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

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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 ($ppFEV_1$) between 40 and 90. Marketing authorizations have been granted for patients at all levels of $ppFEV_1$.

**Methods** To evaluate the safety and effectiveness of LUMA-IVA over the first year of treatment in patients with $ppFEV_1$<40 or $ppFEV_1$≥90 in comparison with those with $ppFEV_1$ [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 $ppFEV_1$ at treatment initiation ($ppFEV_1$<40, n=121; $ppFEV_1$ [40-90[, n=609; $ppFEV_1$≥90, n=97). Treatment discontinuation rate was higher in $ppFEV_1$<40 patients (28.9%) than in those with $ppFEV_1$ [40-90[ (16.4%) or $ppFEV_1$≥90 (17.5%). In patients with uninterrupted treatment, significant increase in $ppFEV_1$ occurred in the $ppFEV_1$ [40-90[ subgroup (+2.9%, $P$<0.001), and in those $ppFEV_1$<40 (+0.5%, $P$=0.03) but not in those with $ppFEV_1$≥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 $ppFEV_1$<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 $ppFEV_1$ 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 restauration 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 ($ppFEV_1$) between 40 and 90 [7]. Reasons for these criteria included the fear of adverse effects in patients with more severe respiratory disease ($ppFEV_1<40$) and the general belief that, in patients with $ppFEV_1\geq90$, an increase in $ppFEV_1$ would be very unlikely. Nonetheless, LUMA-IVA was approved for Phe508del homozygous patients at all levels of $ppFEV_1$ 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 $ppFEV_1<40$ [8-10]. However, few studies have examined the safety profile of LUMA-IVA in patients with $ppFEV_1\geq90$ or its benefits for those with $ppFEV_1<40$ [11, 12] or $ppFEV_1 \geq90$ [13]. Furthermore these studies generally included a limited number of patients from a small

number of centers, who were not compared to patients with $FEV_1$ [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 $ppFEV_1$ 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 ($ppFEV_1<40$) or too high ($ppFEV_1\geq90$) for them to be eligible to participate in clinical trials. The magnitude of improvement in $ppFEV_1$ and body mass index (BMI), and the reduction in exacerbation frequency in these patients was compared with those of patients with baseline $ppFEV_1$ [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 1st and December 31st 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, $ppFEV_1$ 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 ± standard deviation (SD). BMI was calculated as $kg/m^2$ for adults and z-score for adolescents. Three subgroups were defined according to $ppFEV_1$ at study entry (baseline), prior to initiation of LUMA-IVA: $ppFEV_1<40$, $ppFEV_1$ [40-90[, and $ppFEV_1\geq90$. The likelihood of treatment discontinuation between subgroups (e.g. $ppFEV_1<40$ vs. $ppFEV_1$ [40-90[ vs. $ppFEV_1\geq90$) 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 $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1 \geq 5\%$ 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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## 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 $FEV_1$ at baseline. The safety population therefore consisted in 827 patients (537 adults and 290 adolescents) including 121 patients (14.7 %) with $ppFEV_1<40$, 609 (73.6 %) with $ppFEV_1$ [40-90[ and 97 (11.7 %) with $ppFEV_1\geq90$. Patient characteristics by $FEV_1$ 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 $ppFEV_1<40$, 100 patients had $ppFEV_1$ [40-90[ and 17 patients had $ppFEV_1\geq90$. The treatment discontinuation rate was higher in patients with $ppFEV_1<40$ (28.9%) than in those with $ppFEV_1$ [40-90[ (16.4%; $P$=0.002) or $ppFEV_1\geq90$ (17.5%; $P$=0.06). The discontinuation rate was not significantly different in patients with $ppFEV_1$ [40-90[ vs. $ppFEV_1\geq90$ ($P$=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 $ppFEV_1<40$, but represented only 42% and 29% of causes in patients with a $ppFEV_1$ [40-90[ and $ppFEV_1\geq90$, respectively ($P$=0.003 and $P$=0.004 compared with patients with $ppFEV_1<40$). No significant difference was observed when comparing rates of respiratory AEs in patients with $ppFEV_1$ [40-90[ and in those with $ppFEV_1 \geq90$ ($P$=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 $ppFEV_1$ compared with baseline values (median [IQR], +2.9% [-1.8%; +8.0%]; n=484, $P<0.001$) was observed in patients with $ppFEV_1$ [40-90[. A significant increase was also observed in those with $ppFEV_1<40$ (+0.5% [-2.2%; + 4.3%]; n=77; $P=0.03$), but not in those with $ppFEV_1\geq90$ (+1.7% [-3.9%; +5.6%]; n=75, $P=0.46$). The magnitude of increase in $ppFEV_1$ was therefore significantly greater in patients in the [40-90[ range compared to those with $ppFEV_1<40$ or $ppFEV_1\geq90$ ($P=0.03$ and $P=0.05$; respectively). Marked variability in $ppFEV_1$ change was present in all subgroups. The distribution of the difference between $ppFEV_1$ 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 $ppFEV_1$ [40; 90[, but only in 22% and 27% of patients with $ppFEV_1<40$ and $ppFEV_1\geq90$, 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 $kg/m^2$ [0; +1.0] in patients with $ppFEV_1<40$ (n=64; $P<0.0001$), 0 [0; +1.0] $kg/m^2$ in the $ppFEV_1$ [40; 90[ subgroup (n=260; $P<0.001$), and +1.0 [0; +1.0] $kg/m^2$ in those with $ppFEV_1\geq90$ (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 $ppFEV_1<40$ subgroup (n=13; $P=0.01$); +0.50 [0; +0.94] in the $ppFEV_1$ [40; 90[

