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The Effect of Low Dose Corticosteroids and Theophylline on the Risk of Acute Exacerbations of COPD. The TASCS Randomised Controlled Trial

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ABSTRACT

Background The highest burden of Chronic Obstructive Pulmonary Disease (COPD) occurs in low and middle income countries. Low cost oral medications, if effective, could enable affordable, accessible COPD treatment.

Methods In this randomized, 3 arm, double-blind, double dummy, placebo controlled study conducted in 37 centres in China, symptomatic patients with moderate/very severe COPD were randomized 1:1:1 to low dose (LD) theophylline 100mg bd + prednisone 5mg once daily; LD theophylline 100mg bd + placebo once daily; or placebo bd + placebo once daily for 48 weeks. The primary endpoint was annualised exacerbation rate.

Findings 1670 subjects were randomised, and 1242 completed the study (1142 with acceptable Week 48 data). Subjects (75.7% male) were mean age 64.4 years, with mean (SD) baseline post-bronchodilator Forced Expiratory Volume in one second (FEV_1) 1.1 (0.4)L, 42.2% predicted and mean (SD) St Georges Respiratory Questionnaire (SGRQ) score 45.8 (20.1). There were negligible differences between annualised exacerbation rates across the three treatments, being 0.89 (95%CI= 0.78-1.02) on Prednisone-LD Theophylline; 0.86 (0.75-0.99) on LD Theophylline plus placebo, and 1.00 (0.87-1.14) on double placebo. The Rate Ratio between the first and the pooled comparative arms was 0.96 (0.83-1.12), and for LD Theophylline + placebo vs placebo was 0.866, 95% CI 0.728; 1.029, p=0.101 and for LD Theophylline + Low dose oral Prednisone vs placebo was 0.895, 95% CI 0.755; 1.061, p=0.201. Secondary outcomes of hospitalisations, FEV_1, SGRQ and COPD Assessment Test (CAT) score showed no statistically significant difference between treatment arms. Serious adverse events (SAEs) other than exacerbations were < 2% and did not differ between the treatment arms.

Conclusions LD theophylline alone or in combination with prednisone did not reduce exacerbation rates or clinically important secondary endpoints compared to placebo.

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Introduction

The global burden of Chronic Obstructive Pulmonary Disease (COPD) is rising and the majority of this burden falls in low- and middle-income countries (LMICs)[1,2]. The mainstay of pharmacological treatment for COPD is the early and sustained use of bronchodilators, and the later introduction of inhaled corticosteroids (ICS) for exacerbating patients. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends short (SABA) and long acting bronchodilators (beta agonists (LABA) and muscarinic antagonists (LAMA)) alone or in combination for symptomatic COPD, in all GOLD stages[3]. Theophylline is also of benefit but due to its potential toxicity when used in bronchodilating doses, is not recommended as step up therapy from SABA unless inhaled long acting bronchodilators are not available or affordable. This is the case in many LMICs, where currently theophylline is the main treatment for COPD in addition to short acting bronchodilators[4]. Inhaled corticosteroids (ICS) play an important role in reducing exacerbations, especially in frequent exacerbators and people with worse airflow obstruction, but have minimal or no effect on airflow as measured by the forced expiratory volume in one second (FEV_1) or lung function decline, leading to the view that COPD is a corticosteroid resistant disease[5,6].

In LMIC's most inhaled medications, including ICS are neither affordable nor accessible for the majority of patients with COPD[4,7], and affordable oral therapies are frequently used. *In vitro* and *in vivo* studies show that corticosteroids and theophylline, both in low doses, have synergistic and clinically useful anti-inflammatory effects in COPD[8,9]. The molecular mechanisms for this effect suggest that it occurs through theophylline increasing the activity of the nuclear enzyme histone-deacetylase-2 (HDAC2), which is reduced in COPD cells, thus preventing the anti-inflammatory effect of corticosteroids [10,11], an effect separate to the mechanism of bronchodilation[12]. Small clinical studies have suggested that LD theophylline, at levels below those which cause bronchodilatation, can reverse corticosteroid insensitivity in COPD[9,13]. One small study has shown an effect for LD theophylline on FEV1 as well as exacerbations[14]

A recently published randomised controlled trial (RCT), Theophylline with Inhaled Corticosteroids (TWICS) examined this effect in COPD patients taking ICS[15]. One year's treatment with LD theophylline did not reduce the number of COPD exacerbations compared to placebo when added to their maintenance ICS and inhaled bronchodilator therapy although in a *post-hoc* analysis, there was a significant reduction in severe (hospitalised) exacerbations in the theophylline group. The study design did not assess adherence with ICS, so it is not clear if patients were taking adequate amounts to enable this hypothesis to be tested.

