared with those of patients with baseline ppFEV<sub>1</sub> [40-90].

## METHODS

### Patients

The initial study's cohort was described in detail in a previous report [14]. Briefly, the study included all patients aged 12 years and older who initiated LUMA-IVA between January 1<sup>st</sup> and December 31<sup>st</sup> 2016 and were followed in the 47 accredited CF centers in France. The study was registered with (NCT03475391) and 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, in accordance with French laws for observational studies, informed consent was not required. Following the recommendations of the French CF Learning Society, all patients were followed for one full year with a pre-established schedule: visits occurred at 1, 3, 6, and 12 months and included assessment of weight, height, BMI, ppFEV<sub>1</sub> and intravenous (IV) antibiotic courses. Adverse events (AEs) were prospectively collected at each visit and documented in patient charts by the referral physician. The safety evaluation population consisted in all eligible patients who initiated LUMA-IVA in 2016. For effectiveness evaluation, the population was limited to those who received LUMA-IVA continuously over one year, excluding those who discontinued treatment permanently or temporarily during the study (see flow chart in **Figure 1**).

### Statistics

Data are presented as numbers and percentages [%, (n)], median (interquartile range [IQR]), or mean  $\pm$  standard deviation (SD). BMI was calculated as kg/m<sup>2</sup> for adults and z-score for adolescents. Three subgroups were defined according to ppFEV<sub>1</sub> at study entry (baseline), prior to initiation of LUMA-IVA: ppFEV<sub>1</sub><40, ppFEV<sub>1</sub> [40-90[, and ppFEV<sub>1</sub>≥90. The likelihood of treatment discontinuation between subgroups (e.g. ppFEV<sub>1</sub><40 vs. ppFEV<sub>1</sub> [40-90[ vs. ppFEV<sub>1</sub>≥90) was calculated using Kaplan-Meier estimator and log-rank tests with

Tukey-Kramer adjustment for multiple comparisons. Within each subgroup, the change in BMI and ppFEV<sub>1</sub> between baseline and 12 months after treatment initiation was analyzed using the paired samples Wilcoxon test. Comparisons of the number of IV antibiotic courses or days in the 12 months before versus the 12 months after LUMA-IVA initiation were performed within each subgroup using Bowker's test for symmetry [15] for paired nominal data and the paired t-test for quantitative data. Differences in ppFEV<sub>1</sub> observed in the 12 months before versus the 12 months after treatment initiation were calculated within each subgroup. Between subgroup comparison analyses of discontinuation rates by cause and of the proportion of patients with an increase in ppFEV<sub>1</sub>  $\geq 5\%$  were performed using chi-square tests and the Bonferroni-Holm method for multiple comparisons. A *P* value of less than 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc.).

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The funding source played no role in defining the study's design; in data collection, analysis, or interpretation; or in writing of the manuscript. The corresponding author had full access to all the study data and had final responsibility for the decision to submit the manuscript for publication.



## RESULTS

### Study population

Among the 845 patients who initiated LUMA-IVA in 2016, 11 had incomplete follow-up data and 7 patients had missing information on FEV<sub>1</sub> at baseline. The safety population therefore consisted in 827 patients (537 adults and 290 adolescents) including 121 patients (14.7 %) with ppFEV<sub>1</sub><40, 609 (73.6 %) with ppFEV<sub>1</sub> [40-90[ and 97 (11.7 %) with ppFEV<sub>1</sub>≥90. Patient characteristics by FEV<sub>1</sub> subgroup at study entry are presented in **Table 1**. During the first year after LUMA-IVA initiation, treatment was discontinued in 152 patients, intermittent in 39 patients, and uninterrupted in 636 patients. Effectiveness evaluation was limited to those with uninterrupted treatment over one year (n=636). A flow chart describing the study population is provided in **Figure 1**.

