Impact of smoking status and concomitant medications on the effect of high-dose N-acetylcysteine on chronic obstructive pulmonary disease exacerbations: a post-hoc analysis of the PANTHEON study

Short title

High-dose N-acetylcysteine on COPD exacerbations

Authors:

Alberto Papi MD[1]*, Jinping Zheng MD[2]*, Gerard J Criner MD[3], Leonardo M Fabbri MD[1,4], Peter MA Calverley DSc[5]

1. Section of Cardiorespiratory and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

2. State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China.

3. Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA

4. COPD Center, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

5. School of Aging and Chronic Disease, University of Liverpool, Liverpool, UK

*AP and JZ are co-first authors

Corresponding author

Alberto Papi

Mailing address: Research Centre on Asthma and COPD, University of Ferrara, Ferrara, Italy

Email address: ppa@unife.it

Abbreviation list

BMI, body-mass index

CAT, COPD Assessment Test

CI, confidence interval

COPD, chronic obstructive pulmonary disease

FEV_1, forced expiratory volume in 1 second

FVC, forced vital capacity

GOLD, Global Initiative for Chronic Obstructive Lung Disease

HCU, healthcare resource utilisation

ICS, inhaled corticosteroid

LABA, long-acting β_2-agonist

LAMA, long-acting muscarinic antagonist

NAC, N-acetylcysteine

RR, rate ratio

SABA, short-acting β_2-agonist

SAMA, short-acting muscarinic antagonist

Keywords

Mucolytic; chronic obstructive pulmonary disease; exacerbations

Abstract

Background

N-acetylcysteine (NAC) 600 mg twice daily is a well-tolerated oral antioxidant mucolytic that reduces the risk of moderate to severe chronic obstructive pulmonary disease (COPD) exacerbations. PANTHEON was one of the largest studies to evaluate NAC in COPD. It recruited current, ex- and never-smokers, concomitantly treated with other medications, and used a symptom-based definition of COPD exacerbations rather than the conventional healthcare resource utilisation (HCU) criteria.

Methods

This manuscript reports *post-hoc* analyses of the PANTHEON dataset investigating whether smoking status or use of concomitant medications influenced the efficacy of NAC in terms of reducing exacerbations, defined according to HCU.

Results

Compared with placebo (N=482), NAC (N=482) reduced the rate of HCU events by 20% (p=0.0027), with a larger effect in current/ex-smokers (23%; p<0.01). In patients receiving NAC and long-acting inhaled bronchodilator(s) but no ICS, there was a 60% reduction in the rate of exacerbations compared to those receiving placebo, long-acting bronchodilator(s) and ICS (p<0.0001).

Conclusions

Overall, these *post-hoc* hypothesis-generating analyses confirm that NAC reduces the rate of COPD exacerbations, particularly in patients with COPD who have a significant smoking history, and in those not treated with ICS. NAC may provide an alternative to ICS-containing combinations in these patient subgroups.

Clinical Trial Registration

Chinese Clinical Trials Registry, ChiCTR-TRC-09000460.

Introduction

Chronic obstructive pulmonary disease (COPD) severity is assessed in terms of both current symptoms and future exacerbation risk [1]. Although symptoms are often the main reason for patients to seek care, much of the COPD-related cost and healthcare resource utilisation (HCU) is due to exacerbations [2–5]. The recommended first-line treatments to reduce symptoms and prevent exacerbations are inhaled long-acting bronchodilators, alone or in combination, with inhaled corticosteroids (ICSs) recommended for patients at high risk of exacerbations, or who also have features of asthma [1].

N-acetylcysteine (NAC) is a well-tolerated oral antioxidant mucolytic that reduces the risk of COPD exacerbations [6,7]. One of the largest studies to evaluate NAC efficacy was the PANTHEON study (Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease), which randomised 1006 patients with COPD to either NAC 600 mg twice daily or placebo in addition to existing therapy [8]. Over 1 year, the rate of COPD exacerbations was significantly lower in the NAC group, with a similar rate of adverse events in both groups.

Whereas randomised trials in COPD typically recruit current and ex-smokers, PANTHEON also recruited never-smokers, and patients were permitted to receive a range of background medication for the duration of the study. Furthermore, the definition of exacerbations in PANTHEON was based on the symptom-based criteria of Anthonisen et al. [9], rather than more commonly used HCU criteria [1]. In a previous study (BRONCUS), which recruited only current and ex-smokers, a lower dose of NAC (600 mg per day) had no effect on HCU-defined exacerbations in the overall population, but there was a suggestion of an effect in patients not receiving inhaled corticosteroids (ICSs) [10].

We therefore decided to conduct a series of *post-hoc* analyses to investigate: whether the exacerbation definition influenced the main results; to evaluate the effect of NAC 600 mg twice daily in current and former smokers; and to examine the effect of NAC 600 mg

twice daily in patients receiving different background COPD medication, specifically long-acting β_2-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs).

Materials and methods

The design of PANTHEON has been published [11], as have the pre-planned results [8]. This was a randomised, double-blind, placebo-controlled, parallel-group study conducted at 34 hospitals in China. Following screening and a two-week run-in, 1,006 patients were randomised equally to receive either NAC 600 mg twice daily or matching placebo in addition to usual COPD maintenance medications. Randomisation was stratified according to baseline ICS use, with all patients, investigators, and site staff blinded to treatment for the study duration. Patients returned for clinic visits at Months 1, 3, 6, 9 and 12.

All recruited patients had a clinically confirmed diagnosis of COPD (based on Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2011 recommendations), had experienced ≥2 COPD exacerbations in the previous two years but were clinically stable for the four weeks prior to enrolment, were aged 40–80 years, and had post-bronchodilator forced expiratory volume in 1 s (FEV_1) 30–70% predicted and FEV_1 to forced vital capacity ratio <0.7. The main exclusion criteria were poor reliability or compliance, and a clinically confirmed diagnosis of bronchial asthma (based on Global Initiative for Asthma 2011 recommendations, specifically recurrent episodes of respiratory symptoms such as wheezing, breathlessness, chest tightness, and coughing, and confirmed by variable airflow obstruction). All patients provided written informed consent prior to any study-related procedure. The study was approved by local ethics committees and was performed in accordance with the principles of the Declaration of Helsinki, and the International Conference on Harmonization Notes for Guidance on Good Clinical Practice (ICH/CPMP/135/95). This trial is registered in the Chinese Clinical Trials Registry, ChiCTR-TRC-09000460.

The primary endpoint was annual exacerbation rate. In the pre-planned analyses, exacerbations were defined based on data collected from daily patient diaries or hospital visits according to the symptom-based criteria used by Anthonisen et al., with severity graded as: severe, all three major symptoms present (worsening dyspnoea, increase in

sputum purulence and increase in sputum volume); moderate, two of the major symptoms; mild, one major symptom plus at least one minor symptom (upper respiratory tract infection in the previous five days, increased wheezing, increased cough, fever unexplained by other causes, or a 20% increase in respiratory rate or heart rate above baseline) [9,11]. However, given many clinical trials define exacerbations by HCU criteria, we applied the following event-based criteria in these *post-hoc* analyses:

- Mild: resulted in an increase in respiratory symptoms that were managed by the patient with an increase in usual medications, based on data collected in daily patient diaries;
- Moderate: required treatment with systemic corticosteroids and/or antibiotics;
- Severe: resulted in hospitalisation or death.

Exacerbations were also grouped as moderate-to-severe and overall (i.e., mild, moderate and severe) events.

Statistical methods

The *post-hoc* analyses reported here were not formally powered and the reported p values should be viewed as being indicative rather than definitive. The adjusted mean exacerbation rates and rate ratios (RRs) were analysed using a negative binomial regression model, with number of COPD exacerbations as dependent variable, treatment, ICS use, GOLD stage, smoking status, and body-mass index as factors, and age as covariate. Log-time on study in years was used as an offset, to adjust for patients who withdrew prematurely from the study; this assumed there was no relationship between the response and the missing outcome, i.e., the event rate after withdrawal from the study is the same as the event rate on study treatment. All analyses reported in this manuscript were on the set of patients who received at least one dose of study medication and had a record of at least one follow-up study visit.

Results

Baseline demographics and disease characteristics were well balanced between the two groups (Table 1), with a similar proportion of patients completing in both arms (75% with NAC and 76% with placebo; Figure 1).