subgroup (n=224; *P*<0.001), and +0.43 [0; +0.85] in the ppFEV$_1$≥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/m2) in adults and z-score BMI in adolescents by ppFEV$_1$ 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$_1$ 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$_1$ [40-90[ (n=465; *P*<0.001), with a similar trend in those with ppFEV$_1$≥90 (n=74; *P*=0.056). No significant difference was found in those with ppFEV$_1$<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$_1$<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$_1$ [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$_1$≥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 $ppFEV_1$ at baseline that would have been considered either too low ($ppFEV_1$<40) or too high ($ppFEV_1 \geq 90$) to meet eligibility criteria for phase 3 clinical trials, which included only patients with $ppFEV_1$ [40-90[ [7]. A $ppFEV_1$ increase ≥5% was found in 40% of patients with baseline $ppFEV_1$ [40-90[, a proportion that was 1.5 to 2 fold higher than in patients with baseline $ppFEV_1$ <40 or $ppFEV_1 \geq 90$. 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 $ppFEV_1$>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 $ppFEV_1$ [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 $ppFEV_1$<40 treated with LUMA-IVA to a subgroup of 33 controls: CF patients matched for age, sex and $ppFEV_1$, 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 $ppFEV_1$<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 $ppFEV_1$ [40-90[ and many patients still experienced multiple exacerbations under LUMA-IVA.

Variability in pulmonary response was seen in all subgroups of baseline $ppFEV_1$ 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 $ppFEV_1$ than LUMA-IVA, variability in the $ppFEV_1$ response has also been reported [16, 17]. The explanation for variability in the $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$ 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 $ppFEV_1$<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 $FEV_1$ 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., $ppFEV_1$, 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 ppFEV1, 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 $ppFEV_1$, as BMI increase and reduction in IV antibiotics days/year were observed in all subgroups. Findings that the subgroup of patients with $ppFEV_1$<40 were at higher risk of adverse effects, and that both subgroups of patients with

ppFEV$_1$<40 or with ppFEV$_1$≥90 showed less consistent improvement in lung function concur with the choice of limiting recruitment in phase 3 clinical trials to patients with ppFEV$_1$ [40-90[. Importantly, at the individual level, patients with ppFEV$_1$<40 or ppFEV$_1$≥90 could show a significant improvement in ppFEV$_1$ 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
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## TABLES