The aim of the present study, the Theophylline And Steroids in COPD Study (TASCS) randomised controlled trial was to compare the efficacy and safety of LD theophylline and oral prednisone given daily for 48 weeks versus LD theophylline alone or placebo alone, on time to first exacerbation and annualised rate of exacerbations in patients with moderate to very severe COPD.

Methods

Study Design

TASCS was a 48-week, randomized, 3 arm, double-blind, double dummy, placebo-controlled study, in symptomatic patients with moderate-very severe COPD, conducted in 37 centres in China. The study comprised a 2-4 week washout/run-in period followed by a treatment phase.

Study Population

Eligible patients were male or female, aged 40 - 80 years, with diagnosed, stable moderate to very severe COPD [FEV_1/Forced Vital Capacity (FVC) <0.70 and FEV_1 <70% predicted]. They had either a smoking history of at least 10 pack-years, or biomass exposure assessed by a standard exposure questionnaire[16] of > 10 years. Although patients were not required to have had a treated COPD exacerbation in the year prior to screening, investigators were encouraged to consider such patients as eligible. Patients were ineligible if an exacerbation occurred within 4 weeks of screening. They were also excluded if they were prescribed domiciliary oxygen, had coexistent illness precluding participation in the study or suggesting a life expectancy under one year, pulmonary resection or current asthma. In relation to potential risk of treatment, patients were excluded if they had known sensitivity to, or intolerance of theophylline, clinical evidence of chronic liver disease, or transaminase or GGT elevation > 1.5 x ULN, or random blood glucose level > 8mmol/L. Permitted medications included regular inhaled LAMA and/or LABA therapy, short acting anticholinergic and short acting beta agonist (SABA) inhaled rescue medication. Maintenance inhaled corticosteroids, oral corticosteroids, parenteral corticosteroids and oral syrups or other formulations containing theophylline were not permitted during the study.

Intervention

The TASCS study compared placebo and placebo, low-dose theophylline and placebo or low-dose theophylline and low dose oral prednisone. Symptomatic patients with moderate/very severe COPD were randomized 1:1:1 to placebo bd + placebo once daily, theophylline 100mg bd +

placebo once daily or slow-release theophylline 100mg bd + prednisone 5mg once daily for 48 weeks.

Study Procedures

Potential participants were identified through hospital outpatient and inpatient clinics at 37 centres in China, and undertook a screening visit, two to four weeks before the randomisation visit. During the run-in, all prohibited medications, specifically theophylline containing medications and ICS were ceased while LABA, LAMA and SABA were continued. The run-in was undertaken to ensure stability and patients' acceptance of the changes, prior to randomisation. Spirometry before and after bronchodilator was performed at the screening visit to confirm eligibility. Vital signs, spirometry, COPD Assessment Test (CAT) score[17], medical history including bone fracture, medication, demographics, routine pathology and St George's Respiratory Questionnaire (SGRQ)[18] were also recorded prior to randomisation. Study visits took place at 12-week intervals for 48 weeks, with spirometry, SGRQ, CAT score and diary card review as well as medication return and dispensing of new medication. Symptoms attributable to corticosteroid and theophylline toxicity were recorded at each patient visit.

Adherence with study treatment was assessed by return of study drug at clinic visits and by diary card recording of episodes where study drug was discontinued for 5 days or more, with number of days discontinued and reason for discontinuation.

Outcomes

The primary outcome was the number of COPD exacerbations per participant in 48 weeks, annualised as a rate per patient per year. A COPD exacerbation was defined as symptomatic deterioration in COPD symptoms (cough, sputum production or dyspnea) requiring treatment with antibiotics, initiation of a course of systemic corticosteroids, hospitalisation or a combination of these. Exacerbations were graded as mild if they required symptomatic treatment with inhaled bronchodilators only, moderate if managed with antibiotics and/or oral corticosteroids, and severe if the exacerbation also resulted in emergency department presentation or hospitalization. Secondary outcomes included time to first severe exacerbation leading to hospitalisation or death, health status using the SGRQ and the CAT, (CAT), pre- and post-bronchodilator FEV_1, FVC and FEV_1/FVC ratio.