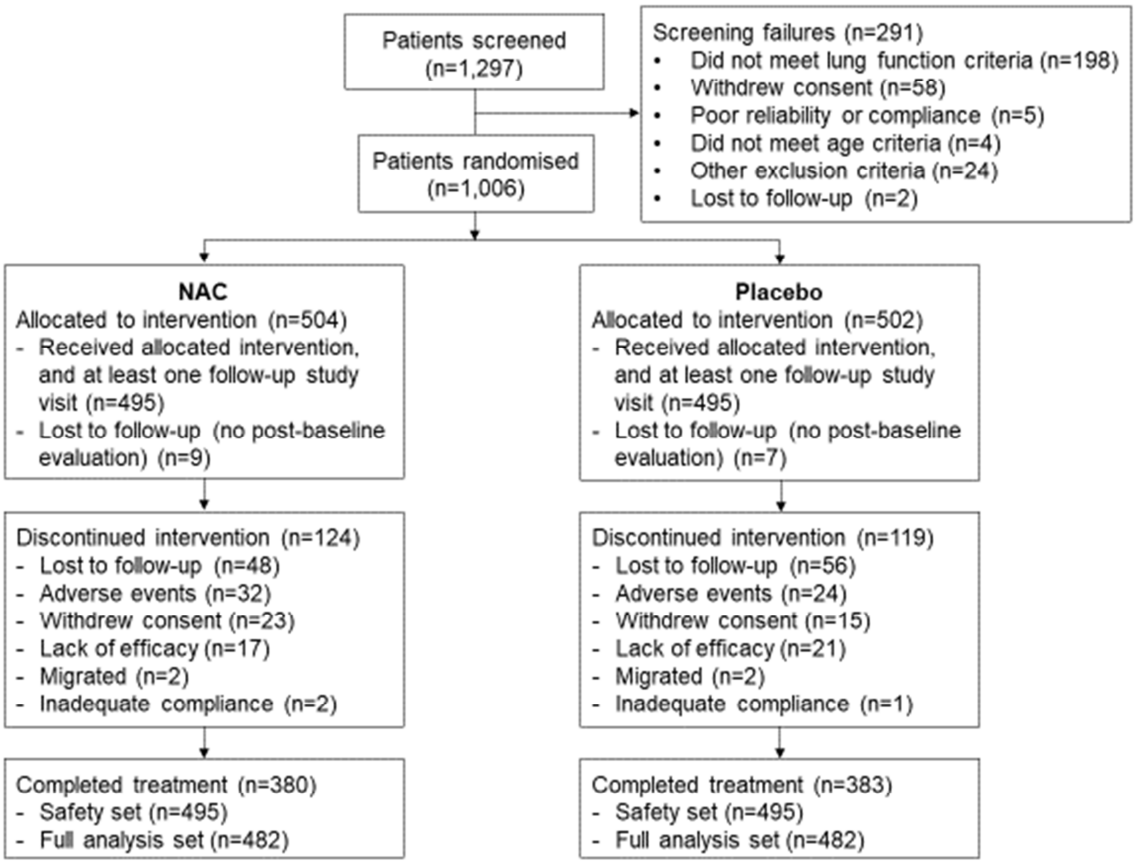
Table 1. Baseline demographics and disease characteristics.

Parameters	**NAC (N=504)**	**Placebo (N=502)**
Sex, n (%)		
Female	89 (18)	93 (19)
Male	415 (82)	409 (81)
Age (years), mean (SD)	66.2 (8.7)	66.4 (8.8)
Smoking status, n (%)		
Current smoker	95 (19)	84 (17)
Ex-smoker	285 (57)	303 (60)
Never smoker	124 (25)	115 (23)
BMI (kg/m^2), mean (SD)	23.1 (3.7)	22.8 (3.6)
Exacerbations in previous 2 years, mean (SD)	3.47 (2.01)	3.53 (1.95)
Predicted post-bronchodilator FEV_1 (%), mean (SD)	49.1 (11.9)	48.8 (11.7)
Post-bronchodilator FEV_1/FVC (%), mean (SD)	50.0 (10.0)	49.0 (9.8)
COPD medication at entry to the study, n (%)		
ICS alone	22 (4.4)	21 (4.2)
ICS-LABA combination	236 (46.8)	243 (48.4)
LABA	11 (2.2)	13 (2.6)
LAMA	48 (9.5)	50 (10.0)
SABA	54 (10.7)	60 (12.0)
SAMA	77 (15.3)	81 (16.1)

Parameters	NAC (N=504)	Placebo (N=502)
Theophylline	135 (26.8)	134 (26.7)

NAC = N-acetylcysteine; BMI = body-mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist; LAMA = long-acting muscarinic antagonist.

Figure 1. Patient flow diagram.



NAC = N-acetylcysteine.

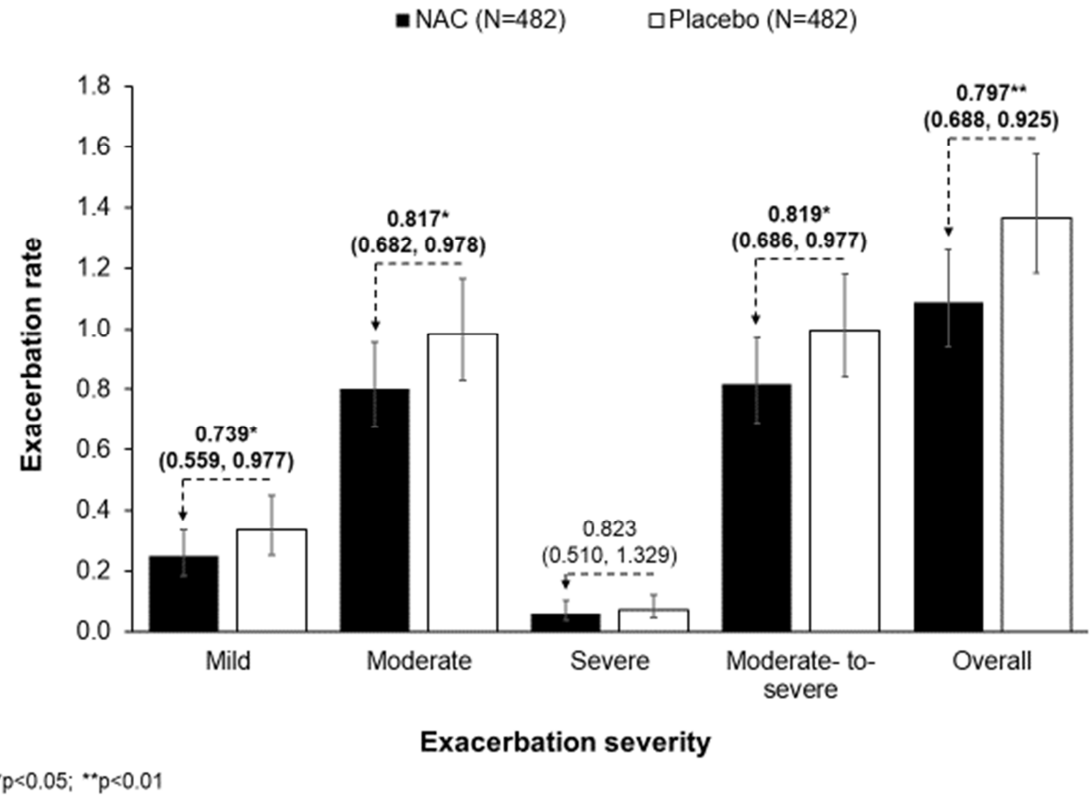
Exacerbation definition

In the original symptom-based analysis, NAC significantly reduced the overall rate of exacerbations by 22% versus placebo (RR 0.78 [95% CI 0.67, 0.60]; p=0.0011), with rates of 1.16 exacerbations per patient per year with NAC and 1.49 with placebo (497 exacerbations in 274 patients receiving NAC and 641 exacerbations in 291 patients receiving placebo) [8]. Using the HCU-based criteria, the reduction in the overall rate of exacerbations with NAC was consistent with the original analysis, with a significant 20% reduction versus placebo

(RR 0.80 [0.69, 0.93]; p=0.0027) (Figure 2), and rates of 1.09 and 1.37 per patient per year, respectively (491 exacerbations in 274 patients receiving NAC and 610 exacerbations in 291 patients receiving placebo).

Most exacerbations in both groups were moderate in severity, for which there was a significant 18% reduction with NAC compared with placebo (p=0.0275; Figure 2). Additionally, there was a statistically significant 26% reduction in the rate of mild exacerbations (p=0.0337). Severe exacerbations were infrequent, and although there was a numerical reduction with NAC, the difference did not reach statistical significance.

Figure 2. Adjusted annualised rates (and 95% CIs) of exacerbations by exacerbation severity in the overall population, together with risk reductions (and 95% CIs).



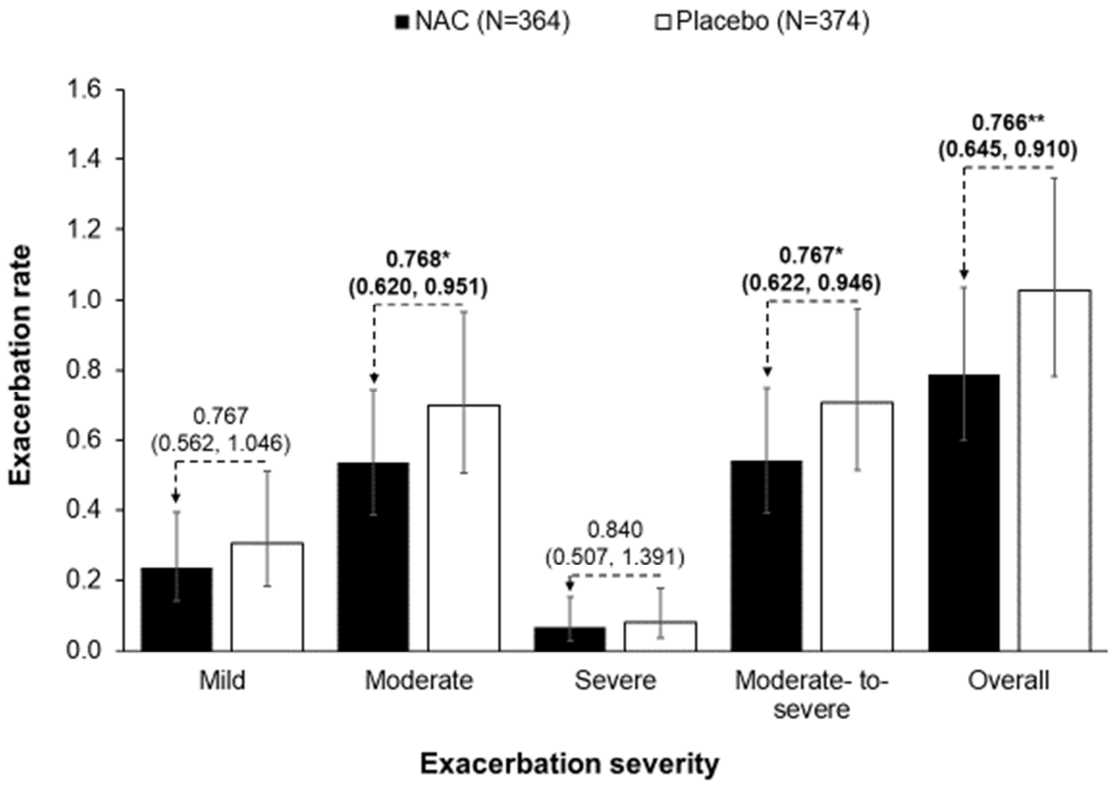
*p<0.05; **p<0.01. CI = confidence interval; NAC = N-acetylcysteine.

