Gender (N=2105)	
Male	1545 (73.4%)
Female	560 (26.6%)
Age (years) (N=2105)	
VALUE RANGE	40-96
MEDIAN	68
MEAN (+/- SD)	68 (9.55)
Age group (N=2105)	
< 65 YoA	732 (34.8%)
≥ 65 YoA	1373 (65.2%)
Height (cm) (N=2105)	
VALUE RANGE	136-197
MEDIAN	170
MEAN (+/- SD)	169.3 (8.68)
Weight (kg) (N=2105)	
VALUE RANGE	34-170
MEDIAN	79
MEAN (+/- SD)	80.71 (17.36)
BMI (kg/m^2) (N=2105)	
VALUE RANGE	13.62-66.41
MEDIAN	27.44
MEAN (+/- SD)	28.1 (5.33)
BMI group (N=2105)	
< 18.5 kg/m^2	29 (1.4%)
18.5 – 24.9 kg/m^2	543 (25.8%)
25 – 29.9 kg/m^2	900 (42.8%)
> 30 kg/m^2	633 (30.1%)
Systolic / Diastolic blood pressure (mmHg) (N=2105)	
VALUE RANGE	90-180 / 50-110
MEDIAN	130 / 80
MEAN (+/- SD)	129.82 (12.05) / 78.96 (8.16)
Heart Rate (bpm) (N=2105)	
VALUE RANGE	50-116
MEDIAN	76
MEAN (+/- SD)	76.78 (8.82)

Supplementary Table 1: Summary statistics (value range, mean, standard deviation and median) of the demographics and vital signs of the study sample.

BMI: body-mass index, bpm: beats per minute, SD: standard deviation

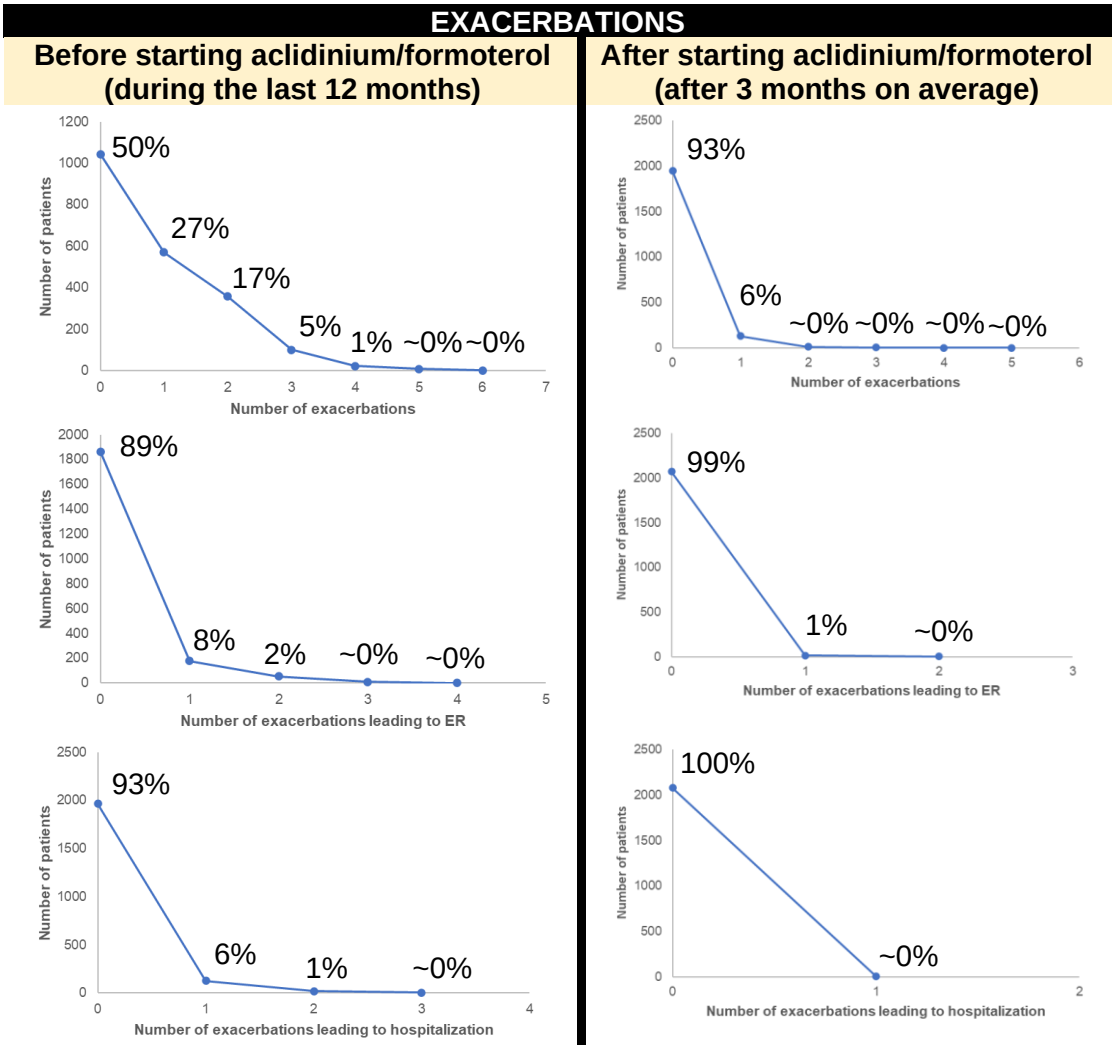
Time since COPD diagnosis (years) **[N=2015]**	MEAN (+/- SD) ---- 5.77 (5.38) MEDIAN ---- 4 VALUE RANGE ---- 0-35
2019 GOLD classification [N=2015]	A ---- 239 (11%) B ---- 1283 (61%) C ---- 211 (10%) D ---- 372 (18%)
Family history [N=2105]	COPD ---- 234 (11%) Asthma ---- 142 (7%) Malignancy ---- 147 (7%) Occupational hazardous exposure ---- 64 (3%)
Presence of Comorbidities [N=2105]	No ---- 1081 (51%) Yes ---- 1024 (49%)