**Table 1. Characteristics of 827 patients with CF according to $ppFEV_1$ at study entry.**

| | **$ppFEV_1$<40 n=121** | **$ppFEV_1$ [40-90[ n=609** | **$ppFEV_1$≥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 |
| **$ppFEV_1$** | 33.7 [30.9-36.9] | 66.2 [53.6-76.9] | 96.4 [93.0-101.7] | <.0001 |
| **BMI. kg/m² (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 |
| ***P. aeruginosa*** | 77.7% (94) | 59.6% (359) | 51.1% (48) | <.0001 |
| ***B. cepacia*** | 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 |
| ***H. influenzae*** | 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 |

**$ppFEV_1$: 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

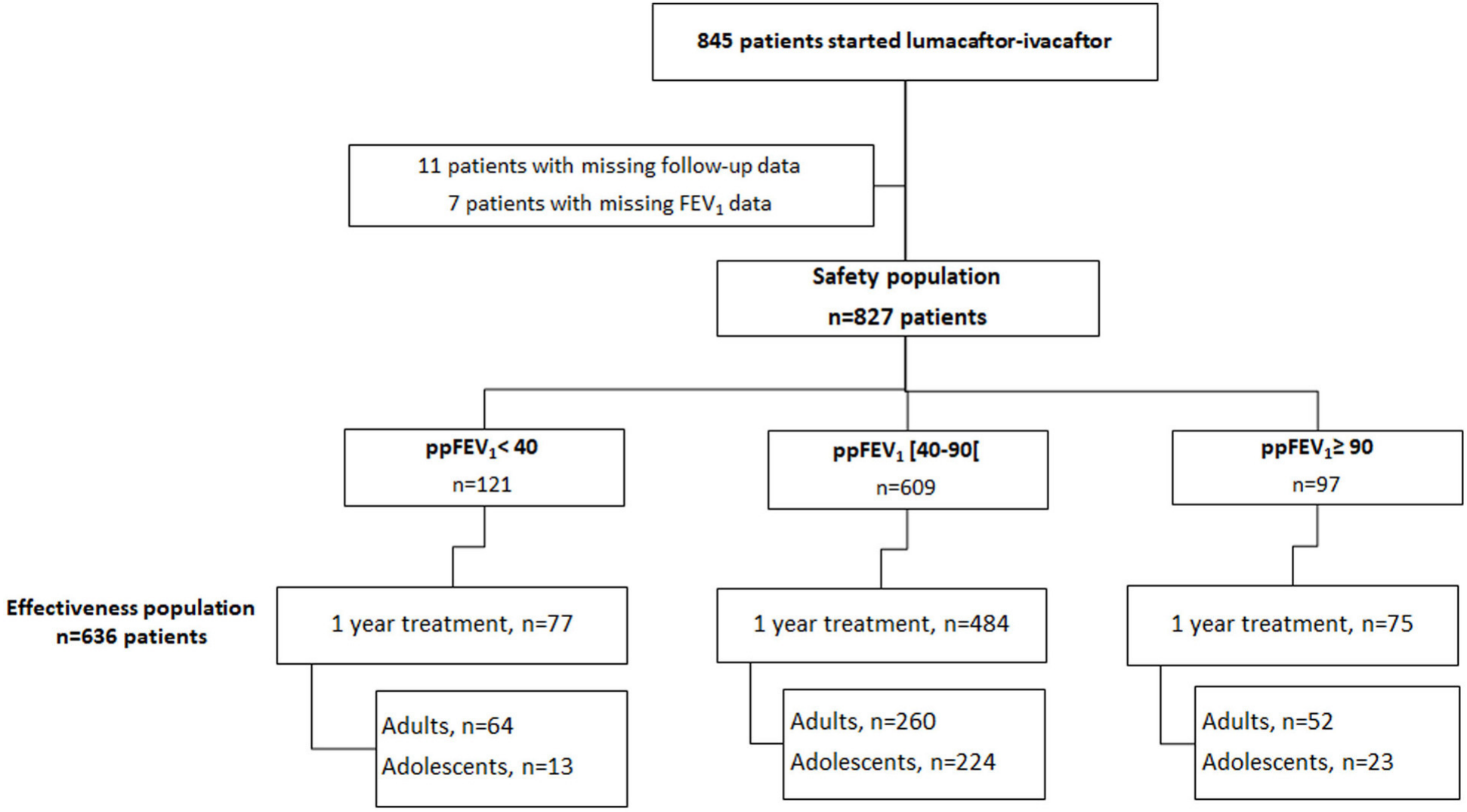
**Figure 1. Flow chart describing the safety and effectiveness populations and the distribution of patients by subgroups of baseline $ppFEV_1$ levels and age groups.**

