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Supplementary Table 1. Baseline characteristics of patients who underwent randomization.

Characteristic	N-acetylcysteine Group (N=484)	Placebo Group (N=484)	P Value
Age — year	62.5±8.4	62.6±8.0	0.79
Male sex — no. (%)	429 (88.6)	424 (87.6)	0.62
Body mass index — kg/m ²	22.7±3.6	22.9±3.4	0.57
Smoking status — no. (%)			0.13
Never smoked	79 (16.3)	90 (18.6)	
Former smoking	140 (28.9)	113 (23.3)	
Current smoking	265 (54.8)	281 (58.1)	
Smoking index — pack-year	44.9±26.8	44.1±23.9	0.72
Biomass use — no. (%)	259 (53.5)	267 (55.2)	0.61
Occupational exposure history — no. (%)	234 (48.3)	252 (52.1)	0.25
Family history of respiratory disease — no. (%)	87 (18.0)	76 (15.7)	0.35
Respiratory Medication for COPD — no. (%)	80 (16.5)	68 (14.0)	0.28
LAMA alone	40 (8.3)	36 (7.4)	0.63
ICS and LABA	28 (5.8)	25 (5.2)	0.67
Traditional Chinese medicine	7 (1.4)	10 (2.1)	0.46
Xanthine	9 (1.9)	3 (0.6)	0.08
Asmeton	3 (0.6)	3 (0.6)	1.00
LABA alone	5 (1.0)	0 (0.0)	0.06
LABA and LAMA	3 (0.6)	1 (0.2)	0.62
ICS alone	1 (0.2)	0 (0.0)	1.00
COPD exacerbations in the previous year — no. (%)	95 (19.6)	115 (23.8)	0.12
Spirometric values at baseline			
Before bronchodilator use			
FEV ₁ — L	1.98±0.55	1.94±0.66	0.32
FEV ₁ % of predicted value — %	78.3±16.7	77.8±17.1	0.64

FVC — L	3.32±0.79	3.26±0.76	0.26
FEV ₁ /FVC, %	59.6±7.5	59.3±7.9	0.67
After bronchodilator use			
FEV ₁ — L	2.08±0.54	2.04±0.54	0.29
FEV ₁ % of predicted value — %	82.5±15.8	81.8±16.8	0.55
FVC — L	3.41±0.75	3.38±0.74	0.49
FEV ₁ /FVC —%	60.7±7.5	60.2±7.7	0.32
Airflow reversibility — no. (%)	71 (14.7)	59 (12.2)	0.26
GOLD stage — no. (%)			0.08
Mild (stage 1)	274 (56.6)	247 (51.0)	
Moderate (stage 2)	210 (43.4)	237 (49.0)	
mMRC dyspnea scale score			
Mean score	0.82±0.80	0.82±0.78	0.97
Distribution — no. (%)			0.80
<2	406 (83.9)	403 (83.3)	
≥2	78 (16.1)	81 (16.7)	
CAT score	8.21±5.96	8.60±6.20	0.32

Data are n (%) or mean (SD). COPD, chronic obstructive pulmonary disease. ICS, inhaled corticosteroids. LABA, long-acting β -agonist. LAMA, long-acting muscarinic antagonist. FEV₁, forced expiratory volume in 1 second. FVC, forced vital capacity. GOLD=Global initiative for chronic obstructive lung disease. mMRC, modified Medical Research Council. CAT, chronic obstructive pulmonary disease assessment test.

Supplementary Table 2. Baseline characteristics of patients (full analysis set for lung function).