Type of comorbidities [N=2105]

Cardiovascular disorders	Hypertension, Ischemic Heart Disease, Heart Failure, Arrhythmias, Peripheral Vascular Disease	36.4%
Metabolic disorders	Metabolic Syndrome, Diabetes Mellitus	10.9%
Psychiatric disorders	Anxiety, Depression	6%
Gastrointestinal disorders	Gastroesophageal reflux	3%
Myoskeletal disorders	Osteoporosis	2.5%
Pulmonary disorders (other than COPD)	Pulmonary CA	1.1%
Other	Dyslipidaemia, Benign Prostate Hypertrophy, Abnormal thyroid function tests, Valvular heart disease, Chronic renal failure, CA Prostate, CA Breast, Tuberculosis, Aortic aneurysm, CA Bladder, Rheumatoid Arthritis, Nephrectomy, Psoriasis, CA Endometrial, Rhinitis, Iron deficiency anemia, Non-Hodgkin's lymphoma, Obesity, CA Colorectal, CA Esophageal, CA Larynx, CA rhinopharyngeal, Angiitis, Ankylosing spondylitis, Alcoholic hepatitis, Alcoholic cirrhosis, Aplastic anemia, Bronchiectasis NOS, Senile dementia, Peptic ulcer, Migraine, Hepatitis-B, Abnormal coagulation time, Cryptogenic organizing pneumonia, Parkinsons' Disease, Kidney stone, Pleural infection, Osteoarthritis, Polyarthritis, Silicosis, Multiple sclerosis, Sleep Apnea Syndrome, Hypertrophic cardiomyopathy, Hysterectomy, Chemical pneumonitis, Pericarditis, Prostatitis	7.7%

Supplementary Table 2: Summary statistics related to the medical history of our study sample.