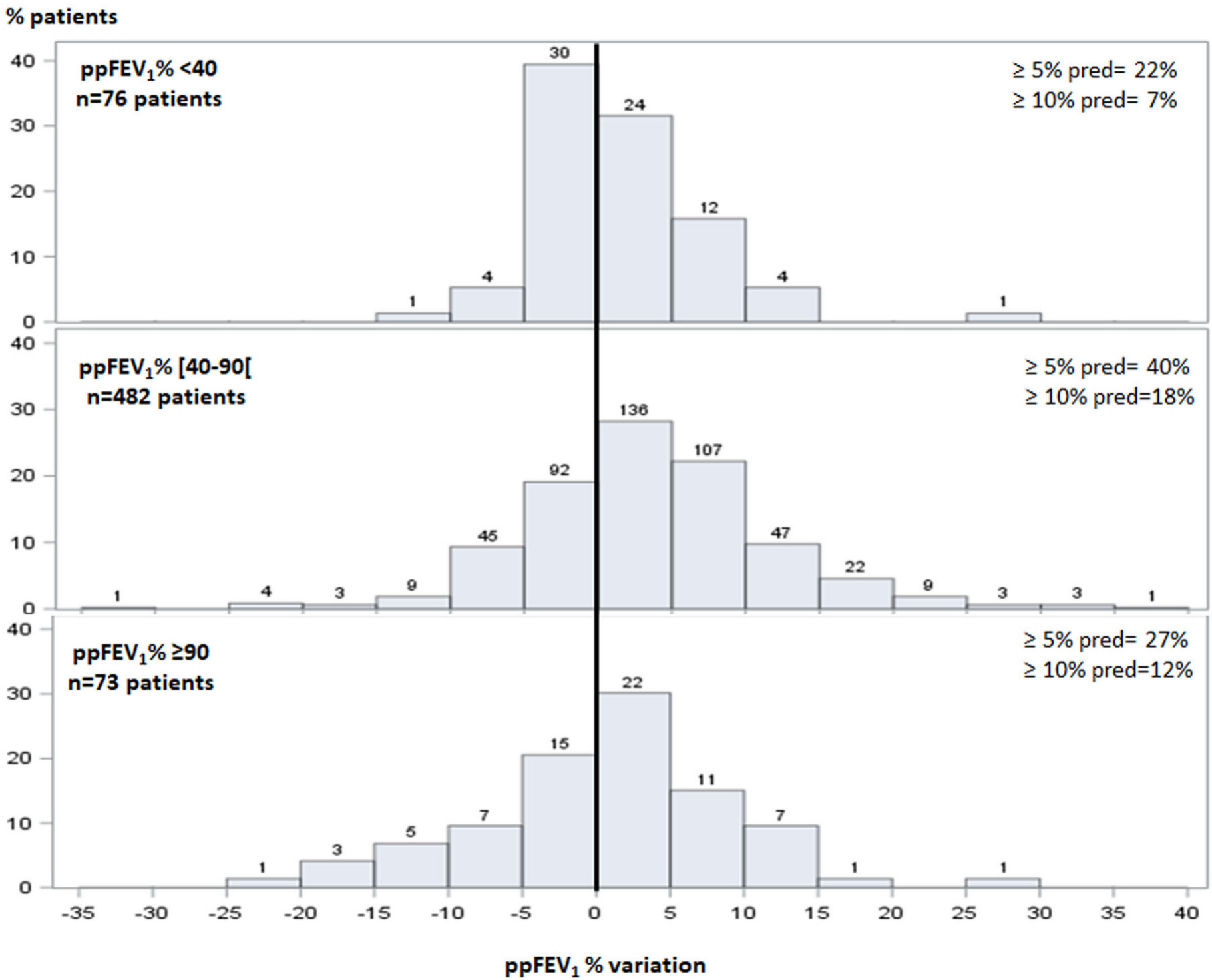
**Figure 2. Distribution of the difference between the best $ppFEV_1$ in the 12 months after versus the 12 months before LUMA-IVA in the effectiveness population (n=631 patients).** Data are presented by subgroups of baseline lung function: $ppFEV_1$<40 (top panel), $ppFEV_1$ [40-90[ (middle panel) and $ppFEV_1$≥90 (lower panel). Bars represent % patients in