Smoking status

In the subset of patients who were current or ex-smokers, the reduction in the overall rate of exacerbations for NAC was similar to that in the overall population, with a significant

23% reduction versus placebo (p=0.0025; Figure 3), and a significant 23% reduction in moderate exacerbations (p=0.0156). Although the rates of mild and severe exacerbations were lower with NAC than placebo, the reductions did not reach significance. In the subset of never-smokers, all evaluable rates were lower with NAC than placebo, but the reductions did not reach statistical significance (Supplementary Figure 1).

Figure 3. Adjusted annualised rates (and 95% CIs) of exacerbations by exacerbation severity in current and ex-smokers, together with risk reductions (and 95% CIs).



*p<0.05; **p<0.01. CI = confidence interval; NAC = N-acetylcysteine.

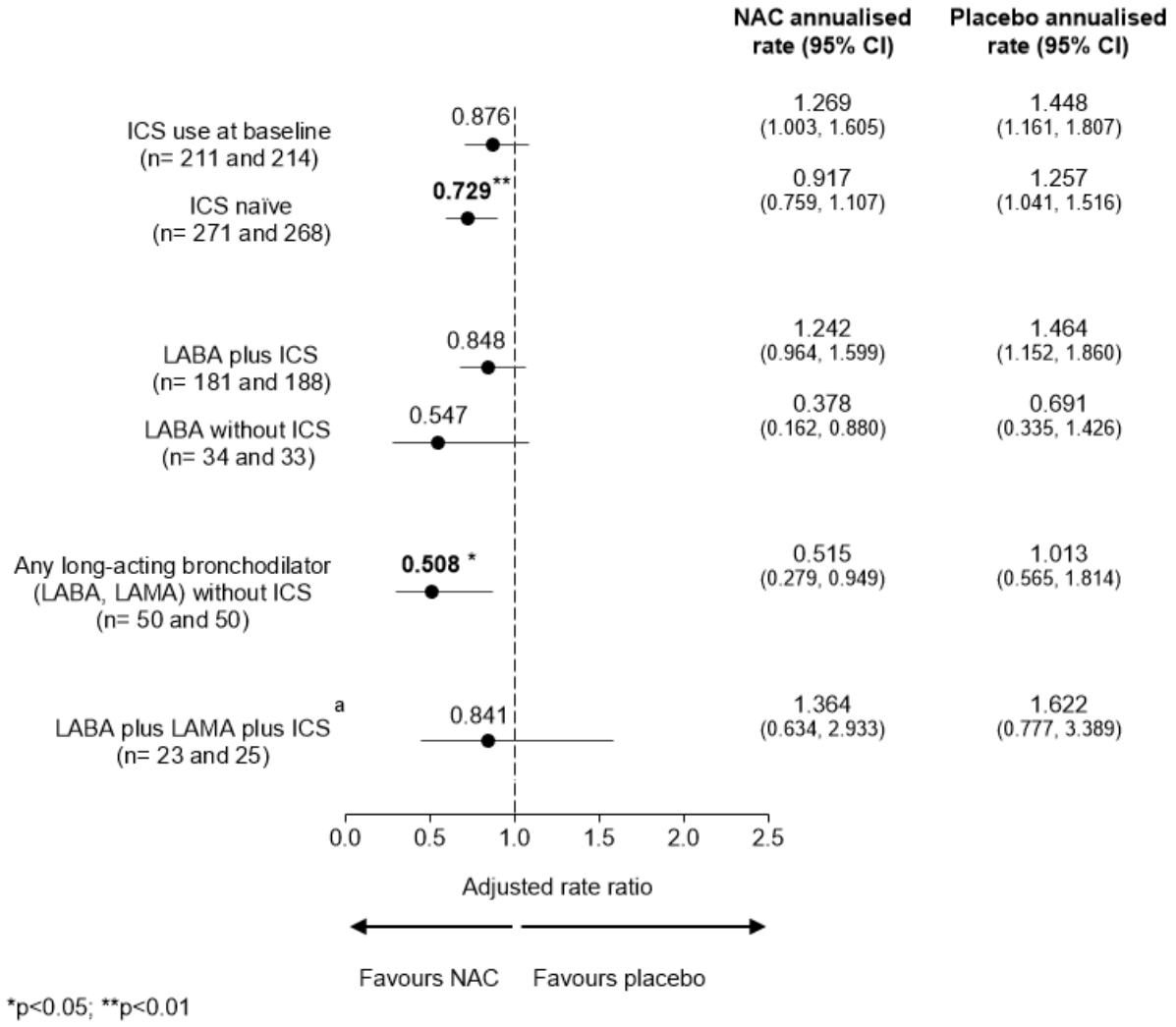
Background COPD medication

When exacerbation rates were analysed according to background medication, the rates were lower in patients receiving NAC than placebo. The majority of events in each subgroup were moderate in severity, with severe exacerbations being infrequent (Figures 4a [overall] 4b [moderate and severe], and Supplementary Figure 2 [moderate]).

In general, the efficacy of NAC was highest in patients not receiving ICS as background COPD medication. There was a significant 27% reduction in the rate of all exacerbations (i.e., mild, moderate and severe) with NAC vs placebo in the ICS naïve subgroup, and a significant 49% reduction with NAC vs placebo in addition to one or more long-acting bronchodilator but without ICS (Figure 4a). For moderate-to-severe exacerbations, there was a significant 57% reduction when NAC rather than placebo was added to LABA without ICS, although this was a relatively small subgroup (Figure 4b); similar results were observed for moderate exacerbations (Supplementary Figure 2).

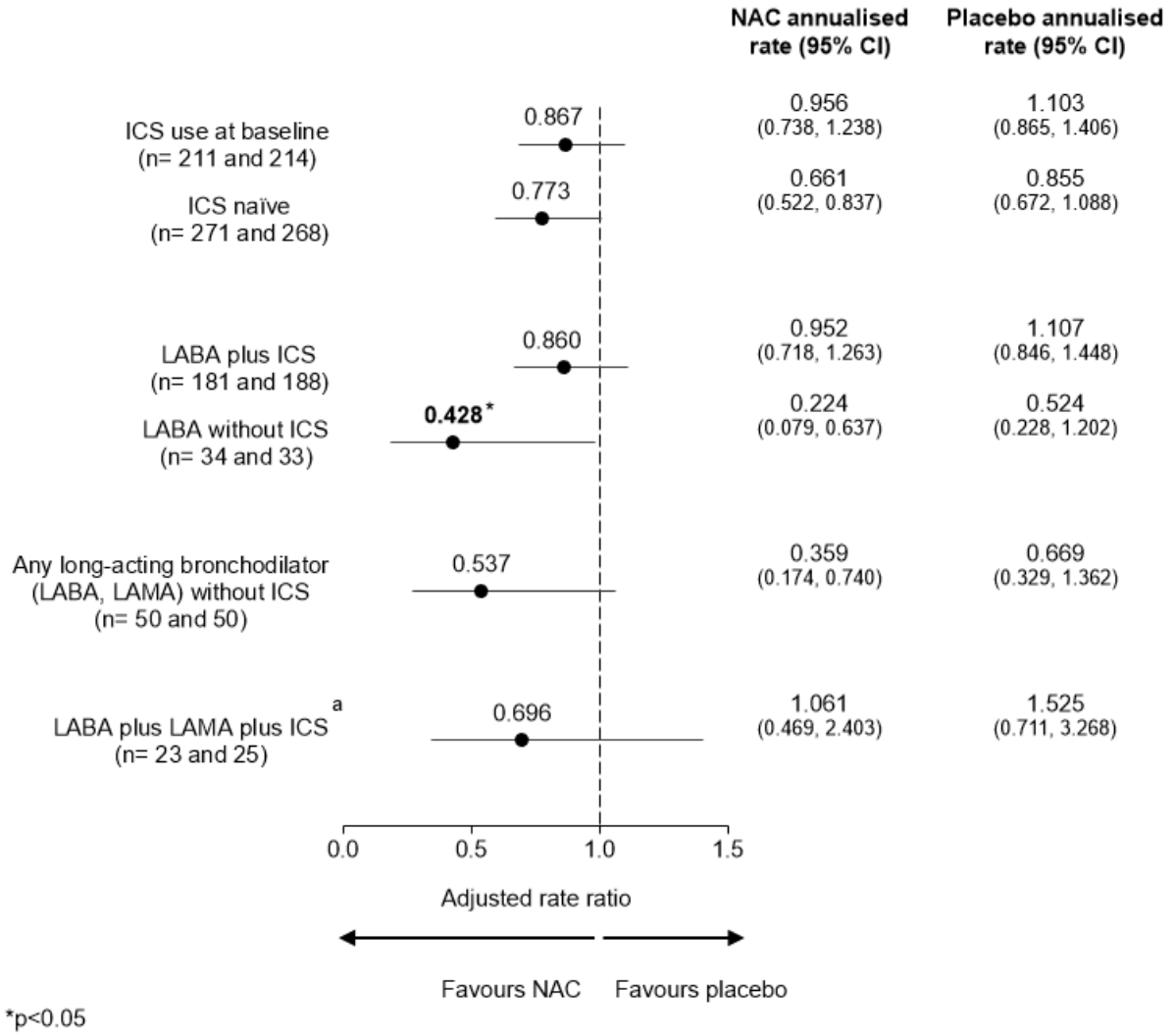
Given these results, an additional subgroup analysis was conducted to evaluate the efficacy of NAC added to long-acting inhaled bronchodilator(s) without ICS compared to placebo plus long-acting bronchodilator(s) with ICS. As shown in Figure 5, for NAC plus bronchodilators versus bronchodilators plus ICS there was a significant 60% reduction in the overall rate of exacerbations, a significant 64% reduction in the rate of moderate exacerbations, and a significant 88% reduction in the rate of severe exacerbations.