CA: cancer, COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease, SD: standard deviation



Supplementary Figure 1: Exacerbations of COPD (overall, leading to the ER or leading to hospitalization) in the study sample, either 12 months prior initiating pharmacotherapy containing aclidinium/formoterol (left panel) or after averagely 3 months on pharmacotherapy containing aclidinium/formoterol (right panel). For the 12-month period preceding initiation of pharmacotherapy containing aclidinium/formoterol, 1062 patients (50% of the total study sample) experienced at least one exacerbation; in particular, 572 patients (27%) experienced 1 exacerbation, 357 patients (17%) experienced two exacerbations, 101 patients (5%) experienced three, 23 patients (1%) experienced four, 8 patients experienced five and 2 patients experienced six exacerbations. In 241 patients (11%), at least one exacerbation was serious enough to lead to the ER; in particular, 178 patients (8%) were transferred to the ER once, 52 patients (2%) were transferred to the ER twice, 10 patients were taken to the ER three times and there was one case where the patient was transferred to the ER four times due to a COPD exacerbation. In 143 patients (7%), at least one exacerbation was serious enough to lead to hospitalization; 124 patients (6%) were hospitalized once, 17 patients (1%) twice and 2 patients three times. For the averagely 3-month period following initiation of pharmacotherapy containing aclidinium/formoterol, 142 patients (7% of the total study sample) experienced at least one exacerbation; in particular, 129 patients (6%) experienced 1 exacerbation, 10 patients experienced two exacerbations, 2 patients experienced three, and one patient experienced five exacerbations. In 17

patients (1%), at least one exacerbation was serious enough to lead to the ER; in particular, 15 patients (1%) were transferred to the ER once, and two patients were transferred to the ER twice. In 8 patients, one exacerbation was serious enough to lead to hospitalization.