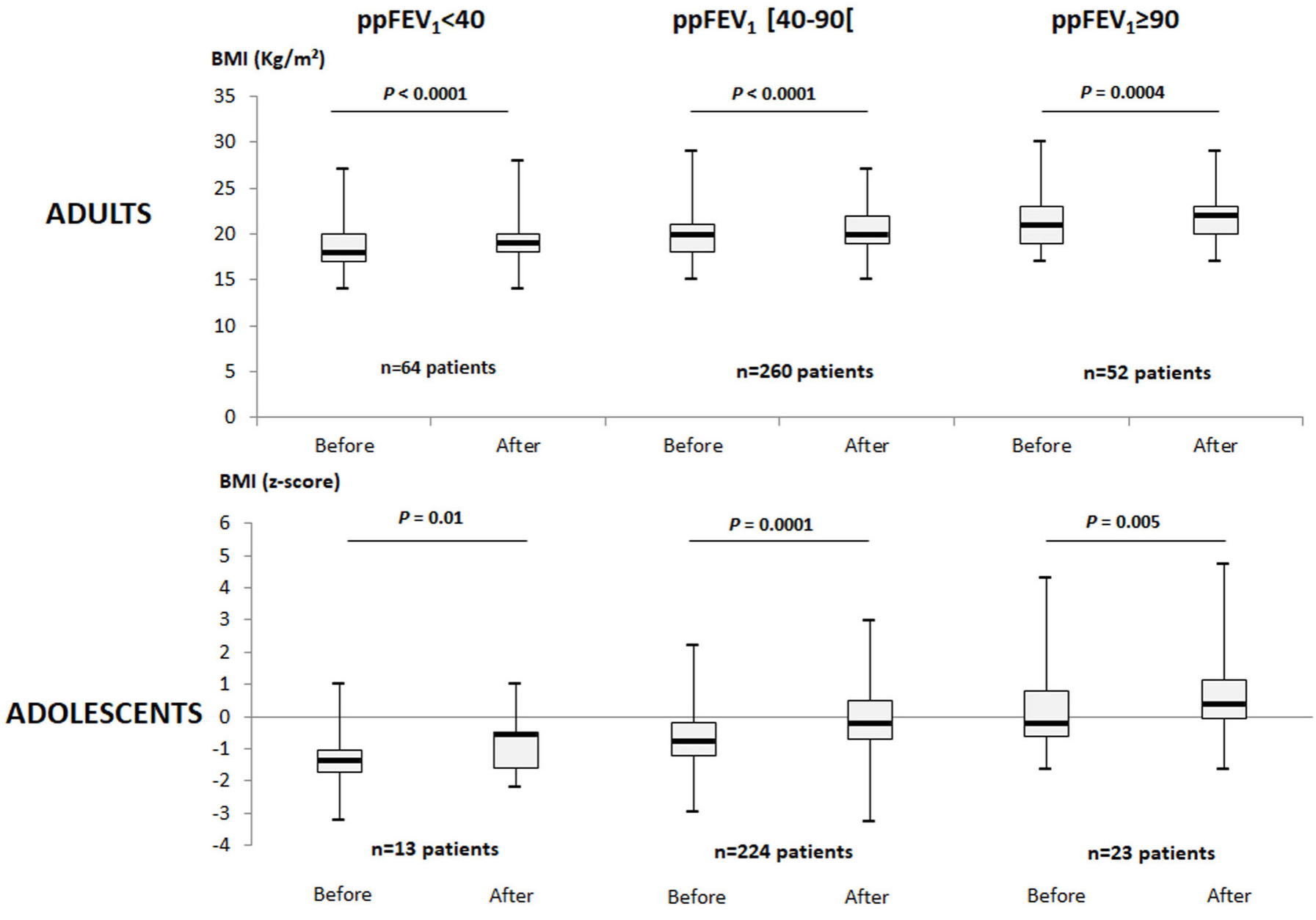
each subgroups. Numbers of patients are indicated on top of the bars. Percentage of patients with difference ≥5% pred or ≥10% pred are indicated in each panel.