Figure 4a. Adjusted rate ratios (and 95% CIs) for overall exacerbations, NAC versus placebo, in subgroups according to baseline medication use.



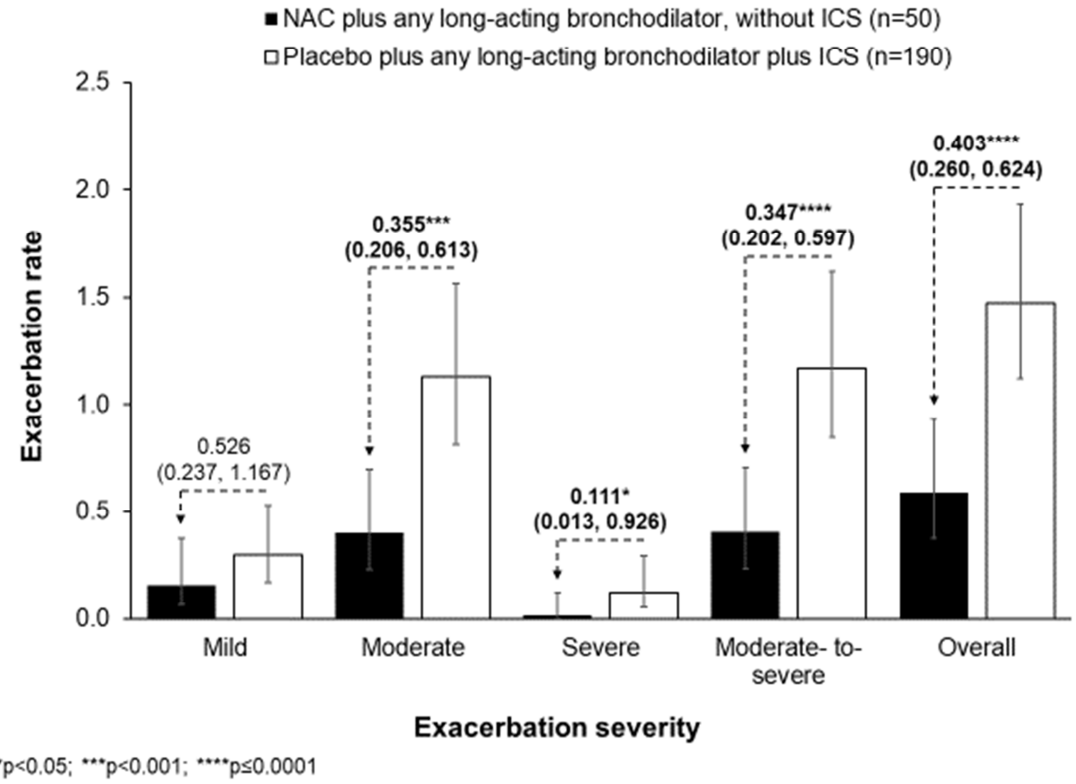
Rate ratios in bold indicate a significant reduction versus placebo; *p<0.05; **p<0.01. The patient numbers in brackets are for NAC then placebo. [a]Insufficient patients were included in the LABA plus LAMA without ICS subgroup for the rate ratio to be analysed. CI = confidence interval; NAC = N-acetylcysteine; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

Figure 4b. Adjusted rate ratios (and 95% CIs) for moderate-to-severe exacerbations, NAC versus placebo, in subgroups according to baseline medication use.



Rate ratios in bold indicate a significant reduction versus placebo; *p<0.05. The patient numbers in brackets are for NAC then placebo. [a]Insufficient patients were included in the LABA plus LAMA without ICS subgroup for the rate ratio to be analysed. CI = confidence interval; NAC = N-acetylcysteine; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

Figure 5. Adjusted annualised rates (and 95% CIs) of exacerbations by exacerbation severity, comparing NAC plus any long-acting bronchodilator (without ICS) with placebo plus any long-acting bronchodilator plus ICS, together with risk reductions (and 95% CIs).



Rate ratios in bold indicate a significant reduction versus placebo; *p<0.05; ***p<0.001; ****p≤0.0001. CI = confidence interval; NAC = N-acetylcysteine; ICS = inhaled corticosteroid; 'any long-acting bronchodilator' includes patients receiving a long-acting β_2-agonist and/or a long-acting muscarinic antagonist.

Discussion

There is growing evidence that antioxidants prevent exacerbations in patients with COPD [8,12]. In the original PANTHEON analysis, using the symptom-based Anthonisen definition of exacerbations, NAC reduced the exacerbation rate by 22% versus placebo. When the event-based definition was applied, there was a very similar 20% reduction in the rate of overall exacerbations (i.e., mild, moderate and severe). Furthermore, the rates of symptom-based and event-based exacerbations were similar (1.16 and 1.09, respectively, for NAC and 1.49 and 1.37 for placebo), suggesting that the two definitions generally identify the same patient event.

Given most clinical trials define exacerbation rate (and severity) using criteria similar to our event-based criteria, the updated analyses make it possible to compare the effect of NAC with other interventions targeted at exacerbations, most of which were studied using the narrower HCU definition of moderate-to-severe exacerbations. The 18% reduction in these events with NAC versus placebo in PANTHEON is broadly consistent with a range of other studies in which patients were permitted a range of background medication. For example, roflumilast significantly reduced the rate of moderate-to-severe exacerbations by 19% compared with placebo in a 1-year study [13], maintenance use of azithromycin significantly reduced the rate of moderate-to-severe exacerbations by 17% compared with placebo [14], and in UPLIFT the use of a LAMA reduced the rate of moderate-to-severe exacerbations by 14% compared with placebo [15]. The results of PANTHEON are also consistent with those from studies in which background medication was more highly controlled. In TORCH, an ICS/LABA combination reduced the rate of moderate-to-severe exacerbations by 12% compared with LABA alone and 9% compared with ICS alone (both $p<0.001$) [16]. The results are also consistent with those of six studies that have evaluated the efficacy of single-inhaler ICS/LABA/LAMA triple therapy [17–22], with reductions in the rate of moderate-to-severe exacerbations of 20% compared with LAMA alone [19], 15–35% vs ICS/LABA [17,18,21], and 15–52% vs LABA/LAMA [20–22].

COPD clinical trials typically exclude non-smoking patients. However, there is a growing recognition that a substantial proportion of patients with COPD have never smoked. Many are believed to develop COPD as a consequence of early events, such as premature birth, recurrent infections in childhood, or poor nutrition [23]. Others are thought to develop COPD due to exposure to indoor, occupational, or environmental pollution [24]. This is not only an issue in low- and middle-income countries [25] – more than 25% of patients with COPD in developed countries are never-smokers [26]. The population recruited into PANTHEON is therefore more likely to be generalisable than typical clinical trials, with approximately 24% of the recruited patients being never-smokers. In the subgroup of patients in PANTHEON who were current or ex-smokers, there was a significant 23% reduction in the rate of both overall and moderate-to-severe exacerbations, with a trend towards a lower rate of exacerbations with NAC in the never smokers, although this reduction did not reach statistical significance. Whether this finding reflects the lower statistical power in the never smoking subgroups or differences in the biology of disease between different causes of COPD cannot be answered here, but merits further study.

NAC is typically used as add-on therapy, and it is important to understand how background COPD medication impacts its efficacy. Unlike typical controlled trials that prohibit or limit the use of background medication, the PANTHEON population was receiving a wide range of COPD treatment. NAC was most effective in patients not receiving ICS. Although compared with the placebo group there were fewer exacerbations in NAC treated patients taking ICS, none of these reductions was statistically significant. These data are consistent with the earlier BRONCUS study, in which patients received NAC for three years, although at a lower dose of 600 mg daily [10].