Characteristic	N-acetylcysteine Group (N=381)	Placebo Group (N=363)	P Value
Age — year	62.5±7.7	63.0±7.6	0.42
Male sex — no. (%)	348 (91.3)	325 (89.5)	0.40
Body mass index — kg/m ²	22.8±3.6	22.7±3.3	0.97
Smoking status — no. (%)			0.06
Never smoked	51 (13.4)	66 (18.2)	
Former smoking	112 (29.4)	84 (23.1)	
Current smoking	218 (57.2)	213 (58.7)	
Smoking index — pack-year			
Biomass use — no. (%)	215 (56.4)	216 (59.5)	0.40
Occupational exposure history — no. (%)	199 (52.2)	209 (57.6)	0.14
Family history of respiratory disease — no. (%)	67 (17.6)	61 (16.8)	0.78
Respiratory Medication for COPD — no. (%)	55 (14.4)	50 (13.8)	0.80
LAMA alone	27 (7.1)	24 (6.6)	0.89
ICS and LABA	19 (5.0)	18 (5.0)	0.99
Traditional Chinese medicine	6 (1.6)	10 (2.8)	0.27
Xanthine	6 (1.6)	2 (0.6)	0.29
Asmeton	3 (0.8)	3 (0.8)	1.00
LABA alone	4 (1.0)	0 (0.0)	0.12
LABA and LAMA	1 (0.3)	1 (0.3)	1.00
ICS alone	1 (0.3)	0 (0.0)	1.00
COPD exacerbations in the previous year — no. (%)	78 (20.5)	89 (24.5)	0.19
Spirometric values at baseline			
Before bronchodilator use			
FEV ₁ — L	1.99±0.55	1.97±0.54	0.64
FEV ₁ % of predicted value, %	78.1±16.7	78.7±17.5	0.62

FVC — L	3.35±0.77	3.32±0.72	0.61
FEV ₁ /FVC — %	59.1±7.4	58.9±8.0	0.73
After bronchodilator use			
FEV ₁ — L	2.08±0.44	2.05±0.45	0.45
FEV ₁ % of predicted value, %	82.3±16.1	82.8±16.9	0.71
FVC — L	3.44±0.73	3.43±0.70	0.84
FEV ₁ /FVC — %	60.4±7.6	60.0±7.8	0.40
Airflow reversibility — no. (%)	59 (15.5)	46 (12.7)	0.27
GOLD stage — no. (%)			0.59
Mild (stage 1)	209 (54.9)	192 (52.9)	
Moderate (stage 2)	172 (45.1)	171 (47.1)	
mMRC dyspnea scale score			
Mean score	0.80±0.76	0.80±0.76	0.90
Distribution — no. (%)			0.90
<2	322 (84.5)	308 (84.8)	
≥2	59 (15.5)	55 (15.2)	
CAT score	8.0±5.6	8.4±5.8	0.40

Data are n (%) or mean (SD). COPD, chronic obstructive pulmonary disease. ICS, inhaled corticosteroids. LABA, long-acting β -agonist. LAMA, long-acting muscarinic antagonist. FEV₁, forced expiratory volume in 1 second. FVC, forced vital capacity. GOLD=Global initiative for chronic obstructive lung disease. mMRC, modified Medical Research Council. CAT, chronic obstructive pulmonary disease assessment test.

Supplementary Table 3. Baseline characteristics of patients who withdrew from the study.

Characteristic	N-acetylcysteine Group (N=151)	Placebo Group (N=161)	P Value
Age —year	63.1±9.6	61.5±8.8	0.12
Male sex — no. (%)	124 (82.1)	129 (80.1)	0.65
Body mass index — kg/m ²	22.8±3.6	23.0±3.6	0.68
Smoking status — no. (%)			0.19
Never smoked	38 (25.2)	35 (21.7)	
Former smoking	42 (27.8)	34 (21.1)	
Current smoking	71 (47.0)	92 (57.1)	
Smoking index — pack-year	45.2±23.7	41.4±26.1	0.26
Biomass use — no. (%)	70 (46.4)	74 (46.0)	0.94
Occupational exposure history — no. (%)	60 (39.7)	65 (40.4)	0.91
Family history of respiratory disease — no. (%)	30 (19.9)	22 (13.7)	0.14
Respiratory Medication for COPD, no. (%)	32 (21.8)	21 (13.5)	0.06
LAMA alone	14 (9.3)	14 (8.7)	0.86
ICS and LABA	11 (7.3)	7 (4.3)	0.27
Traditional Chinese medicine	2 (0.6)	2 (0.6)	1.00
Xanthine	3 (2.0)	1 (0.6)	0.36
Asmeton	1 (0.7)	0 (0.0)	0.48
LABA alone	3 (2.0)	0 (0.0)	0.11
LABA and LAMA	3 (2.0)	0 (0.0)	0.11
ICS alone	0 (0.0)	0 (0.0)	1.00
COPD exacerbations in the previous year — no. (%)	23 (15.2)	40 (24.8)	0.035
Spirometric values at baseline			
Before bronchodilator use			
FEV ₁ — L	1.93±0.55	1.86±0.53	0.26
FEV ₁ % of predicted value — %	77.9±16.1	74.6±16.3	0.07