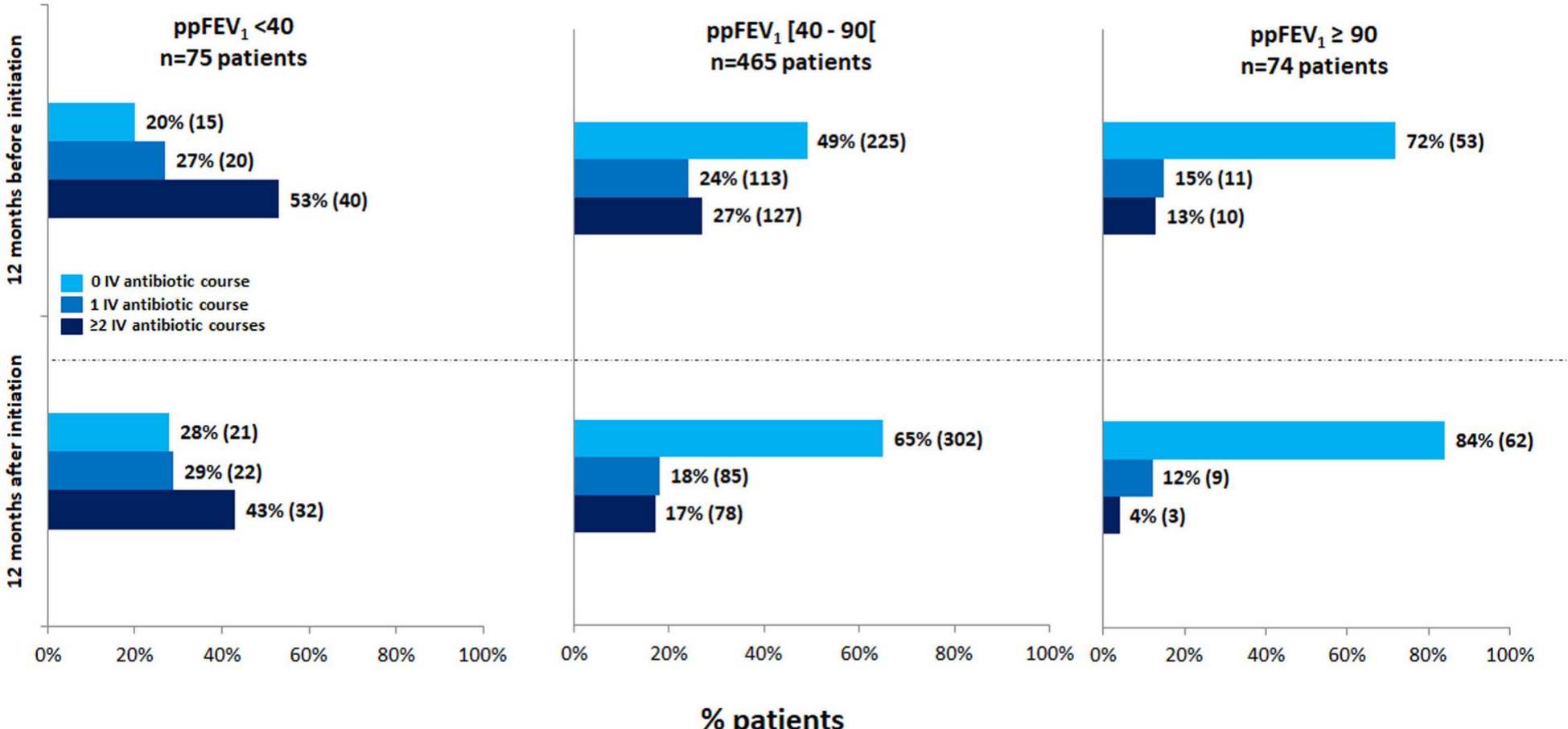
**Figure 3. Evolution of body mass index (kg/m2) in adults (top panel) or body mass index (z-score) in adolescents (lower panel) between baseline and 12 months after initiation of LUMA-IVA.** Data are presented according to subgroups of $ppFEV_1$ ($ppFEV_1$<40; $ppFEV_1$ [40-90[, $ppFEV_1$ ≥90) at baseline. 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 $ppFEV_1$ 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 $ppFEV_1$ subgroups: $ppFEV_1$<40 (left), $ppFEV_1$ [40-90[ (middle) and $ppFEV_1$≥90 (right). The number of patients with exacerbations was reduced in patients with $ppFEV_1$ [40-90[ (n=465; $P$<0.001; paired analysis by the Bowker's test for symmetry), with a similar trend in those with $ppFEV_1$≥90 (n=74; $P$=0.056) but not in those with $ppFEV_1$<40 (n=75; $P$=0.29). Data are presented as percentage and number [% (n)] of patients within each subgroup.