### Safety

Among the 152 patients who discontinued treatment during the first year after initiation, 35 patients had ppFEV<sub>1</sub><40, 100 patients had ppFEV<sub>1</sub> [40-90[ and 17 patients had ppFEV<sub>1</sub>≥90. The treatment discontinuation rate was higher in patients with ppFEV<sub>1</sub><40 (28.9%) than in those with ppFEV<sub>1</sub> [40-90[ (16.4%; *P*=0.002) or ppFEV<sub>1</sub>≥90 (17.5%; *P*=0.06). The discontinuation rate was not significantly different in patients with ppFEV<sub>1</sub> [40-90[ vs. ppFEV<sub>1</sub>≥90 (*P*=0.27). Kaplan-Meier estimator showing the probability of pursuing LUMA-IVA are presented in **Figure S1**. The main reasons for treatment discontinuation are presented in **Table S1 (online supplement)**. Respiratory adverse events (AEs) were the main cause (74%) of treatment discontinuation in patients with ppFEV<sub>1</sub><40, but represented only 42% and 29% of causes in patients with a ppFEV<sub>1</sub> [40-90[ and ppFEV<sub>1</sub>≥90, respectively (*P*=0.003 and *P*=0.004 compared with patients with ppFEV<sub>1</sub><40). No significant difference was observed when comparing rates of respiratory AEs in patients with ppFEV<sub>1</sub> [40-90[ and in those with ppFEV<sub>1</sub> ≥90 (*P*=0.78).

## **Effectiveness**

### Lung function

Effectiveness evaluation was limited to patients who received uninterrupted treatment over the twelve months of the study (n=636). After a median [IQR] of 369 [357-385] days of exposure to LUMA-IVA, a significant increase in ppFEV<sub>1</sub> compared with baseline values (median [IQR], +2.9% [-1.8%; +8.0%]; n=484, *P*<0.001) was observed in patients with ppFEV<sub>1</sub> [40-90[. A significant increase was also observed in those with ppFEV<sub>1</sub><40 (+0.5% [-2.2%; + 4.3%]; n=77; *P*=0.03), but not in those with ppFEV<sub>1</sub>≥90 (+1.7% [-3.9%; +5.6%]; n=75, *P*=0.46). The magnitude of increase in ppFEV<sub>1</sub> was therefore significantly greater in patients in the [40-90[ range compared to those with ppFEV<sub>1</sub><40 or ppFEV<sub>1</sub>≥90 (*P*=0.03 and *P*=0.05; respectively). Marked variability in ppFEV<sub>1</sub> change was present in all subgroups. The distribution of the difference between ppFEV<sub>1</sub> at the end of the study vs. baseline by subgroup is presented in **Figure 2**. A ≥5% increase in absolute value was found in 40% of patients with ppFEV<sub>1</sub> [40; 90[, but only in 22% and 27% of patients with ppFEV<sub>1</sub><40 and ppFEV<sub>1</sub>≥90, respectively (*P*=0.01 and *P*=0.08 compared with the [40-90[ subgroup).

### Body mass index

An increase in weight (not shown) and in BMI was consistently found at all ages and in all subgroups. In adults, median [IQR] improvement in BMI over 1 year was +1.0 kg/m<sup>2</sup> [0; +1.0] in patients with ppFEV<sub>1</sub><40 (n=64; *P*<0.0001), 0 [0; +1.0] kg/m<sup>2</sup> in the ppFEV<sub>1</sub> [40; 90[ subgroup (n=260; *P*<0.001), and +1.0 [0; +1.0] kg/m<sup>2</sup> in those with ppFEV<sub>1</sub>≥90 (n=52; *P*=0.0004). Improvement in BMI was not significantly different between subgroups (*P*=0.33). In adolescents, median [IQR] improvement in z-score BMI over 1 year was +0.47 [0; +0.82] in the ppFEV<sub>1</sub><40 subgroup (n=13; *P*=0.01); +0.50 [0; +0.94] in the ppFEV<sub>1</sub> [40; 90[

subgroup (n=224;  $P<0.001$ ), and +0.43 [0; +0.85] in the ppFEV<sub>1</sub>≥90 subgroup (n=23;  $P=0.005$ ). Improvement in z-score BMI was not significantly different between subgroups ( $P=0.27$ ). Variation in BMI (kg/m<sup>2</sup>) in adults and z-score BMI in adolescents by ppFEV<sub>1</sub> subgroup is presented in **Figure 3**.