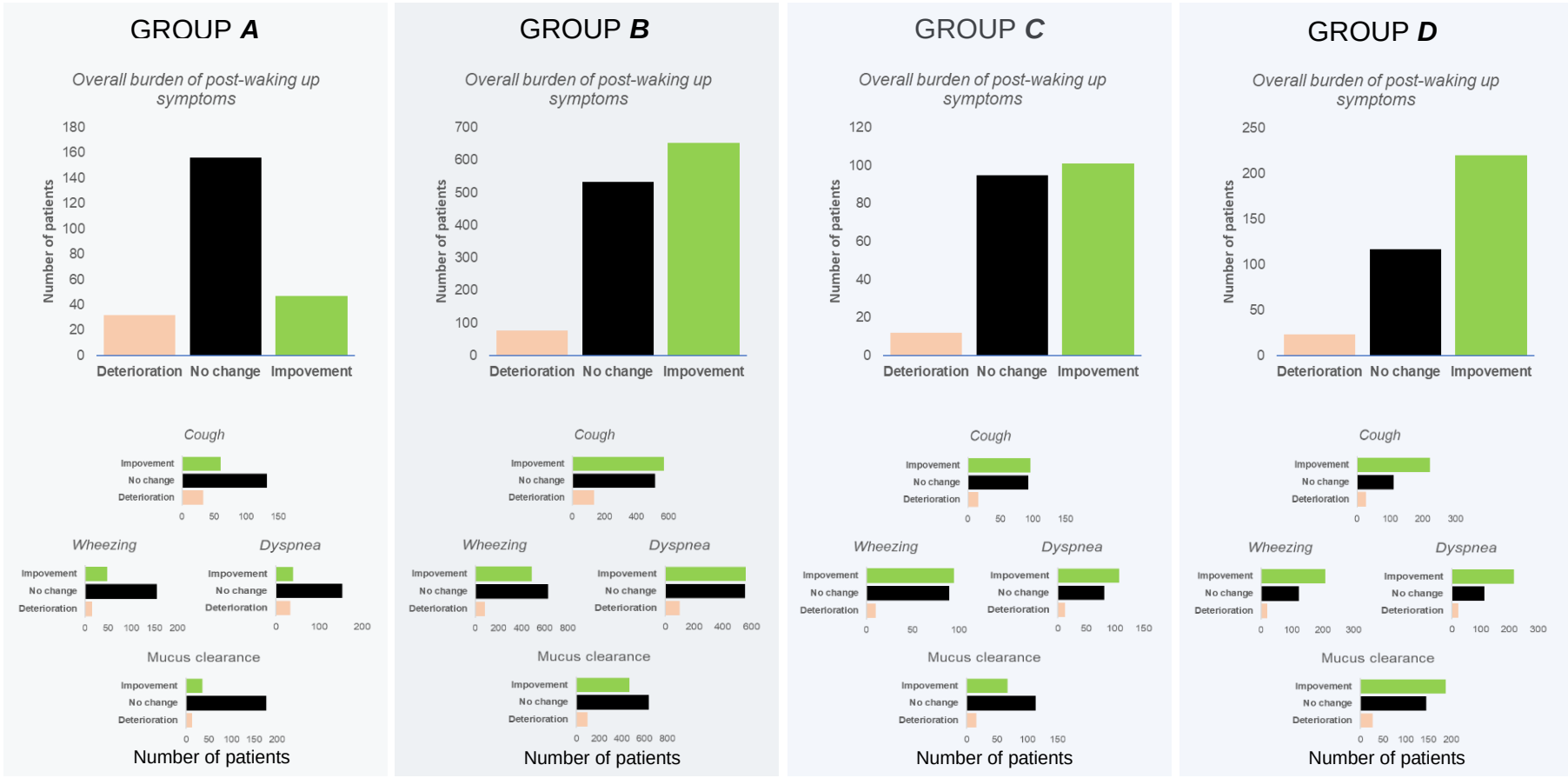
ER: emergency room

	MEAN	SD
Prior starting aclidinium/formoterol [N=2105]		
TOTAL SCORE (sum of partial domains)	**16.7**	**6.9**
Coughing	2.26	1.03
Phlegm in the chest	2.12	1.08
Feeling of tightness in the chest	1.78	1.16
Breathlessness when walking up a hill or one flight of stairs	2.77	1.15
Limitation in doing activities at home	2.03	1.20
Confidence on leaving home despite the lung condition	1.85	1.25
Sleeping soundly	1.70	1.17
Having lots of energy	2.14	1.11
After 3 months on average on aclidinium/formoterol [N=2086]		
TOTAL SCORE (sum of partial domains)	**11.4**	**5.8**
Coughing	1.55	0.82
Phlegm in the chest	1.45	0.91
Feeling of tightness in the chest	1.19	0.95
Breathlessness when walking up a hill or one flight of stairs	1.92	1.07
Limitation in doing activities at home	1.45	1.02
Confidence on leaving home despite the lung condition	1.29	1.03
Sleeping soundly	1.08	0.92
Having lots of energy	1.51	0.98

Supplementary Table 3: Summary statistics of CAT, which consists of 8 items, each of which describes the best to worst (0 to 5) case of a state on a Likert-type scale.

CAT: COPD assessment test, COPD: chronic obstructive pulmonary disease, N: number of cases, SD: standard deviation

Evolution of early morning (post-waking up) symptoms after starting aclidinium/formoterol



Supplementary Figure 2

A Wilcoxon signed-rank test was conducted to determine the effect of a 3-month (on average) treatment period with aclidinium/formoterol as part of the COPD therapeutic strategy (either monotherapy or in combination with other pharmacological agents) on the overall burden of early morning (post-waking up) symptoms and specific early morning problems (cough, wheezing, dyspnea, mucus clearance) of COPD patients per 2019 GOLD ABCD group. The variables were determined twice through a corresponding questionnaire using a 5-point Likert-type scale, ranging from no symptoms (0) to very severe symptoms (4): at baseline (visit 1) and after the averagely 3-month period on aclidinium/formoterol (visit 2). Positive within-subject differences (visit 2 – visit 1) indicate a clinical deterioration, while negative within-subject differences indicate a clinical improvement. No within-subject difference indicates a stable condition. The difference scores were approximately symmetrically distributed, as assessed by a histogram with superimposed normal curve.