The greater efficacy in the non-ICS subgroups led to the additional hypothesis that NAC could be added to bronchodilator therapy in place of ICS. Therefore, we compared NAC plus long-acting bronchodilator(s) without ICS to placebo plus long-acting bronchodilator(s) with ICS – in other words, NAC versus ICS, both on top of background

long-acting bronchodilator(s). There was a significant 60% reduction in the risk of overall exacerbations with NAC, supporting the hypothesis that NAC could be a useful alternative to ICS in preventing COPD exacerbations. These reductions are substantially higher than typically seen with pharmacological interventions, where a difference of 11–20% is considered clinically relevant [27,28]. This potential ICS-replacement role is of interest since ICSs are known to increase the risk of adverse events such as oral thrush, hoarseness and pneumonia [29]. Overall in PANTHEON the safety profile of NAC was similar to placebo [8]. In particular, there was only one pneumonia serious adverse event (a death, occurring in the NAC group but not considered related to study treatment) [11], with two treatment-emergent pneumonia adverse events (one in each group, neither considered related to treatment). In contrast, pneumonia adverse events are typically reported in 2–3% of patients receiving ICS in clinical trials [17–19], with the rates increasing with increasing treatment duration (pneumonia was reported in 20% of patients receiving ICS/LABA in the 3-year TORCH [16]).

The current analyses have some limitations which mean that these data should be considered hypothesis generating. Firstly, the original analyses were derived from symptom-based criteria; the event-based criteria were not pre-planned – although the similarity of the rates using the two definitions suggests that both largely detect the same events. Secondly, a number of the subgroups are small in size, limiting the conclusions that can be drawn from the results. In particular, 53 patients were receiving both a LABA and a LAMA, only five of whom were not also receiving an ICS; ideally, we would like to evaluate the effect of NAC added to dual bronchodilation. However, the consistency of the results (with the relative efficacy of NAC greater in the non-ICS subgroups than in the ICS-containing subgroups) suggest that this is a valid (and generalisable) finding. Finally, PANTHEON was conducted in a single country (although covering a geographical area similar to Western Europe), with these results being from *post-hoc* analyses rather than from a specifically designed, prospective clinical trial.Conclusion

Overall, these hypothesis-generating analyses suggest that the role of NAC could be to reduce COPD exacerbation risk as an add-on to long-acting bronchodilators, in particular as an alternative to ICS. NAC may be especially beneficial in both current and ex-smokers, who represent the largest portion of COPD populations globally.

Acknowledgements

The authors would like to thank the investigators and patients at the investigative sites for their support of this study.

This study was sponsored by Hainan Zambon Pharmaceutical Co. Ltd. The funding source had no role in the study design, data collection, analysis, or interpretation. Writing support for this manuscript was provided by David Young of Young Medical Communications and Consulting Ltd. This support, which included assisting the authors with creating the first draft and incorporating comments into subsequent drafts, was funded by Zambon SpA.

Financial/non-financial disclosure

AP reports personal fees and non-financial support from Zambon; outside the submitted work he reports grants, personal fees, non-financial support and other from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Mundipharma and TEVA, and personal fees and non-financial support from Menarini and Novartis.

JZ has received consulting and speaking fees from AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline, Takeda/Nycomed, and Zambon Company SpA.

GJC reports grants from US NIH and the Department of Defense, consulting from AstraZeneca, Boehringer Ingelheim, Holaira, Mereo, Third Pole, Pulmonx, Pearl, CSA Medical, Broncus, AVISA, Lungpacer and GlaxoSmithKline, Zambon, Novartis, Chiesi, Verona, Regeneron, Phillips Respironics, and Olympus, and contracted clinical trials from AstraZeneca, Avisa, Mereo, Boehringer Ingelheim, Broncus, GlaxoSmithKline, Lungpacer, Novartis, PneumRx/BTG, Pulmonx, Olympus, Phillips Respironics, Fischer Paykel and Yungjin.

LMF reports grants, personal fees and non-financial support from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Takeda, AstraZeneca, Novartis, Menarini, Laboratori Guidotti, and Almirall, personal fees and non-

financial support from Pearl Therapeutics, Mundipharma, and Boston Scientific, personal fees from Kyorin, Bayer, and Zambon, and grants from Pfizer, Dompè, Malesci, Biofutura Italia, and Vree Health Italia, all outside the submitted work.

PMAC has received consulting and personal fees from AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline, Regeneron Sanofi, Recipharm, Phiilips Medical and Zambon Company SpA who sponsored this analysis.

References

[1] Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, (2018). www.goldcopd.org (accessed December 12, 2017).

[2] F. Andersson, S. Borg, S.A. Jansson, A.C. Jonsson, A. Ericsson, C. Prütz, E. Rönmark, B. Lundbäck, The costs of exacerbations in chronic obstructive pulmonary disease (COPD), Respir. Med. 96 (2002) 700–8.

[3] A. Dhamane, C. Moretz, Y. Zhou, K. Burslem, K. Saverno, G. Jain, A.M. Renda, S. Kaila, COPD exacerbation frequency and its association with health care resource utilization and costs, Int. J. Chron. Obstruct. Pulmon. Dis. 10 (2015) 2609–18. doi:10.2147/COPD.S90148.

[4] M. Thomas, A. Radwan, C. Stonham, S. Marshall, COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care, COPD. 11 (2014) 300–9. doi:10.3109/15412555.2013.841671.

[5] Y.S. Punekar, A. Shukla, H. Müllerova, COPD management costs according to the frequency of COPD exacerbations in UK primary care, Int. J. Chron. Obstruct. Pulmon. Dis. 9 (2014) 65–73. doi:10.2147/COPD.S54417.

[6] M. Cazzola, L. Calzetta, C. Page, J. Jardim, A.G. Chuchalin, P. Rogliani, M. Gabriella Matera, Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis, Eur. Respir. Rev. 24 (2015) 451–461. doi:10.1183/16000617.00002215.

[7] H.N. Tse, L. Raiteri, K.Y. Wong, K.S. Yee, L.Y. Ng, K.Y. Wai, C.K. Loo, M.H. Chan, High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study, Chest. 144 (2013) 106–18. doi:10.1378/chest.12-2357.

[8] J.-P. Zheng, F.-Q. Wen, C.-X. Bai, H.-Y. Wan, J. Kang, P. Chen, W.-Z. Yao, L.-J. Ma, X. Li, L. Raiteri, M. Sardina, Y. Gao, B.-S. Wang, N.-S. Zhong, Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial, Lancet Respir. Med. 2 (2014) 187–194. doi:10.1016/S2213-2600(13)70286-8.

[9] N.R. Anthonisen, J. Manfreda, C.P. Warren, E.S. Hershfield, G.K. Harding, N.A. Nelson, Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease, Ann. Intern. Med. 106 (1987) 196–204. doi:10.7326/0003-4819-106-2-196.

[10] M. Decramer, M. Rutten-van Mölken, P.N.R. Dekhuijzen, T. Troosters, C. van Herwaarden, R. Pellegrino, C.P.O. van Schayck, D. Olivieri, M. Del Donno, W. De Backer, I. Lankhorst, A. Ardia, Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial, Lancet. 365 (2005) 1552–60. doi:10.1016/S0140-6736(05)66456-2.

[11] J.-P. Zheng, F.-Q. Wen, C.-X. Bai, H.-Y. Wan, J. Kang, P. Chen, W.-Z. Yao, L.-J. Ma, Q. Xia, Y. Gao, N.-S. Zhong, High-dose N-acetylcysteine in the prevention of COPD exacerbations: Rationale and design of the PANTHEON Study, COPD J. Chronic Obstr. Pulm. Dis. 10 (2013) 164–171. doi:10.3109/15412555.2012.732628.

[12] S.D. Aaron, K.L. Vandemheen, D. Fergusson, F. Maltais, J. Bourbeau, R. Goldstein, M. Balter, D. O'Donnell, A. McIvor, S. Sharma, G. Bishop, J. Anthony, R. Cowie, S. Field, A. Hirsch, P. Hernandez, R. Rivington, J. Road, V. Hoffstein, R. Hodder, D. Marciniuk, D. McCormack, G. Fox, G. Cox, H.B. Prins, G. Ford, D. Bleskie, S.

Doucette, I. Mayers, K. Chapman, N. Zamel, M. FitzGerald, C.T.S.R.C.R. Consortium, Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial, Ann. Intern. Med. 146 (2007) 545–555. doi:10.7326/0003-4819-146-8-200704170-00152.

[13] F.J. Martinez, P.M.A. Calverley, U.-M. Goehring, M. Brose, L.M. Fabbri, K.F. Rabe, Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial, Lancet. 385 (2015) 857–866. doi:10.1016/S0140-6736(14)62410-7.

[14] R.K. Albert, J. Connett, W.C. Bailey, R. Casaburi, J.A.D. Cooper, G.J. Criner, J.L. Curtis, M.T. Dransfield, M.K. Han, S.C. Lazarus, B. Make, N. Marchetti, F.J. Martinez, N.E. Madinger, C. McEvoy, D.E. Niewoehner, J. Porsasz, C.S. Price, J. Reilly, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, G.R. Washko, P.G. Woodruff, N.R. Anthonisen, COPD Clinical Research Network, Azithromycin for prevention of exacerbations of COPD, N. Engl. J. Med. 365 (2011) 689–98. doi:10.1056/NEJMoa1104623.

[15] D.P. Tashkin, B. Celli, S. Senn, D. Burkhart, S. Kesten, S. Menjoge, M. Decramer, U.S. Investigators, A 4-year trial of tiotropium in chronic obstructive pulmonary disease, N. Engl. J. Med. 359 (2008) 1543–1554. doi:10.1056/NEJMoa0805800.