FVC — L	3.20±0.80	3.11±0.78	0.35
FEV ₁ /FVC — %	60.2±7.6	59.6±7.6	0.42
After bronchodilator use			
FEV ₁ — L	2.00±0.50	1.95±0.52	0.39
FEV ₁ % of predicted value —%	82.0±14.9	78.7±16.2	0.07
FVC — L	3.27±0.74	3.24±0.78	0.70
FEV ₁ /FVC — %	61.0±7.3	60.4±7.3	0.46
Airflow reversibility — no. (%)	19 (12.6)	23 (14.3)	0.66
GOLD stage — no. (%)			0.03
Mild (stage 1)	88 (58.3)	74 (46.0)	
Moderate (stage 2)	63 (41.7)	87 (54.0)	
mMRC dyspnea scale score			
Mean score	0.95±0.90	0.92±0.84	0.73
Distribution — no. (%)			0.60
<2	120 (79.5)	124 (77.0)	
≥2	31 (20.5)	37 (23.0)	
CAT score	8.9±6.9	8.8±7.2	0.92

Data are n (%) or mean (SD). COPD, chronic obstructive pulmonary disease. ICS, inhaled corticosteroids. LABA, long-acting β -agonist. LAMA, long-acting muscarinic antagonist. FEV₁, forced expiratory volume in 1 second. FVC, forced vital capacity. GOLD=Global initiative for chronic obstructive lung disease. mMRC, modified Medical Research Council. CAT, chronic obstructive pulmonary disease assessment test.

Supplementary Table 4. Medication compliance, concomitant drugs and smoking status during the study (full analysis set for exacerbation). *.

	N-acetylcysteine Group (N=464)	Placebo Group (N=460)	P Value
Medication compliance — no. (%)			0.13
Compliance $\geq$ 80%	329 (70.9)	330 (71.7)	
Compliance 50-80%	127 (27.4)	113 (24.6)	
Compliance < 50%	8 (1.7)	17 (3.7)	
Respiratory medication — no. (%)	112 (24.1)	107 (23.3)	0.75
Traditional Chinese medicine [†]	31 (6.7)	39 (8.5)	0.30
β 2 agonists/inhaled corticosteroids [†]	30 (6.5)	30 (6.5)	0.97
Anticholinergic agents [†]	41 (8.8)	34 (7.4)	0.42
Xanthine [†]	21 (4.5)	14 (3.0)	0.24
β 2 agonists [†]	14 (3.0)	16 (3.5)	0.69
Asmeton [†]	14 (3.0)	14 (3.0)	0.98
Montelukast sodium [†]	6 (1.3)	9 (2.0)	0.43
Inhaled corticosteroids [†]	4 (0.9)	2 (0.4)	0.69
β 2 agonists/Anticholinergic agents [†]	3 (0.6)	1 (0.2)	0.62
Smoking status[‡] — no. (%)			0.33
Never smokers	70 (15.1)	85 (18.5)	
Sustained smokers	218 (47.0)	224 (48.7)	
Intermittent smokers	52 (11.2)	46 (10.0)	
Stopped smoking	33 (7.1)	35 (7.6)	
Sustained ex-smokers	124 (26.7)	105 (22.8)	

* Data are shown as n (%).