(*Overall burden of early morning symptoms - Upper panel in each ABCD group*) In group A, 28 patients deteriorated their early morning symptomatology, while 51 improved it (and 156 remained stable), $z = -2.72$, $p = 0.007$. Improvement-to-non-improvement ratio was 0.28. In Group B, 66 patients deteriorated their early morning symptomatology, while 662 improved it (and 534 remained stable). Improvement-to-non-improvement ratio was 1.1. In Group C, only 11 patients deteriorated their early morning symptomatology, while 102 improved it (and 96 remained stable), $z = -8.33$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.95. Finally, in Group D, only 21 patients deteriorated their early morning symptomatology, while 224 improved it (and 122 remained stable). Improvement-to-non-improvement ratio was 1.57. In Groups B and D, there was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -21.22$ ($p < 0.001$) and $z = -12.29$ ($p < 0.001$) respectively.

(*Specific early morning symptoms <cough> - Lower panel in each ABCD group*) In group A, 33 patients deteriorated their early morning cough, while 60 improved it (and 132 remained stable), $z = -2.3$, $p = 0.021$. Improvement-to-non-improvement ratio was 0.36. In Group B, 135 patients deteriorated their early morning cough, while 570 improved it (and 516 remained stable), $z = -15.34$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.88. In Group C, only 16 patients deteriorated their early morning cough, while 96 improved it (and 93 remained stable), $z = -7.5$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.88. In groups A-C, no changes in the median score of the Likert-type scale have been observed between the two study visits. Finally, in Group D, just 28 patients deteriorated their early morning cough, while 222 improved it (and 112 remained stable). There was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -11.49$, $p < 0.001$. Improvement-to-non-improvement ratio was 1.59.

(*Specific early morning symptoms <wheezing> - Lower panel in each ABCD group*) In group A, 16 patients deteriorated their early morning wheezing, while 48 improved it (and 156 remained stable), $z = -4.31$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.28. In Group B,

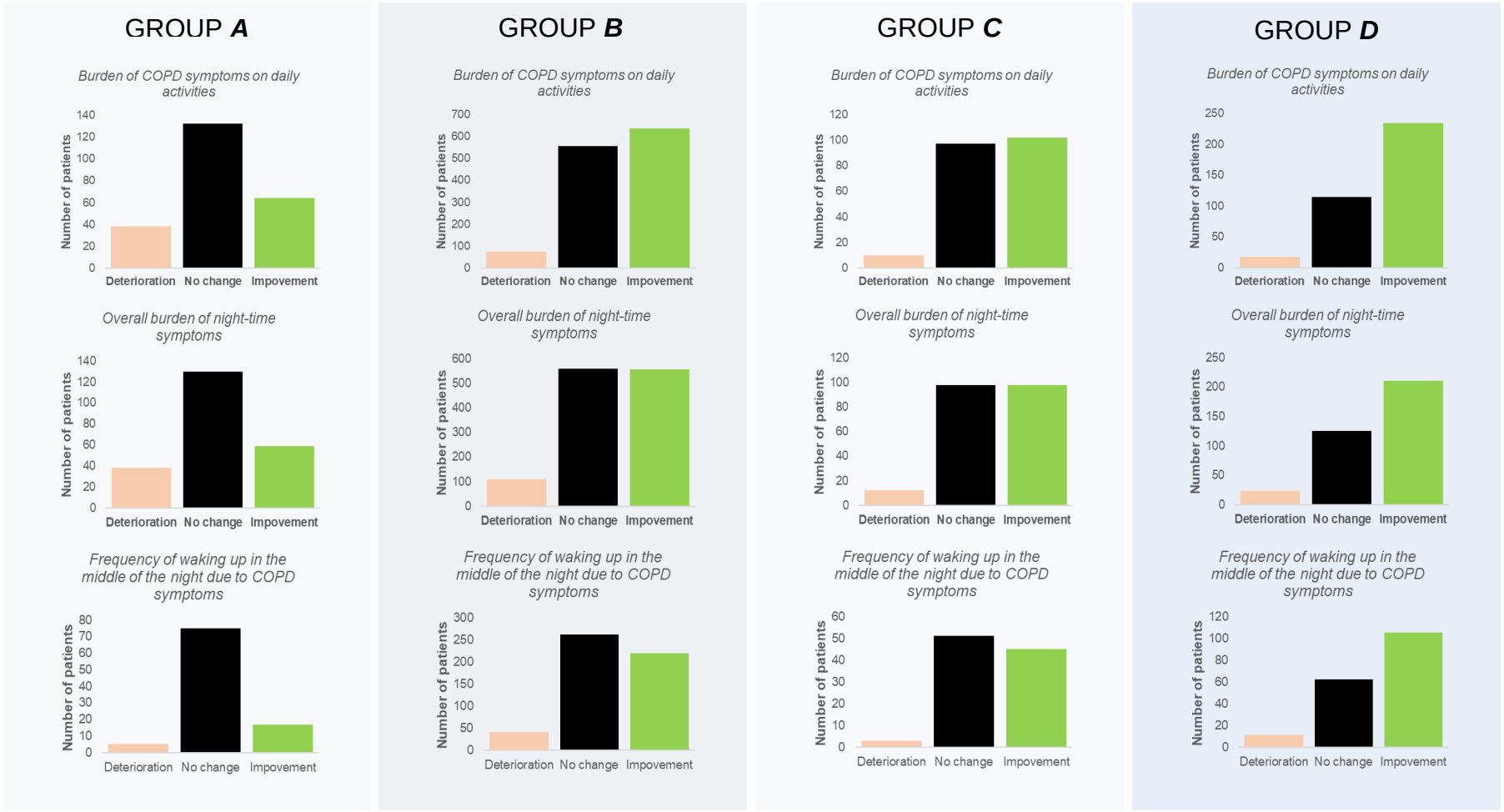
85 patients deteriorated their early morning wheezing, while 488 improved it (and 634 remained stable), $z = -15.77$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.68. In Group C, only 10 patients deteriorated their early morning wheezing, while 95 improved it (and 90 remained stable), $z = -8.19$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.95. In groups A-C, no changes in the median score of the Likert-type scale have been observed between the two study visits. Finally, in Group D, just 20 patients deteriorated their early morning cough, while 209 improved it (and 123 remained stable). There was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -11.58$, $p < 0.001$. Improvement-to-non-improvement ratio was 1.46.