[16] P.M.A. Calverley, J.A. Anderson, B. Celli, G.T. Ferguson, C. Jenkins, P.W. Jones, J.C. Yates, J. Vestbo, on behalf of the TORCH Investigators, Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease, N. Engl. J. Med. 356 (2007) 775–789. doi:10.1056/NEJMoa063070.

[17] D.A. Lipson, H. Barnacle, R. Birk, N. Brealey, N. Locantore, D.A. Lomas, A. Ludwig-Sengpiel, R. Mohindra, M. Tabberer, C.-Q. Zhu, S.J. Pascoe, FULFIL Trial: Once-daily triple therapy for patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 196 (2017) 438–446. doi:10.1164/rccm.201703-0449OC.

[18] D. Singh, A. Papi, M. Corradi, I. Pavlišová, I. Montagna, C. Francisco, G. Cohuet, S. Vezzoli, M. Scuri, J. Vestbo, Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial, Lancet. 388 (2016) 963–973. doi:10.1016/S0140-6736(16)31354-X.

[19] J. Vestbo, A. Papi, M. Corradi, V. Blazhko, I. Montagna, C. Francisco, G. Cohuet, S. Vezzoli, M. Scuri, D. Singh, Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial, Lancet. 389 (2017) 1919–1929. doi:10.1016/S0140-6736(17)30188-5.

[20] A. Papi, J. Vestbo, L. Fabbri, M. Corradi, H. Prunier, G. Cohuet, A. Guasconi, I. Montagna, S. Vezzoli, S. Petruzzelli, M. Scuri, N. Roche, D. Singh, Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial, Lancet. 391 (2018) 1076–1084. doi:10.1016/S0140-6736(18)30206-X.

[21] D.A. Lipson, F. Barnhart, N. Brealey, J. Brooks, G.J. Criner, N.C. Day, M.T. Dransfield, D.M.G. Halpin, M.K. Han, C.E. Jones, S. Kilbride, P. Lange, D.A. Lomas, F.J. Martinez, D. Singh, M. Tabberer, R.A. Wise, S.J. Pascoe, for the IMPACT investigators, Once-daily single-inhaler triple versus dual therapy in patients with COPD, N. Engl. J. Med. 378 (2018) 1671–80. doi:10.1056/NEJMoa1713901.

[22] G.T. Ferguson, K.F. Rabe, F.J. Martinez, L.M. Fabbri, C. Wang, M. Ichinose, E. Bourne, S. Ballal, P. Darken, K. DeAngelis, M. Aurivillius, P.M. Dorinsky, C. Reisner,

Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, ph 3 randomised controlled trial, Lancet Respir. Med. 6 (2018) 747–58. doi:10.1016/S2213-2600(18)30327-8.

[23] S. Carraro, N. Scheltema, L. Bont, E. Baraldi, Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing, Eur. Respir. J. 44 (2014) 1682–1696. doi:10.1183/09031936.00084114.

[24] C.H. Miele, D. Jaganath, J.J. Miranda, A. Bernabe-Ortiz, R.H. Gilman, C.M. Johnson, G.B. Diette, R.A. Wise, W. Checkley, CRONICAS Cohort Study Group, Urbanization and daily exposure to biomass fuel smoke both contribute to chronic bronchitis risk in a population with low prevalence of daily tobacco smoking, COPD J. Chronic Obstr. Pulm. Dis. 13 (2016) 186–195. doi:10.3109/15412555.2015.1067765.

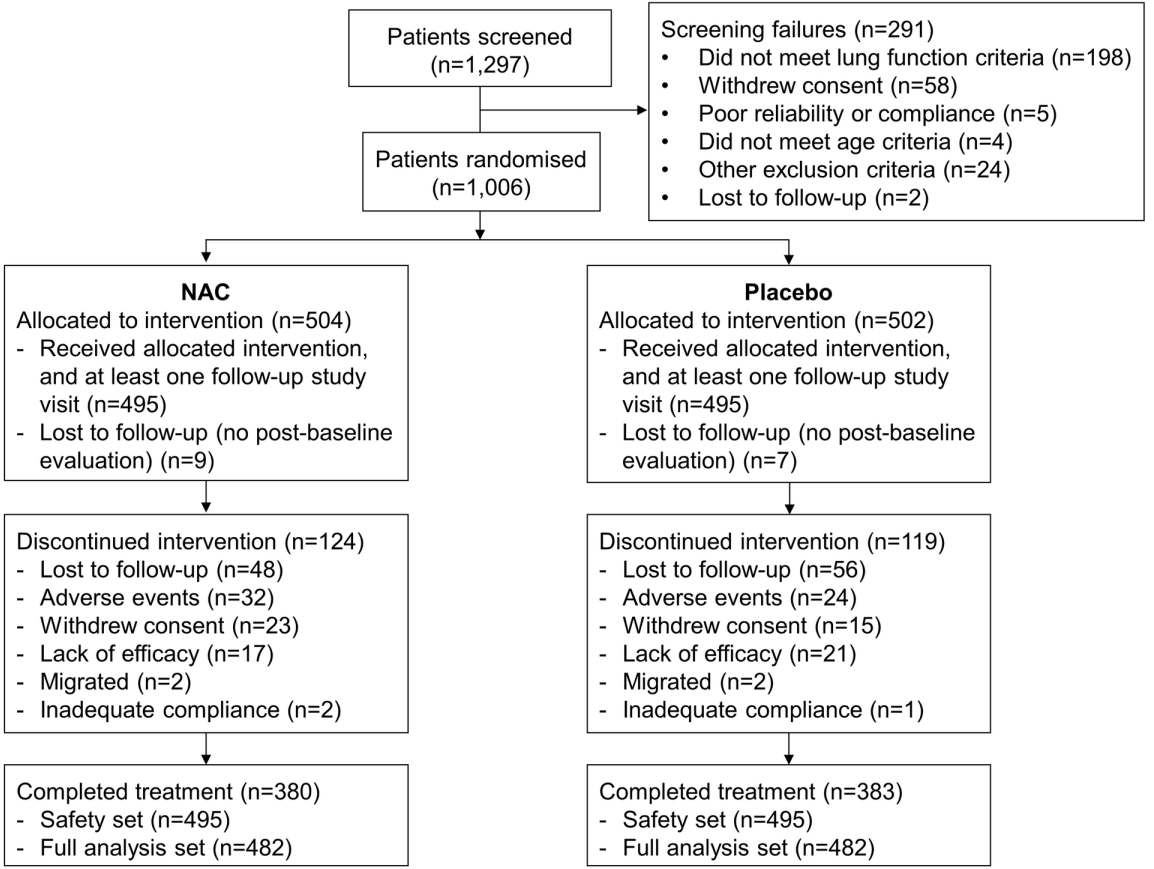
[25] M. Grigsby, T. Siddharthan, M.A. Chowdhury, A. Siddiquee, A. Rubinstein, E. Sobrino, J.J. Miranda, A. Bernabe-Ortiz, D. Alam, W. Checkley, Socioeconomic status and COPD among low- and middle-income countries, Int. J. Chron. Obstruct. Pulmon. Dis. 11 (2016) 2497–2507. doi:10.2147/COPD.S111145.

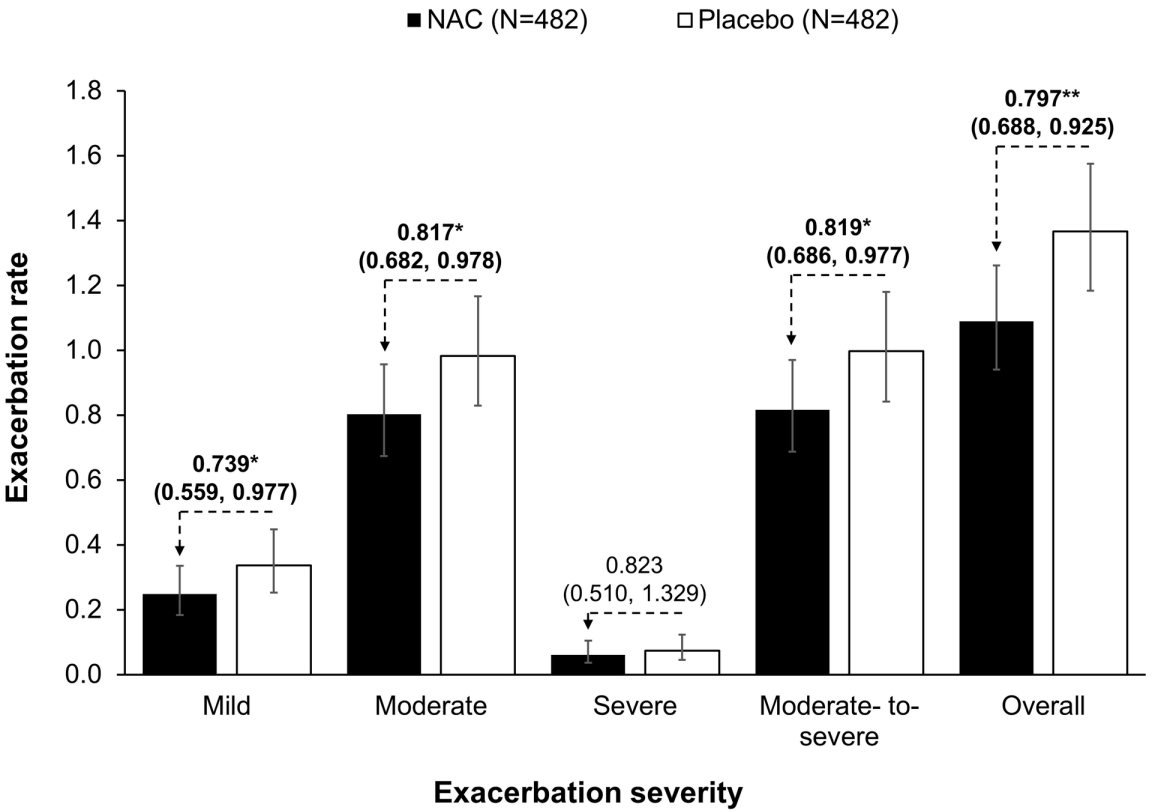
[26] S.S. Salvi, P.J. Barnes, Chronic obstructive pulmonary disease in non-smokers, Lancet. 374 (2009) 733–43. doi:10.1016/S0140-6736(09)61303-9.