#### Intravenous antibiotic courses

First we examined exacerbations (defined as requiring intravenous antibiotics), by analysing the exacerbation status (0 exacerbation, 1 exacerbation, 2 or more exacerbations) within each ppFEV<sub>1</sub> subgroup, comparing the twelve months prior to LUMA-IVA initiation to the twelve months after LUMA-IVA initiation. Significant improvement in patient's exacerbation status occurred in patients with ppFEV<sub>1</sub> [40-90[ (n=465;  $P<0.001$ ), with a similar trend in those with ppFEV<sub>1</sub>≥90 (n=74;  $P=0.056$ ). No significant difference was found in those with ppFEV<sub>1</sub><40 (n=75;  $P=0.29$ ) (see **Figure 4**).

Next, comparing trends in the year after treatment initiation to the year prior, the mean ± SD number of IV antibiotic days/patient was significantly reduced in all subgroups: 29.4 ±26.5 vs. 35.5 ±35.7 days/year in patients with ppFEV<sub>1</sub><40 (difference -6.0±30.7 days; n=75,  $P=0.02$ ). The difference was -6.6±19.2 days (n=465,  $P<0.0001$ ) in the ppFEV<sub>1</sub> [40-90[ subgroup (9.7±17.6 vs. 16.3±23.7 days/year) and -4.1±12.8 days (n=75,  $P=0.006$ ) in the ppFEV<sub>1</sub>≥90 subgroup (2.8±7.0 vs. 6.9±13.3 days/year).

## DISCUSSION

The present study took advantage of data collected in a large and heterogeneous cohort of unselected adolescents and adults with CF who were treated with LUMA-IVA, with the aim of examining its effects at various levels of baseline lung function. One third of patients had a ppFEV<sub>1</sub> at baseline that would have been considered either too low (ppFEV<sub>1</sub><40) or too high (ppFEV<sub>1</sub>≥90) to meet eligibility criteria for phase 3 clinical trials, which included only patients with ppFEV<sub>1</sub> [40-90[ [7]. A ppFEV<sub>1</sub> increase ≥5% was found in 40% of patients with baseline ppFEV<sub>1</sub> [40-90[, a proportion that was 1.5 to 2 fold higher than in patients with baseline ppFEV<sub>1</sub> <40 or ppFEV<sub>1</sub>≥90. Improvement in BMI was found in all patients, and the magnitude of improvement was comparable across all subgroups. The number of IV antibiotic days per year was also reduced in all subgroups, but the effects of LUMA-IVA on exacerbation rates appeared less robust in patients with severe respiratory impairment. These findings underscore the clinical benefits that can be achieved in patients at all levels of severity, although the clinical impact of LUMA-IVA varies at different levels of baseline lung function.

For this study, data was collected for 97 patients with baseline ppFEV<sub>1</sub>>90 (69 adults, 28 adolescents), representing the largest cohort of adults and adolescents with preserved lung function ever treated with LUMA-IVA. In this subgroup of patients, the rate (17.5%) and causes of treatment discontinuation were comparable to those of patients with ppFEV<sub>1</sub> [40-90[. To the best of our knowledge only one other study, by Aalbers et al., evaluated the effects of LUMA-IVA over one year, but in a smaller cohort (n=40) of patients, who were younger (12 patients<11 years, 13 adolescents, 14 adults) and followed at a single center [13]. The present analysis was not only obtained in larger numbers of patients compared to the study by Aalbers et al. It was also obtained in a much diverse population that was followed in multiple centers and was predominantly composed of adults. Aalbers et al. reported treatment discontinuation in only 2.5% of patients (1/40), which is markedly lower than in the present

study [13]. This result is consistent with our previous report, which found that treatment discontinuation rate was higher in adults compared to younger patients[14]. In the subgroup of patients with  $ppFEV_1 \geq 90$ , treatment with LUMA-IVA failed to significantly improve  $ppFEV_1$ , confirming the results of Aalbers et al.[13]. However, our data extend these findings by showing that individual response was markedly heterogeneous, with some patients increasing their  $ppFEV_1$  by more than 25% (see **Figure 2**). Our analysis showed significant improvement in BMI and a decreasing trend in the number of pulmonary exacerbations, with a reduction in the number of IV antibiotic days/year, largely confirming results by Aalbers et al [13]. Altogether, these findings strengthen the clinical benefits associated with LUMA-IVA in adolescents and adults with  $ppFEV_1 \geq 90$ .