[†] Used alone or in combination.

[‡] Never smokers referred to subjects who were never smoking in his life; continuing smokers referred to subjects who were recorded as smoking at baseline and having continued to smoke at all visits; intermittent smokers referred to subjects who changed their smoking behavior from randomization on at least one visit; stopped smoking referred to subjects who were recorded as smoking at baseline and did not smoke during the trial; sustained ex-smokers referred to subjects who were recorded as having quit smoking prior to randomization and having maintained smoking abstinence at all visits. Chi-square or Fisher's exact test was adopted.

Supplementary Table 5. Serum N-acetylcysteine levels in two group at baseline and 24 months in subgroup.

N-acetylcysteine (ng/L)	N-acetylcysteine Group	Placebo Group	P Value
Baseline			
N	213	208	
Mean $\pm$ standard deviation	26.9 $\pm$ 9.1	26.6 $\pm$ 13.8	0.79
Median (interquartile range)	25.1 (20.9-29.9)	23.6 (19.9-30.1)	0.23
Month 24			
N	196	202	
Mean (standard deviation)	252.6 $\pm$ 490.1	31.7 $\pm$ 10.4	<0.001
Median (interquartile range)	142.0 (34.2-245.3)	29.1 (23.9-38.3)	<0.001

Data are shown as mean $\pm$ standard deviation or median (interquartile range).

Mixed-effects model for repeated measures is adopted.

Supplementary Table 6. Difference of CAT scores between the two groups at different time points.

Follow-up	N-acetylcysteine		Placebo		Difference (Placebo - N-acetylcysteine) (95% CI)	Adjusted P Value
Baseline	n=464	8.1±0.3	n=460	8.5±0.3	0.4 (-0.3 to 1.2)	0.27
Month 3	n=462	5.9±0.2	n=454	6.1±0.2	0.3 (-0.5 to 0.8)	0.43
Month 6	n=422	5.4±0.2	n=416	5.2±0.2	-0.1 (-0.8 to 0.5)	0.74
Month 9	n=405	4.7±0.2	n=399	4.9±0.2	0.1 (-0.5 to 0.7)	0.50
Month 12	n=385	4.8±0.2	n=371	5.0±0.2	0.2 (-0.4 to 0.9)	0.36
Month 15	n=362	4.2±0.2	n=352	4.1±0.2	-0.1 (-0.7 to 0.5)	0.72
Month 18	n=354	4.2±0.2	n=344	4.4±0.2	0.2 (-0.4 to 0.8)	0.26
Month 21	n=348	4.2±0.2	n=342	4.5±0.2	0.3 (-0.3 to 0.9)	0.22
Month 24	n=332	4.0±0.2	n=319	4.1±0.2	0.1 (-0.5 to 0.7)	0.49

*Data were shown as mean (SE).

Mixed-effects model for repeated measures is adopted. We adopted the measured value at each visit as the dependent variable and the fixed effects includes treatment allocation, individual baseline value, baseline smoking status, age, sex, body mass index, COPD exacerbations in the previous year, COPD treatment at baseline, centre, follow-up, interactions between the treatment allocations and participating centers. Subjects served as the random effect. The follow-up was treated as the categorical variable. Values at visit 1 served as the baseline.

Supplementary Table 7. Difference of mMRC scores between the two groups at different time points.