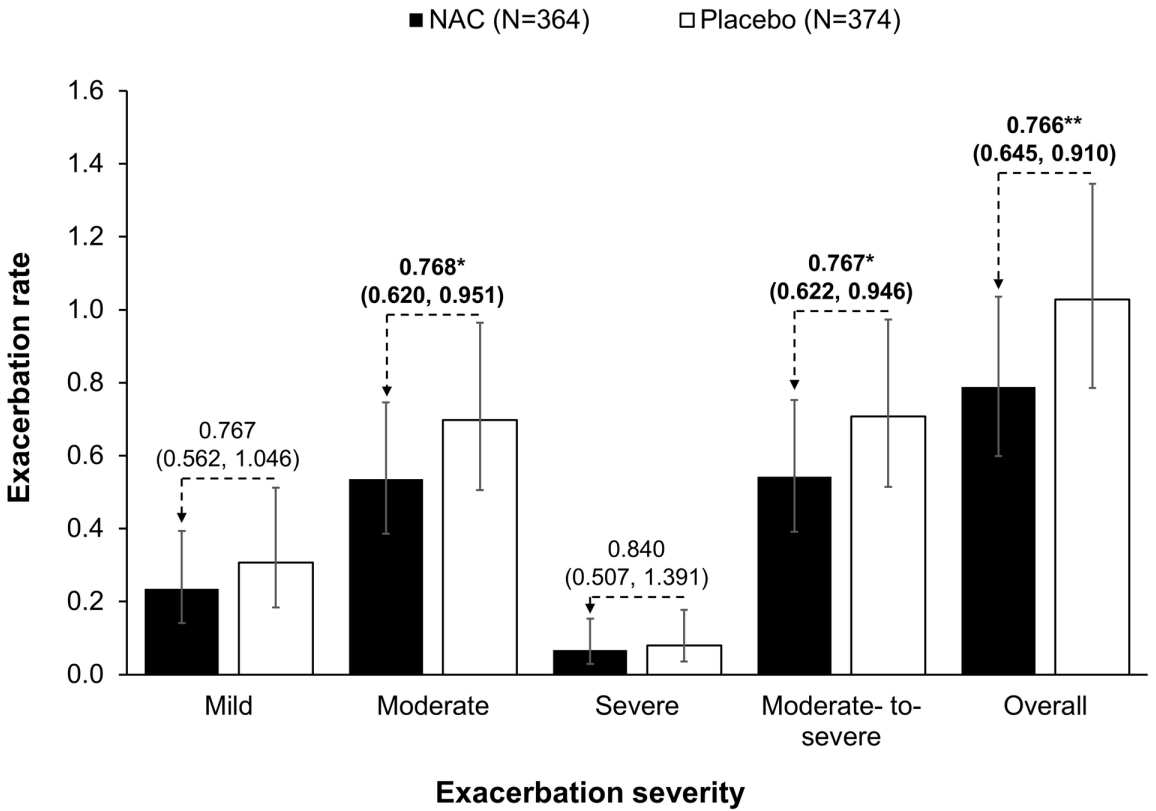
[27] P.W. Jones, K.M. Beeh, K.R. Chapman, M. Decramer, D.A. Mahler, J.A. Wedzicha, Minimal clinically important differences in pharmacological trials, Am. J. Respir. Crit. Care Med. 189 (2014) 250–255. doi:10.1164/rccm.201310-1863PP.

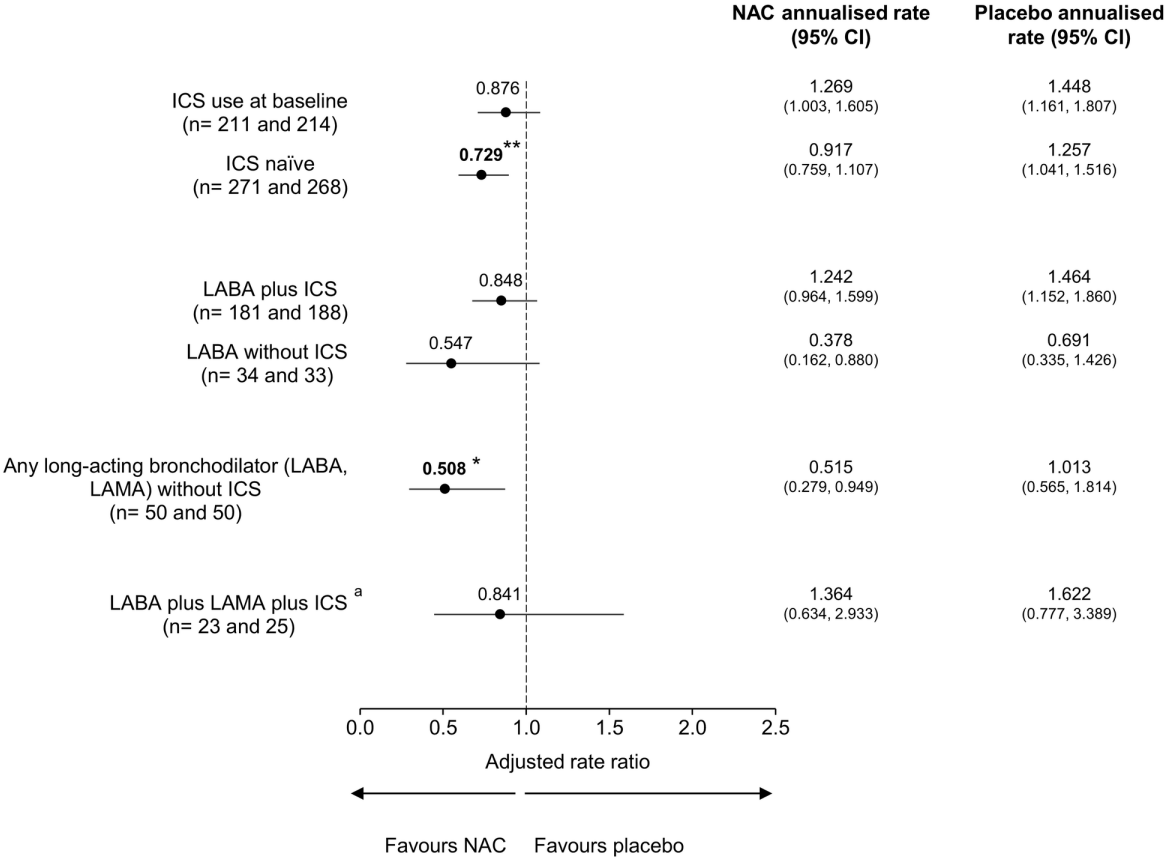
[28] K.R. Chapman, C. Bergeron, M. Bhutani, J. Bourbeau, R.F. Grossman, P. Hernandez, R.A. McIvor, I. Mayers, Do we know the minimal clinically important difference (MCID) for COPD exacerbations?, COPD. 10 (2013) 243–9. doi:10.3109/15412555.2012.733463.