A subgroup of 75 patients based at 3 major centres had blood samples taken at baseline, 12 and 48 weeks for serum theophylline, which was analysed in a central laboratory, blinded, after completion of the study. Morning serum cortisol (08.00-10.00) was performed in a subgroup of 91 patients at 50 weeks. The 50 week time point (2 weeks following completion of the 48 week study drug administration) was chosen to assess adrenal recovery and the safety of administration of prednisone 5mgs daily for 48 weeks[19].

Trial Oversight

The trial protocol and informed consent procedures were approved centrally by the University of Sydney Human Research Ethics Committee and by the institutional review board at each study site. Patient Information and Consent forms, questionnaires and diary cards were forward and back translated. Participant Information Statements and Consent Forms were approved by each ethics committee and formatted in accordance with their own guidelines and requirements. All patients provided written informed consent prior to undertaking any study-specific procedures. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

The trial was conducted under the direct supervision of the principal investigators (NB and CJ). The trial was registered on clinical trials.gov (NCT02261727).

Randomisation and Masking

Treatment randomisation was stratified by smoking status and clinical site, using a secure web based randomisation system and centrally administered in agreement with The George Institute's standard operating procedures on randomisation. Study drug manufacture, packaging and labelling was undertaken by approved Chinese suppliers and distributors.

Statistical Methods

All analyses were performed on an intention to treat basis (ITT).

To compare COPD rates we fitted multivariable negative binomial regressions with a pre-specified covariate set which included: treatment arm, hospital region, history of smoking, sex, exacerbation in the year prior to randomisation and post-bronchodilator percent FEV1 at screening. For time-to-event outcomes we used proportional hazard Cox regressions and for continuous secondary outcomes we assessed the difference across treatments by analysis of covariance (ANCOVA).

Pre-specified subgroup analyses included for the primary outcome, age (<65 and >=65 years), sex, smoking status (current, past and never smoker), biomass exposure, on oral steroid at baseline (Yes and No), COPD exacerbation in last 12 months (Yes and No), SGRQ score (<85 vs >=85), CAT score (<20 vs >=20), FEV1 thresholds (<50% and >=50%), eosinophils (10^9cells/L) (<0.30 vs >=0.30), eosinophils (10^9cells/L) (<0.20 vs >=0.20), eosinophils (10^9cells/L) (<0.15 vs >=0.15).

To overcome the potential issue of multiple testing among three treatment groups, the primary comparison was pre-specified as the treatment group of low-dose theophylline and low dose oral prednisone versus combination of other two groups (low-dose theophylline along and placebo group). We specified a hierarchical process where, if the primary comparison was found as statistically significant, the comparison between the two treatment groups versus placebo group separately would be conducted. No multiple testing adjustments were performed although we have critically assessed any p-value <0.05. All statistical analyses were performed using SAS 9.3. Further statistical information is included in the Supplementary files.

Results

Participants commenced enrolling in the study June 2014 and the last patient completed the study on 14 May 2018. In total, 2325 patients were screened, 1670 were randomly assigned to study treatment and 1242 completed the study, a 26% withdrawal rate (Figure 1, CONSORT diagram). Out of 2325 screened, 665 were not eligible to proceed to randomisation at baseline. Failure to meet spirometric requirements was the principal reason for not meeting eligibility criteria: either due to post-bronchodilator FEV1>70% or FEV1/FVC > 0.7, or inability to perform reproducible spirometry meeting ATS-ERS reproducibility standards. Protocol non-compliance was the other major cause, primarily physician decision regarding participant's difficulty with trial adherence or failure to return for randomisation visit within 4 weeks of screening.

There were no clinically significant differences between the treatment groups with regard to baseline demographic characteristics, COPD history or treatment (Table 1). The mean (SD) age of participants was 64.4 years (8.0), of whom 75.7% were male. Current smokers had a mean 42.7 (23.9) pack year history, and comprised 19.9% of the total, ex-smokers 53.3% and never smokers 26.8%. Of the total population, 38.4% participants had a biomass exposure history and 17.1% had dust and fume exposure of > 10 years' duration. Mean baseline post-bronchodilator FEV_1 was 1.1 (0.4)L, was 42.2% predicted, and mean acute bronchodilator reversibility was 0.10 (0.04)L. 47%

patients reported having an acute exacerbation of COPD requiring treatment with an antibiotic, systemic steroids or both in the previous 12 months.