Follow-up	N-acetylcysteine		Placebo		Difference (Placebo - N-acetylcysteine) (95% CI)	Adjusted P Value
Baseline	n=464	0.82±0.04	n=460	0.80±0.04	-0.02 (-0.12 to 0.09)	0.75
Month 3	n=462	0.67±0.03	n=454	0.66±0.03	-0.01 (-0.10 to 0.09)	0.64
Month 6	n=422	0.63±0.03	n=415	0.62±0.03	-0.000 (-0.09 to 0.09)	0.87
Month 9	n=405	0.55±0.03	n=399	0.54±0.03	-0.01 (-0.10 to 0.08)	0.74
Month 12	n=385	0.52±0.03	n=371	0.58±0.03	0.06 (-0.04 to 0.15)	0.74
Month 15	n=362	0.58±0.04	n=352	0.57±0.03	-0.003 (-0.10 to 0.90)	0.74
Month 18	n=354	0.57±0.03	n=344	0.63±0.04	0.60 (-0.04 to 0.16)	0.52
Month 21	n=346	0.61±0.04	n=34-	0.62±0.03	0.01 (-0.09 to 0.11)	0.94
Month 24	n=332	0.60±0.03	n=319	0.60±0.04	0.01 (-0.09 to 0.10)	0.72

*Data were shown as mean ± SE.

Cochran's and Mantel-Haenszel test was adopted to compare differences between two group.

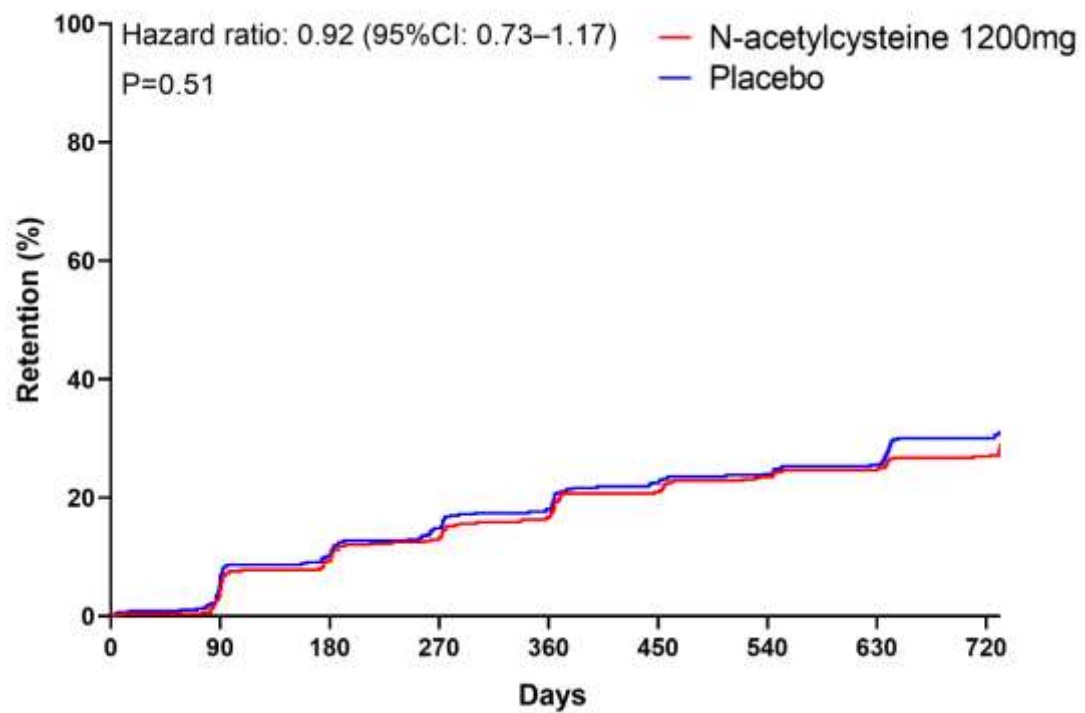
Supplementary Table 8. Comparison of medication-related adverse events between N-acetylcysteine and placebo groups (safety analysis set).