845 patients started lumacaftor-ivacaftor
11 patients with missing follow-up data
7 patients with missing FEV1 data
Safety population
n=827 patients
ppFEV1< 40
n=121
ppFEV1 [40-90[
n=609
ppFEV1≥ 90
n=97
Effectiveness population
n=636 patients
1 year treatment, n=77
1 year treatment, n=484
1 year treatment, n=75
Adults, n=64
Adolescents, n=13
Adults, n=260
Adolescents, n=224
Adults, n=52
Adolescents, n=23


% patients
ppFEV1% <40
n=76 patients
≥ 5% pred= 22%
≥ 10% pred= 7%
ppFEV1% [40-90[
n=482 patients
≥ 5% pred= 40%
≥ 10% pred=18%
ppFEV1% ≥90
n=73 patients
≥ 5% pred= 27%
≥ 10% pred=12%
ppFEV1 % variation


ppFEV1<40
ppFEV1 [40-90[
ppFEV1≥90
ADULTS
BMI (Kg/m²)
P < 0.0001
P < 0.0001
P = 0.0004
35
30
25
20
15
10
5
0
n=64 patients
n=260 patients
n=52 patients
Before
After
Before
After
Before
After
ADOLESCENTS
BMI (z-score)
P = 0.01
P = 0.0001
P = 0.005
6
5
4
3
2
1
0
-1
-2
-3
-4
n=13 patients
n=224 patients
n=23 patients
Before
After
Before
After
Before
After


ppFEV1 <40
n=75 patients
ppFEV1 [40 - 90[
n=465 patients
ppFEV1 ≥ 90
n=74 patients
12 months before initiation
12 months after initiation
0 IV antibiotic course
1 IV antibiotic course
≥2 IV antibiotic courses
20% (15)
27% (20)
53% (40)
49% (225)
24% (113)
27% (127)
72% (53)
15% (11)
13% (10)
28% (21)
29% (22)
43% (32)
65% (302)
18% (85)
17% (78)
84% (62)
12% (9)
4% (3)
0%
20%
40%
60%
80%
100%
% patients