Annualised exacerbation rates across the three treatment arms were similar, being 0.89 (0.77 - 1.02) on Prednisone-LD Theophylline; 0.86 (0.75-0.99) on LD Theophylline plus placebo, and 1.00 (0.87-1.14) on placebo plus placebo at Week 48 (Table 2). There was no statistical difference in the rate ratio of exacerbations in the comparison between arm 3 (LD theophylline and prednisone) versus vs the pooled arms 1+2 (LD theophylline-placebo added to placebo-placebo), which was 0.96 (0.83-1.12), p=0.6084. The Rate Ratio for LDT + placebo vs placebo was 0.866, 95% CI 0.728; 1.029, p=0.101 and for LDT + Low dose oral Prednisone vs placebo was 0.895, 95% CI 0.755; 1.061, p=0.201. Time to first COPD exacerbation did not differ between the treatment arms (Figure 2).

A per-protocol (PP) analysis was undertaken for the annualised exacerbation rate (primary outcome). The PP population included all participants who completed the study within an 8 week window of Week 48 and who were not withdrawn or discontinued due to AEs (4.2%). Other reasons for exclusion from the PP population were death (4.0%), protocol non-compliance including major protocol deviations or treatment adherence < 60% (8.1%), loss to follow up (38.6%), investigator decision (1.6%), withdrawal based on patient decision (41.2%) or ineligible based on the protocol entry criteria (2.7%). There were no significant differences between the three treatment groups for total, mild, moderate or severe annualised exacerbation rates in the PP population (Table 2B).

Secondary outcomes of hospitalisations, FEV_1, SGRQ and CAT score showed negligible differences between treatment arms (Table 3). In view of the lack of difference between treatment arms we did not undertake the pre-specified subgroup analyses based on age, gender, smoking status, exacerbation history, SGRQ and CAT score for the primary outcome. Mean FEV_1, SGRQ and CAT scores were numerically better during and at the end of the study in all arms than at baseline, although statistical analysis was not undertaken for these comparisons.

Medication compliance, estimated based on pill return at each clinic visit was > 80% in over 85% subjects. Random serum theophylline levels and morning serum cortisol levels at 50 weeks were consistent with treatment allocation, the mean theophylline levels being significantly higher in the two theophylline containing arms than the double placebo arm, and the mean morning cortisol being lower in the prednisone containing arm compared to the non-prednisone arms (Table S1).

Patients were more likely to complete the study on the LD theophylline plus prednisone treatment arm compared to the other two study arms combined, but not comparing the arms individually (Table S2). The number of adverse events was low, with an expected incidence across the treatment arms.

Discussion

In this large RCT in China, we showed no difference in the annualised rate of exacerbations on combined LD theophylline and prednisone versus placebo or LD theophylline alone. Nor was there any benefit for this combination in our secondary outcomes, which included quality of life and lung function. Our findings indicate that the treatment combination of LD theophylline and prednisone does not confer benefit over LD theophylline alone and that LD theophylline alone provided no clinical benefits compared to placebo.

The patients in our study had moderate to very severe COPD based on their lung function and exacerbation history, although we could not allocate a GOLD grading for GOLD A-D[3], as we did not collect a history of hospitalised exacerbations in the previous 12 months. The mean baseline CAT score of 18.1 and baseline SGRQ of 45.8 suggest that patients in China record a lower impact of COPD for their severity of airflow obstruction than is the case in many other countries in COPD studies.

Although there was no evidence of benefit of LD Theophylline and prednisone in this study, on average the TASCS participants improved their COPD status during the study year. Although the mean rate of exacerbations reported in the prior year (0.7) was slightly lower than the rate recorded during the study year (0.9-1.0), the prior year rate was based on self-report only, and likely subject to recall bias and under-reporting. All pre-specified secondary endpoints – lung function and health status outcomes improved between study commencement and completion in all treatment arms. The consistency of this response suggests that the patients gained benefit from clinical trial participation, even if not from the study drug interventions, although we cannot exclude the possibility that patients who dropped out of the study were sicker and this helped improve the scores of all outcomes studied.