In patients with  $ppFEV_1 < 40$ , treatment discontinuation occurred in more than a quarter of patients and were often due to respiratory causes, confirming our previous report[14] and results obtained by other teams [3, 9]. LUMA-IVA was associated with a consistent increase in BMI in adolescents and in adults. Changes in  $ppFEV_1$  in the  $ppFEV_1 < 40$  subgroup were minimal, with a median of +0.5%, but were statistically significant. The increase in  $ppFEV_1$  appeared less important than described in patients with  $ppFEV_1 < 40$  in Phase 3 trials in which  $ppFEV_1$  increased by a mean of 3.7% (95% CI, 0.5 to 6.9) over 24 weeks [12]. However, patients in this latter study had less severe respiratory impairment (with  $ppFEV_1 > 30$ ) [12] than in the present study and were presumably more stable for being included in clinical trials. There was no significant change in the exacerbation status when comparing the 12 months prior to the 12 months after treatment initiation, and 43% of patients still experienced two or more exacerbations requiring IV antibiotics per year despite being under LUMA-IVA. However, a significant decrease (by approximately one week) in the number of days/year of IV antibiotics was observed, which is comparable to data obtained in a previous study reporting data collected over 24 weeks in 46 patients with  $ppFEV_1 < 40$  [9]. A recent Australian multicenter 12-month observational study compared exacerbations rates in 72

Phe508del homozygous patients with ppFEV<sub>1</sub><40 treated with LUMA-IVA to a subgroup of 33 controls: CF patients matched for age, sex and ppFEV<sub>1</sub>, but with mutations ineligible for LUMA-IVA [3]. The authors reported that treatment was associated with lower rates of pulmonary exacerbations[3]. Altogether, these findings suggest that, in patients with ppFEV<sub>1</sub><40, treatment with LUMA-IVA is associated with a consistent benefit for BMI, but has minimal effects on lung function. Although LUMA-IVA was associated with a reduction in the number of IV antibiotic days, the decrease was less consistent than in patients with ppFEV<sub>1</sub> [40-90] and many patients still experienced multiple exacerbations under LUMA-IVA.

Variability in pulmonary response was seen in all subgroups of baseline ppFEV<sub>1</sub> and very few patients completely normalized their lung function. Although newer combinations of CFTR modulators (e.g., elexacaftor-tezacaftor-ivacaftor) have been shown to induce greater improvement in ppFEV<sub>1</sub> than LUMA-IVA, variability in the ppFEV<sub>1</sub> response has also been reported [16, 17]. The explanation for variability in the ppFEV<sub>1</sub> response to CFTR modulators is currently unknown. It has been hypothesized that it could be explained by differences in drug exposure due to pharmacokinetics/pharmacodynamics or variable compliance to the treatment regimen. However, recent studies showed that lumacaftor and ivacaftor blood levels were not correlated with ppFEV<sub>1</sub> improvement in a cohort of 18 children and young adults [18] and compliance rates in a recent French study were high[19]. Because LUMA-IVA partially restores ion transport, thus changing the physical characteristics of mucus secretions, it likely leads to reduced mucus plugging, an important determinant of airflow limitation in CF patients [20]. We speculate that the variable effect of LUMA-IVA on ppFEV<sub>1</sub> reflected, at least in part, the heterogeneous distribution of pathological findings in the patient population (e.g., mucus plugging vs. airway narrowing, fibrosis or destruction) [21, 22]. In addition, a weak increase in ppFEV<sub>1</sub> could be related to the presence of irreversible structural damage (e.g., small airway destruction) that is known to occur in patients with severe CF [23]. This

hypothesis is supported by preliminary data showing a reduction in mucus plugging but not improvement in bronchiectasis in CT scans of CF patients treated with ivacaftor[24]. Large CT scan analysis studies examining the morphological features associated with improvement in lung function should be undertaken in the future.