(*Specific early morning symptoms <dyspnea> - Lower panel in each ABCD group*) In group A, 33 patients deteriorated their early morning dyspnea, while 39 improved it (and 154 remained stable), $z = -0.21$, $p = 0.836$. Improvement-to-non-improvement ratio was 0.21. In Group B, 101 patients deteriorated their early morning dyspnea, while 561 improved it (and 558 remained stable), $z = -16.97$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.85. In groups A and B, no changes in the median score of the Likert-type scale have been observed between the two study visits. In Group C, only 13 patients deteriorated their early morning dyspnea, while 107 improved it (and 81 remained stable). Improvement-to-non-improvement ratio was 1.14. Finally, in Group D, just 22 patients deteriorated their early morning dyspnea, while 217 improved it (and 118 remained stable). Improvement-to-non-improvement ratio was 1.55. In Groups C and D, there was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -8.04$ ($p < 0.001$) and $z = -11.55$ ($p < 0.001$) respectively.

(*Specific early morning symptoms <mucus clearance> - Lower panel in each ABCD group*) In group A, 14 patients deteriorated their early morning mucus clearance, while 36 improved it (and 177 remained stable), $z = -2.68$, $p = 0.007$. Improvement-to-non-improvement ratio was 0.19. In Group B, 101 patients deteriorated their early morning mucus clearance, while 467 improved it (and 642 remained stable), $z = -14.71$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.63. In Group C, 16 patients deteriorated their early morning mucus clearance, while 68 improved it (and 114 remained stable), $z = -5.68$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.52. In groups A-C, no changes in the median score of the Likert-type scale have been observed between the two study visits. Finally, in Group D, only 28 patients deteriorated their early morning mucus clearance, while 188 improved it (and 146 remained stable). There was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -10.21$, $p < 0.001$. Improvement-to-non-improvement ratio was 1.08.

COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease

Evolution of daily and night-time symptoms after starting aclidinium/formoterol



Supplementary Figure 3

A Wilcoxon signed-rank test was conducted to determine the effect of a 3-month (on average) treatment period with aclidinium/formoterol as part of the COPD therapeutic strategy (either monotherapy or in combination with other pharmacological agents) on the burden of daily and night-time symptoms of COPD patients per 2019 GOLD ABCD group, as well as the frequency of waking up in the middle of the night due to COPD symptoms. The variables were determined twice through a corresponding questionnaire using a 5-point Likert-type scale, ranging from no symptoms (0) to very severe symptoms (4), for evaluating the severity of daily and night-time symptoms, and an 11-point Likert-type scale, ranging from never (0) to more than once daily (10), for evaluating the frequency of overnight waking up: at baseline (visit 1) and after the averagely 3-month period on aclidinium/formoterol (visit 2). Positive within-subject differences (visit 2 – visit 1) indicate a clinical deterioration, while negative within-subject differences indicate a clinical improvement. No within-subject difference indicates a stable condition. The difference scores were approximately symmetrically distributed, as assessed by a histogram with superimposed normal curve.

(*Burden of daily symptoms - Upper panel in each ABCD group*) In group A, 38 patients deteriorated their daily symptomatology, while 64 improved it (and 132 remained stable), $z = -2.61$, $p = 0.009$. Improvement-to-non-improvement ratio was 0.38. In Group B, 75 patients deteriorated their daily symptomatology, while 636 improved it (and 555 remained stable). Improvement-to-non-improvement ratio was 1.01. In Group C, just 10 patients deteriorated their daily symptomatology, while 102 improved it (and 97 remained stable), $z = -8.46$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.95. Finally, in Group D, only 18 patients deteriorated their daily symptomatology, while 234 improved it (and 115 remained stable). Improvement-to-non-improvement ratio was 1.76. In groups A and C, no changes in the median score of the Likert-type scale have been observed between the two study visits. In Groups B and D, on the other hand, there was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -20{,}31$ ($p < 0.001$) and $z = -12.92$ ($p < 0.001$) respectively.

(*Overall burden of night-time symptoms - Middle panel in each ABCD group*) In group A, 38 patients deteriorated their night-time symptomatology, while 59 improved it (and 130 remained stable), $z = -2.66$, $p = 0.031$. Improvement-to-non-improvement ratio was 0.35. In Group B, 110 patients deteriorated their night-time symptomatology, while 556 improved it (and 560 remained stable), $z = -16.9$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.83. In Group C, only 12 patients deteriorated their night-time symptomatology, while 98 improved it (and another 98 remained stable), $z = -7.7$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.89. In groups A-C, no changes in the median score of the Likert-type scale have been observed between the two study visits. Finally, in Group D, just 23 patients deteriorated their night-time symptomatology, while 211 improved it (and 125 remained stable). There was a statistically significant median decrease in the Likert-type scale by 1 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -11.19$, $p < 0.001$. Improvement-to-non-improvement ratio was 1.43.

(*Frequency of overnight waking up due to COPD symptoms - Lower panel in each ABCD group*) In group A, 5 patients increased the frequency of overnight waking up due to COPD symptoms, while 17 decreased it (and 75 remained unchanged), $z = -1.89$, $p = 0.058$. Improvement-to-non-improvement ratio was 0.21. In Group B, 40 patients increased the frequency of overnight waking up due to COPD symptoms, while 219 decreased it (and 261 remained unchanged), $z = -10.42$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.73. In Group C, only 3 patients increased the frequency of overnight waking up due to COPD symptoms, while 45 decreased it (and 51 remained unchanged), $z = -5.83$, $p < 0.001$. Improvement-to-non-improvement ratio was 0.83. In groups A-C, no changes in the median score of the Likert-type scale have been observed between the two study visits. Finally, in Group D, just 11 patients increased the frequency of overnight waking up due to COPD symptoms, while 105 decreased it (and 62 remained unchanged). There was a statistically significant median decrease in the Likert-type scale by 2 in the corresponding evaluation of subjects during their second study visit compared to their baseline evaluation, $z = -8.42$, $p < 0.001$. Improvement-to-non-improvement ratio was 1.44.

COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Lung Disease