It is possible that LD theophylline does improve corticosteroid responses at a cellular level in COPD, but does not restore HDAC levels or activity adequately enough to produce a clinically evident benefit[20]. On the basis of the random blood tests in TASCS, we can conclude that the patients in the prednisone containing arm on the whole were adherent to the intervention, and

we do not consider poor adherence was an issue in TASCS. Even 2 weeks after ceasing the study and daily administration of prednisone, randomly selected patients still had lower mean morning cortisol levels than the patients in the other two study arms[19]. Additionally, study medication adherence was high, and although it dropped slightly during the study, at week 48 on the basis of pill returns, 88% participants were > 80% adherent with the medication.

There are some limitations to our study although we consider the findings are consistent and robust and support our conclusions for no effect of these interventions. There was a 26% withdrawal rate in this study, with a higher rate of withdrawals occurring earlier in the trial. Patients requested withdrawal if they felt the treatment was not helping them and in particular if they suffered an exacerbation. This was most evident at the first study visit after treatment commencement, as can be seen in Figure 4 at the 12-week visit, when the greatest number of withdrawals occurred.

During the study, owing to slow recruitment we reduced the power of the study from 90% to 80% in order to reduce our target study population. Estimation of study sample size based on 80% power is the case for several published studies of COPD exacerbations[21,22]. Even so, the TASCS results do not suggest any trend to a difference between treatments that would become statistically significant if we had maintained 90% power by having a higher number of study participants.

Many of the patients in this study were from rural towns in China located a significant distance from major centres and some patients travelled 2-3 hours to reach the study centre. As a result, severe exacerbations requiring oral corticosteroids and/or antibiotics were often identified by hospital presentations and the proportion of hospitalised exacerbations is relatively high in TASCS compared to some other COPD other study populations[23-25]. Conversely, we consider that a proportion of milder exacerbations were not diagnosed, treated or recorded. Whilst it is recognised that mild COPD exacerbations often go unrecognised by patients and clinicians, in China we believe this is even more likely to be the case. The mean exacerbation rate in TASCS of 0.8/patient/year almost certainly underestimates the true exacerbation rate for the study population.

In conclusion, in this large RCT comparing LD theophylline and prednisone with placebo or LD theophylline alone, there was no demonstrable effect on exacerbation rate, lung function or COPD related quality of life.

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AUTHORS' CONTRIBUTIONS

CRJ, NB, PJB, BC contributed to the study concept and design, data interpretation and final approval of the manuscript. AM contributed to implementation of the study, data collection, cleaning, interpretation and final approval of the manuscript. AS, G-LDT and TB contributed to statistical analysis and interpretation, and final approval of the manuscript. F-QW, N-SZ, J-PZ and AM contributed to the study execution, data interpretation, review and final approval of the manuscript. CRJ wrote the primary manuscript and all authors revised and contributed to its final review. CRJ, the corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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TABLES AND FIGURES

TABLE 1: Baseline Characteristics of the patients in the Intention To Treat (ITT) population of TASCS‡