The present study has several strengths compared to previous studies. Although safety and effectiveness profile of lumacaftor-ivacaftor in patients with ppFEV<sub>1</sub><40 has been previously reported by several groups, including another French study by Hubert et al. [8], these study were generally shorter (e.g., 3 months for the study by Hubert et al.). The present study has the advantage of providing longer follow-up over 1 year, which allowed to examine effects of lumacaftor-ivacaftor on FEV<sub>1</sub> and BMI at 1 year, but also to examine their effects on exacerbations, which was not possible in shorter studies. The present study has also several limitations. Although LUMA-IVA may have multiple extra-pulmonary effects [25], they were not captured here. Indeed, the analysis focused on data recorded in routine clinical practice (i.e., ppFEV<sub>1</sub>, BMI and exacerbations), which are also documentation endpoints required by regulatory agencies. Data on exacerbations was limited to those treated with IV antibiotics, as no data was available on exacerbations treated with oral antibiotics, which are difficult to capture in large observational studies. Furthermore, it was not possible to assess health-related quality of life, which is not usually documented for patients with CF during routine clinical visits. In sensitivity analyses, we examined whether there could be differences in the effects of lumacaftor-ivacaftor. Although we found no difference on the effects of lumacaftor on ppFEV<sub>1</sub>, BMI or exacerbation in patients followed in different centers, our study was not specifically designed to address these questions.

In conclusion, the present analysis indicates that CF adolescents and adults may benefit from LUMA-IVA at all levels of baseline ppFEV<sub>1</sub>, as BMI increase and reduction in IV antibiotics days/year were observed in all subgroups. Findings that the subgroup of patients with ppFEV<sub>1</sub><40 were at higher risk of adverse effects, and that both subgroups of patients with

ppFEV<sub>1</sub><40 or with ppFEV<sub>1</sub>≥90 showed less consistent improvement in lung function concur with the choice of limiting recruitment in phase 3 clinical trials to patients with ppFEV<sub>1</sub> [40-90]. Importantly, at the individual level, patients with ppFEV<sub>1</sub><40 or ppFEV<sub>1</sub>≥90 could show a significant improvement in ppFEV<sub>1</sub> after initiation of CFTR modulator therapy, which further reinforces the decision from regulatory agencies to grant treatment indication to all patients with eligible *CFTR* genotypes, regardless of baseline lung function.



## **AUTHOR CONTRIBUTIONS**

**Design:** JLP, PRB, AM, ID, IS-G, HC, DH

**Acquisition of data:** JDS

**Analysis of data:** JLP, JDS, CM, PRB

**Interpretation of data:** All authors

**Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work:** All authors

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### **Participating Investigators of the French CF Reference network study group:**

Julie Mounard, Claire Poulet, Cinthia Rames, (Amiens); Christine Person, Françoise Troussier, Thierry Urban (Angers); Marie-Laure Dalphin, Jean-Claude Dalphin, Didier Pernet, Bénédicte Richaud-Thiriez (Besançon); Stéphanie Bui, Mickael Fayon, Julie Macey-Caro (Bordeaux); Karine Campbell, Muriel Laurans (Caen); Corinne Borderon, Marie-Christine Heraud, André Labbé, Sylvie Montcouquiol (Clermont-Ferrand); Laurence Bassinet, Natascha Remus (Créteil); Annlyse Fanton, Anne Houzel-Charavel, Frédéric Huet, Stéphanie Perez-Martin (Dijon); Amale Boldron-Ghaddar, Manuela Scalbert (Dunkerque); Laurent Mely (Giens); Boubou Camara, Catherine Llerena, Isabelle Pin, Sébastien Quéant (Grenoble); Aurélie Cottereau, Antoine Deschildre, Alice Gicquello, Thierry Perez, Lidwine Stervinou-Wemeau, Caroline Thumerelle, Benoit Wallaert, Nathalie Wizla (Lille); Jane Languepin, Céline Ménétrey, Magalie Dupuy-Grasset (Limoges); Lucie Bazus, Clelia Buchs, Virginie Jubin, Marie-Christine Werck-Gallois, Catherine Mainguy, Thomas Perrin, Philippe Reix, Agnès Toutain-Rigolet (Lyon Pédiatrie); Isabelle Durieu, Stéphane Durupt, Quitterie Reynaud, Raphaelle Nove-Josserand (Lyon adultes); Melisande Baravalle-Einaudi, Bérangère Coltey, Nadine Dufeu, Jean-Christophe Dubus, Nathalie Stremmler (Marseille); Davide Caimmi, Raphaël Chiron (Montpellier); Yves Billon, Jocelyne Derelle, Sébastien Kieffer, Anne-Sophie Pichon, Cyril Schweitzer, Aurélie Tatopoulos (Nancy); Sarah Abbes, Tiphaine Bihouée, Isabelle Danner-Boucher, Valérie David, Alain Haloun, Adrien Tissot (Nantes); Sylvie Leroy, Carole Bailly-Piccini (Nice); Annick Clément, Harriet Corvol, Aline Tamalet (Paris, Trousseau); Pierre-Régis Burgel, Isabelle Honoré, Dominique Hubert, Reem Kanaan, Clémence Martin (Paris, Cochin); Cécile Bailly, Frédérique Chédevergne, Jacques De Blic, Brigitte Fauroux, Murielle Le Bourgeois, Isabelle Sermet-Gaudelus (Paris, Necker); Bertrand Delaisi, Michèle Gérardin, Anne Munck (Paris, Robert Debré); Michel Abély, Bruno Ravoninjatovo (Reims); Chantal Belleguic, Benoit Desrues, Graziella Brinchault (Rennes);