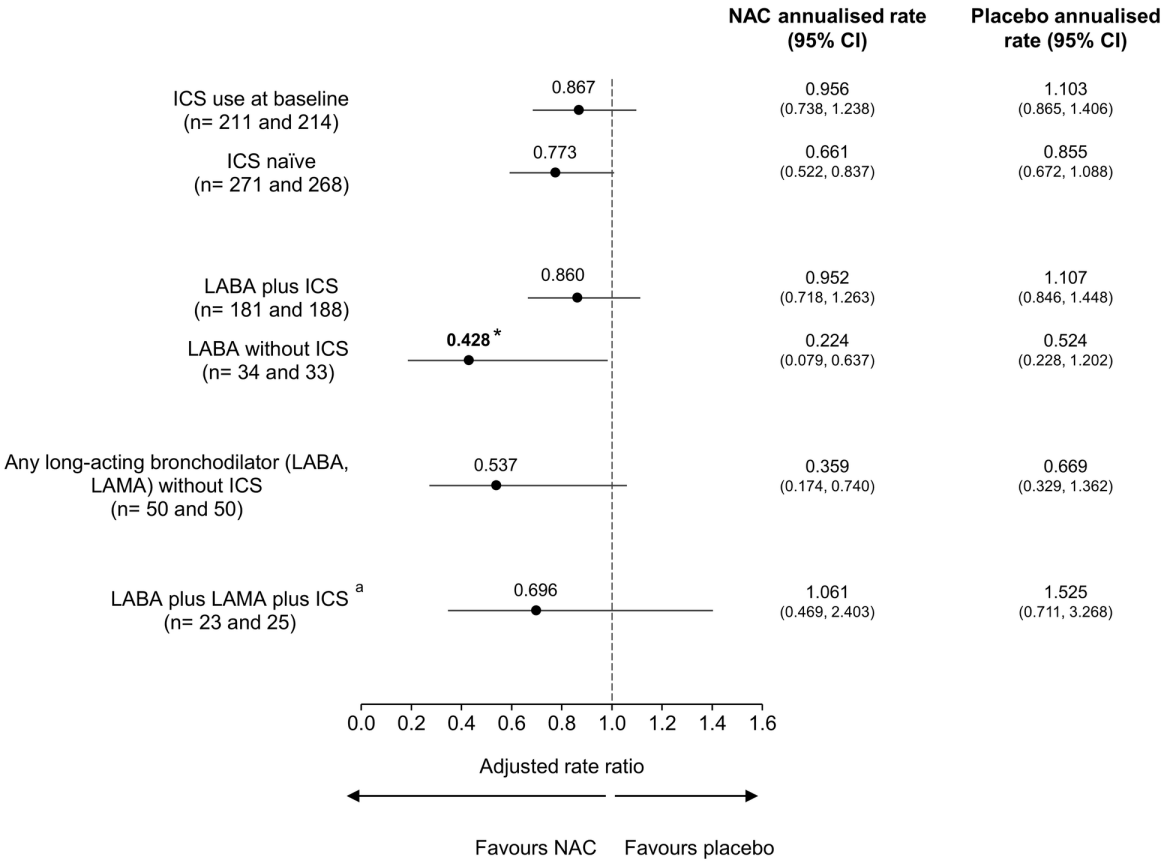
[29] I.A. Yang, M.S. Clarke, E.H.A. Sim, K.M. Fong, Inhaled corticosteroids for stable chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. Issue 7 (2012) CD002991. doi:10.1002/14651858.CD002991.pub3.

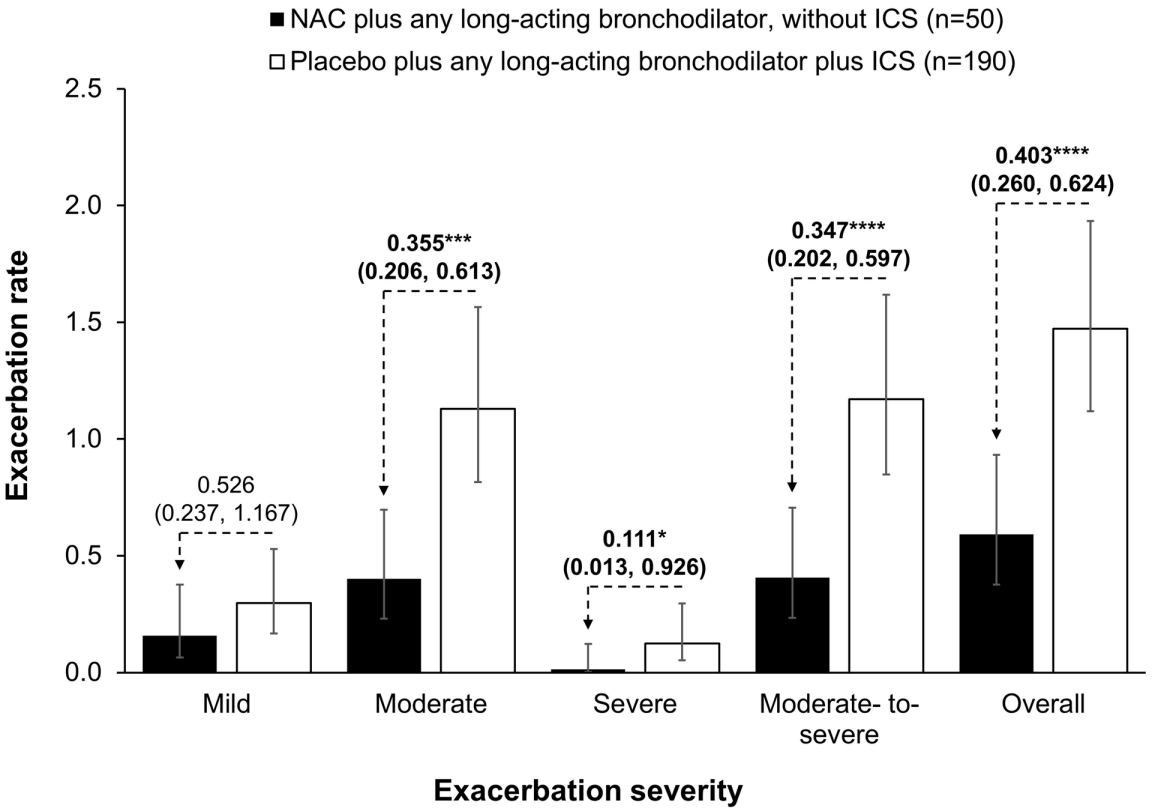

Patients screened
(n=1,297)
Screening failures (n=291)
• Did not meet lung function criteria (n=198)
• Withdrew consent (n=58)
• Poor reliability or compliance (n=5)
• Did not meet age criteria (n=4)
• Other exclusion criteria (n=24)
• Lost to follow-up (n=2)
Patients randomised
(n=1,006)
NAC
Allocated to intervention (n=504)
- Received allocated intervention, and at least one follow-up study visit (n=495)
- Lost to follow-up (no post-baseline evaluation) (n=9)
Placebo
Allocated to intervention (n=502)
- Received allocated intervention, and at least one follow-up study visit (n=495)
- Lost to follow-up (no post-baseline evaluation) (n=7)
Discontinued intervention (n=124)
- Lost to follow-up (n=48)
- Adverse events (n=32)
- Withdrew consent (n=23)
- Lack of efficacy (n=17)
- Migrated (n=2)
- Inadequate compliance (n=2)
Discontinued intervention (n=119)
- Lost to follow-up (n=56)
- Adverse events (n=24)
- Withdrew consent (n=15)
- Lack of efficacy (n=21)
- Migrated (n=2)
- Inadequate compliance (n=1)
Completed treatment (n=380)
- Safety set (n=495)
- Full analysis set (n=482)
Completed treatment (n=383)
- Safety set (n=495)
- Full analysis set (n=482)


NAC (N=482)
Placebo (N=482)
Exacerbation rate
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.739*
(0.559, 0.977)
0.817*
(0.682, 0.978)
0.823
(0.510, 1.329)
0.819*
(0.686, 0.977)
0.797**
(0.688, 0.925)
Mild
Moderate
Severe
Moderate- to-severe
Overall
Exacerbation severity


NAC (N=364)
Placebo (N=374)
Exacerbation rate
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.767
(0.562, 1.046)
0.768*
(0.620, 0.951)
0.840
(0.507, 1.391)
0.767*
(0.622, 0.946)
0.766**
(0.645, 0.910)
Mild
Moderate
Severe
Moderate- to-severe
Overall
Exacerbation severity


NAC annualised rate (95% CI)
Placebo annualised rate (95% CI)
ICS use at baseline (n= 211 and 214)
0.876
1.269 (1.003, 1.605)
1.448 (1.161, 1.807)
ICS naïve (n= 271 and 268)
0.729**
0.917 (0.759, 1.107)
1.257 (1.041, 1.516)
LABA plus ICS (n= 181 and 188)
0.848
1.242 (0.964, 1.599)
1.464 (1.152, 1.860)
LABA without ICS (n= 34 and 33)
0.547
0.378 (0.162, 0.880)
0.691 (0.335, 1.426)
Any long-acting bronchodilator (LABA, LAMA) without ICS (n= 50 and 50)
0.508 *
0.515 (0.279, 0.949)
1.013 (0.565, 1.814)
LABA plus LAMA plus ICS a (n= 23 and 25)
0.841
1.364 (0.634, 2.933)
1.622 (0.777, 3.389)
0.0
0.5
1.0
1.5
2.0
2.5
Adjusted rate ratio
Favours NAC
Favours placebo


NAC annualised rate (95% CI)
Placebo annualised rate (95% CI)
ICS use at baseline (n= 211 and 214)
0.867
0.956 (0.738, 1.238)
1.103 (0.865, 1.406)
ICS naïve (n= 271 and 268)
0.773
0.661 (0.522, 0.837)
0.855 (0.672, 1.088)
LABA plus ICS (n= 181 and 188)
0.860
0.952 (0.718, 1.263)
1.107 (0.846, 1.448)
LABA without ICS (n= 34 and 33)
0.428 *
0.224 (0.079, 0.637)
0.524 (0.228, 1.202)
Any long-acting bronchodilator (LABA, LAMA) without ICS (n= 50 and 50)
0.537
0.359 (0.174, 0.740)
0.669 (0.329, 1.362)
LABA plus LAMA plus ICS a (n= 23 and 25)
0.696
1.061 (0.469, 2.403)
1.525 (0.711, 3.268)
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6
Adjusted rate ratio
Favours NAC
Favours placebo


NAC plus any long-acting bronchodilator, without ICS (n=50)
Placebo plus any long-acting bronchodilator plus ICS (n=190)
Exacerbation rate
2.5
2.0
1.5
1.0
0.5
0.0
0.526
(0.237, 1.167)
0.355***
(0.206, 0.613)
0.111*
(0.013, 0.926)
0.347****
(0.202, 0.597)
0.403****
(0.260, 0.624)
Mild
Moderate
Severe
Moderate- to-severe
Overall
Exacerbation severity