Variables	N-acetylcysteine Group (N =484)	Placebo Group (N =484)	P value
Adverse event (Reported by >1% of patients) — no. (%)	117 (25.2)	98 (21.1)	0.16
Epigastric discomfort	13 (2.7)	11 (2.3)	
Gastrointestinal pain	7 (1.4)	15 (3.0)	
Coronary heart disease	3 (0.6)	7 (1.4)	
Cerebral infarction	5 (1.0)	3 (0.6)	
Dizziness	4 (0.8)	5 (1.0)	
Severe adverse event — no. (%)	40 (8.6)	31 (6.7)	0.32
Death — no. (%)	3 (0.6)	5 (1.0)	0.72

Data were shown as n (%).

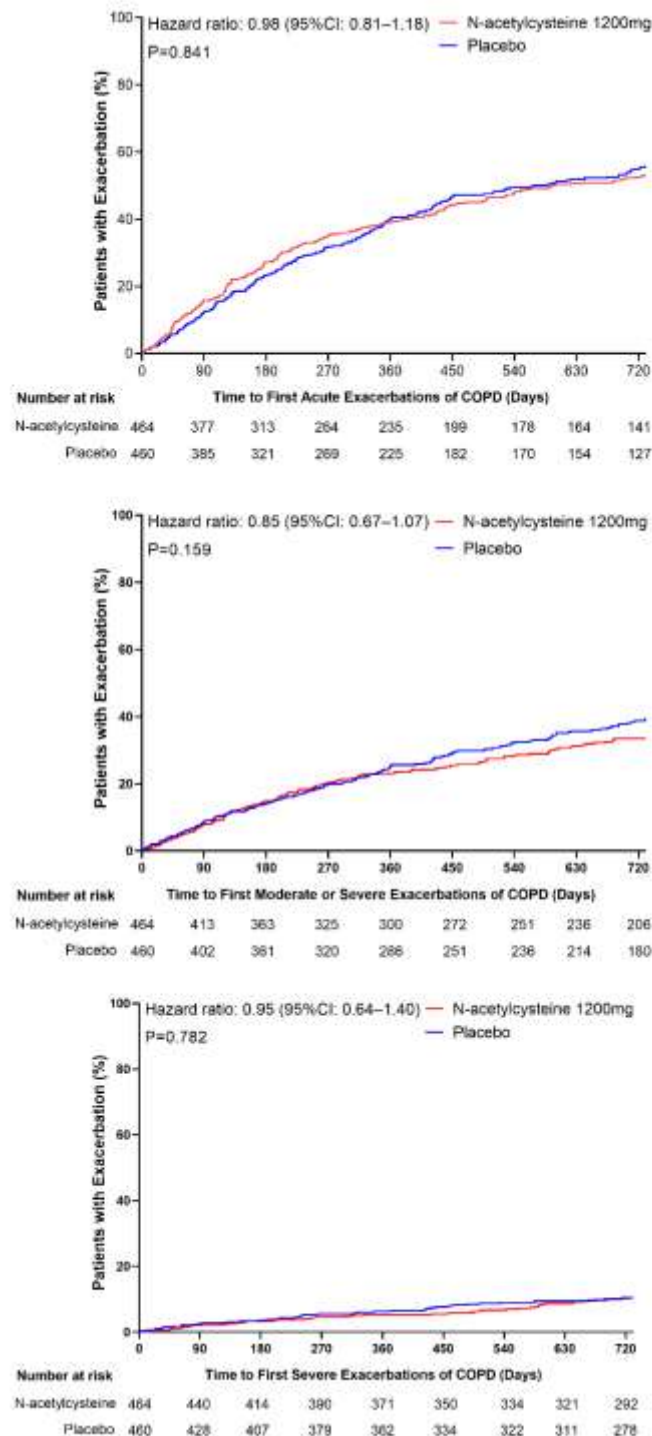
Chi-square or Fisher's exact test was adopted.

Supplementary Figure 1. Kaplan-Meier plot of drop-out during the trial.



Cox proportional hazards regression model was adopted to compare differences between two group.

Supplementary Figure 2. Time to first acute exacerbation of chronic obstructive pulmonary disease (COPD) and hospitalization due to COPD (full analysis set for exacerbation).



Cox proportional hazards regression model was adopted to compare differences between two group.