Michel Dagherne, Eric Deneuille, Sylvaine Lefeuvre (Rennes-Saint Brieu); Anne Dirou, Jean Le Bihan, Sophie Ramel (Roscoff); Stéphane Dominique, Christophe Marguet (Rouen) ; Annabelle Payet (La Réunion) ; Romain Kessler, Michele Porzio, Vincent Rosner, Laurence Weiss (Strasbourg) ; Sandra de Miranda, Dominique Grenet, Abdoul Hamid, Clément Picard (Suresnes) ; François Brémont, Alain Didier, Géraldine Labouret, Marie Mittaine, Marlène Murriss-Espin, Laurent Têtu (Toulouse) ; Laure Cosson, Charlotte Giraut, Anne-Cécile Henriot, Julie Mankikian, Sophie Marchand (Tours) ; Sandrine Hugé, Véronique Storni (Vannes) ; Emmanuelle Coirier-Duet (Versailles).

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## TABLES

**Table 1. Characteristics of 827 patients with CF according to ppFEV<sub>1</sub> at study entry.**

	ppFEV <sub>1</sub> <40 n=121	ppFEV <sub>1</sub> [40-90[ n=609	ppFEV <sub>1</sub> ≥90 n=97	P value
Age, years	30 [24 -34]	21 [15.5 - 29]	20 [18 - 25]	<.0001
Female sex	39.7% (48)	45.2% (275)	45.4% (44)	0.53
Adolescents / adults	12.4% (15)/87.6% (106)	40.6% (247)/59.4% (362)	28.9% (28)/71.1% (69)	<.0001
ppFEV <sub>1</sub>	33.7 [30.9-36.9]	66.2 [53.6-76.9]	96.4 [93.0-101.7]	<.0001
BMI, kg/m <sup>2</sup> (adults only)	18.0 [17.0 - 20.0] (106)	20.0 [ 18.0 - 21.0] (362)	21.0 [ 20.0 - 23.0] (69)	<.0001
BMI, z-score (adolescents only)	-1.4 [ -1.8 ; -0.5] (15)	-0.7 [ -1.2 - -0.2] (247)	-0.3 [ -0.8 ; 0.7] (28)	0.0005
<i>P. aeruginosa</i>	77.7% (94)	59.6% (359)	51.1% (48)	<.0001
<i>B. cepacia</i>	1.7% (2)	3.3% (20)	1.1% (1)	0.33
MSSA	43.8% (53)	72.3% (435)	73.4% (69)	<.0001
MRSA	15.7% (19)	15.9% (96)	13.8% (13)	0.87
<i>H. influenzae</i>	8.3% (10)	13.0% (79)	25.8% (25)	0.001
Diabetes mellitus	41.3% (50)	26.8% (163)	19.6% (19)	0.001
Cirrhosis/portal hypertension	4.1% (5)	4.9% (30)	7.2% (7)	0.001
Elevated liver enzymes	14% (17)	11.5% (70)	12.4% (12)	0.73
IV antibiotic courses per patient in the previous 12 months	2.0 [1.0; 4.0] Mean 2.5	1.0 [0; 2.0] Mean 1.2	0 [0; 1.0] Mean 0.4	<.0001
Maintenance pulmonary medications				
Azithromycin	76% (92)	58.1% (354)	50.5% (49)	<.0001
Inhaled antibiotics	70.2% (85)	61.4% (374)	47.4% (46)	0.003
Dornase alfa	57% (69)	70.9% (432)	70.1% (68)	0.01
Inhaled hypertonic saline	9.9% (12)	13.3% (81)	11.3% (11)	0.54
Inhaled bronchodilators	81.8% (99)	75.9% (462)	68% (66)	0.06
Inhaled corticosteroids	51.2% (62)	57% (347)	51.5% (50)	0.36
Oral corticosteroids	9.9% (12)	8.4% (51)	7.2% (7)	0.77