Characteristic	Total (n=1670)	Placebo (n=554)	Placebo & Theophylline (n=568)	Prednisone & Theophylline (n=548)
Age	64.4±8.0	63.9±8.5	64.4±7.8	64.9±7.7
Male	1264 (75.7)	426 (76.9)	434 (76.4)	404 (73.7)
Body Mass Index^*	22.3±3.5	22.4±3.5	22.3±3.5	22.3±3.5
Smoking Status*				
Current	332 (19.9)	98 (17.7)	121 (21.3)	113 (20.6)
Former	889 (53.3)	309 (55.8)	299 (52.7)	281 (51.3)
Never	448 (26.8)	147 (26.5)	147 (25.9)	154 (28.1)
Pack Years				
Current	42.7±23.9	43.5±27.1	40.5±22.3	44.4±22.7
Former	38.2±20.8	39.3±22.7	38.5±19.8	36.7±19.6
Spirometry				
Pre BD# FEV1 (L)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	0.9 (0.4)
Post BD FEV1 (L)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)
% Predicted Post BD FEV1	42.2 (15.8)	42.1 (15.5)	43.0 (15.8)	41.6 (15.9)
Post BD FEV1/FVC	0.48	0.48	0.46	0.43
GOLD[3] Severity of Airflow Limitation				
Mild	22 (1.3)	5 (0.9)	12 (2.1)	5 (0.9)
Moderate	429 (25.8)	146 (26.7)	152 (26.8)	131 (23.9)
Severe	821 (49.4)	265 (48.4)	279 (49.2)	277 (50.6)
Very Severe	389 (23.4)	131 (23.9)	124 (21.9)	134 (24.5)
Prior year Exacerbation Rate†	0.7±1.0	0.7±1.1	0.7±1.0	0.7±1.1
Dust Exposure*	286 (17.1)	97 (17.5)	99 (17.5)	90 (16.4)
Biomass Exposure*	641 (38.4)	209 (37.7)	214 (37.8)	218 (39.8)
COPD Assessment Test Score	18.1±7.4	18.3±7.4	17.8±7.6	18.1±7.3
St. George Respiratory Questionnaire Total Score	45.8±20.1	46.5±19.9	44.8±20.7	46.2±19.5
Total WBC ($x10^9$/L) β	6.7±2.2	6.8±2.1	6.7±2.2	6.8±2.2
Eosinophils ($x10^9$/L)	0.3±0.6	0.3±0.7	0.3±0.7	0.3±0.5

‡ Plus-minus values denote mean ± SD; closed parentheses denote n (%)

Post bronchodilator (BD) – 15 minutes following 400 mcgs salbutamol

* Assessed at screening (≤2 weeks from Baseline);

^ Body Mass Index (BMI) calculated as mass (kg) divided by $height(m)^2$

† Defined as a worsening of respiratory symptoms necessitating the use of antibiotics, oral corticosteroids or both in the year prior to randomisation

β Blood tests were conducted at screening (≤2 weeks from Baseline)

TABLE 2A: Annualised Exacerbation Rate in each study arm at 48 Weeks in the ITT population

ANNUALISED COPD EXACERBATION RATE	Placebo (n=554)	Placebo & Theophylline (n=568)	Prednisone & Theophylline (n=548)	Rate Ratio (95% CI)*
TOTAL	1.00 (0.87-1.14)	0.86 (0.75-0.99)	0.89 (0.78-1.02)	0.96 (0.83-1.12)
MILD	0.32 (0.25-0.40)	0.35 (0.28-0.44)	0.27 (0.21-0.34)	0.81 (0.63-1.05)
MODERATE	0.33 (0.26-0.42)	0.25 (0.20-0.32)	0.32 (0.26-0.41)	1.12 (0.88-1.43)
SEVERE	0.29 (0.23-0.37)	0.20 (0.15-0.26)	0.23 (0.18-0.29)	0.95 (0.73-1.23)
MODERATE + SEVERE	0.67 (0.57-0.78)	0.50 (0.42-0.59)	0.62 (0.52-0.72)	1.07 (0.89-1.27)

* Primary outcome analysis was performed between the Oral Prednisone & Theophylline arm and the pool of the Placebo and Placebo & Theophylline arms of the trial

TABLE 2B: Annualised Exacerbation Rate in each study arm in the Per Protocol (PP) population at 48 Weeks

ANNUALISED COPD EXACERBATION RATE†	Placebo (n=416)	Placebo & Theophylline (n=437)	Prednisone & Theophylline (n=419)	Rate Ratio (95% CI)*
TOTAL	1.09 (0.93-1.27)	0.86 (0.73 -1.01)	0.92 (0.78-1.07)	0.95 (0.80-1.12)
MILD	0.35 (0.27-0.45)	0.34 (0.27-0.44)	0.29 (0.22-0.38)	0.84 (0.63-1.12)
MODERATE	0.36 (0.28-0.47)	0.27 (0.20-0.35)	0.34 (0.27-0.44)	1.11 (0.84-1.45)
SEVERE	0.31 (0.23-0.41)	0.19 (0.14-0.26)	0.22 (0.16-0.29)	0.89 (0.65-1.20)
MODERATE + SEVERE	0.72 (0.60-0.87)	0.50 (0.41-0.61)	0.62 (0.51-0.75)	1.03 (0.84-1.27)

* Primary outcome analysis was performed between the Oral Prednisone & Theophylline arm and the pooled Placebo and Placebo & Theophylline arms of the trial