ppFEV<sub>1</sub>: percent predicted forced expiratory volume in 1 second; BMI: body mass index; MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; IV: intravenous;

## FIGURE LEGENDS

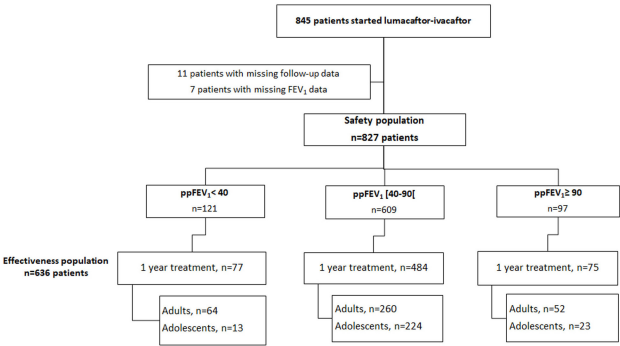
**Figure 1.** Flow chart describing the safety and effectiveness populations and the distribution of patients by subgroups of baseline ppFEV<sub>1</sub> levels and age groups.

**Figure 2.** Distribution of the difference between the best ppFEV<sub>1</sub> in the 12 months after versus the 12 months before LUMA-IVA in the effectiveness population (n=631 patients). Data are presented by subgroups of baseline lung function: ppFEV<sub>1</sub><40 (top panel), ppFEV<sub>1</sub> [40-90[ (middle panel) and ppFEV<sub>1</sub>≥90 (lower panel). Bars represent % patients in

each subgroups. Numbers of patients are indicated on top of the bars. Percentage of patients with difference  $\geq 5\%$  pred or  $\geq 10\%$  pred are indicated in each panel.

**Figure 3. Evolution of body mass index (kg/m<sup>2</sup>) in adults (top panel) or body mass index (z-score) in adolescents (lower panel) between baseline and 12 months after initiation of LUMA-IVA.** Data are presented according to subgroups of ppFEV<sub>1</sub> (ppFEV<sub>1</sub><40; ppFEV<sub>1</sub> [40-90[, ppFEV<sub>1</sub>  $\geq 90$ ) at baseline. Comparison of data within each subgroup were analyzed using Wilcoxon paired test. Tests were conducted by subgroup and no correction for multiple test was necessary.

**Figure 4. Exacerbations requiring intravenous antibiotics in the 12 months before (upper panels) and the 12 months after (lower panels) by baseline ppFEV<sub>1</sub> subgroups.** Horizontal bars depict the proportion of patients with no exacerbation, with one exacerbation or two or more exacerbations. Patients are grouped according to baseline ppFEV<sub>1</sub> subgroups: ppFEV<sub>1</sub><40 (left), ppFEV<sub>1</sub> [40-90[ (middle) and ppFEV<sub>1</sub> $\geq 90$  (right). The number of patients with exacerbations was reduced in patients with ppFEV<sub>1</sub> [40-90[ (n=465;  $P < 0.001$ ; paired analysis by the Bowker's test for symmetry), with a similar trend in those with ppFEV<sub>1</sub> $\geq 90$  (n=74;  $P = 0.056$ ) but not in those with ppFEV<sub>1</sub><40 (n=75;  $P = 0.29$ ). Data are presented as percentage and number [% (n)] of patients within each subgroup.



% patients