TABLE 2C Time to first (Mild, Moderate or Severe) COPD exacerbation in ITT Population *					
	Placebo (n=554) Arm 1	Placebo & Theophylline (n=568) Arm 2	Prednisone & Theophylline (n=548) Arm 3	Hazard ratio (95% CI)	P value
Time to first COPD exacerbation (days) N, Median (Q1,Q3)	232, 137 (58.5; 233.5)	233, 150 (66.0; 242.0)	229, 151 (71.0;247.0)		
Had ≥ 1 COPD exacerbation	232/554 (41.9%)	233/568 (41.0%)	229/548 (41.8%)		0.95
HAZARD RATIO *					
Arm 3 vs (Arm 1+2)				0.92 (0.79 - 1.08)	0.32
Arm 3 vs Arm 1				0.90 (0.75 - 1.08)	0.25
Arm 3 vs Arm 2				0.95 (0.79 - 1.14)	0.56
Arm 2 vs Arm 1				0.95 (0.79 - 1.14)	0.57

*Adjusted for hospital region, history of smoking, sex, exacerbation in the year prior to randomisation and post-bronchodilator %FEV1 at screening

TABLE 3: Secondary outcomes in each of the three study arms in the ITT population at 48 weeks: Change compared to baseline

	Placebo (n=554)	Placebo & Theophylline (n=568)	Prednisone & Theophylline (n=548)	Least Squares Means (95% CI)*
Change in Post-BD Spirometry†				
FEV_1 (L)	-0.02±0.01	-0.01±0.01	-0.02±0.01	-0.002 (-0.034-0.029)
FEV_1/FVC	0.13±0.44	0.34±0.44	0.25±0.43	0.015 (-1.023-1.053)
COPD Assessment Test (CAT) Score Change	-2.29±0.33	-2.77±0.33	-2.57±0.33	-0.043 (-0.830-0.744)
St. George Respiratory Questionnaire (SGRQ) Score Change	-4.95±0.91	-6.85±0.91	-6.48±0.89	-0. 58 (-2.73-1.58)
Number of SAE Hospitalisations**	120,77 (13.9%)	101,71 (12.5%)	122,73 (13.3%)	

† Plus-minus values denote mean ± SD

* Analysis was performed between the Oral Prednisone & Theophylline arm and the pooled Placebo and Placebo & Theophylline arms of the trial

** For SAE hospitalisations, values presented as #events, #patients (% of patients in study arm)

Table 4: Adverse Events by treatment group in the ITT population

	Placebo (N=554)	Placebo and Theophylline (N=568)	Oral Prednisone & Theophylline (N=548)	Total N=1670
Total number of AE's	553, 267 (48.2%)	529, 281 (49.5%)	532, 264 (48.2%)	1614, 812 (48.6%)
AECOPD	441, 233 (42.1%)	392, 235 (41.4%)	421, 231 (42.2%)	1254, 699 (41.9%)
URTI	37, 28 (5.1%)	54, 41 (7.2%)	34, 29 (5.3%)	125, 98 (5.9%)
Weight Gain	1, 1 (0.2%)	1, 1 (0.2%)	3, 3 (0.5%)	5, 5 (0.3%)
Pneumonia	3, 3 (0.5%)	0, 0 (0.0%)	3, 2 (0.4%)	6, 5 (0.3%)
Fractures	6, 6 (1.1%)	2, 2 (0.4%)	5, 5 (0.9%)	13, 13 (0.8%)
Non-Infectious GI Upset	13, 12 (2.2%)	21, 18 (3.2%)	13, 11 (2.0%)	47, 41 (2.5%)

All values presented as #events, #patients (% of patients affected in each study arm)

FIGURES and LEGENDS

Figure 1

CONSORT diagram

Study participant flow from Screening, run-in, randomization, all visits and study completion.

Figure 2

Time to First COPD event*

* COPD events were COPD exacerbations defined as a symptomatic deterioration in COPD symptoms (cough, sputum production or dyspnea) requiring treatment with antibiotics, initiation of a course of systemic corticosteroids, hospitalisation or a combination of these

Figure 3

3A Time to First Mild[#] COPD event

a COPD exacerbation requiring symptomatic treatment with inhaled bronchodilators and/or inhaled corticosteroids only

3B Time to First Moderate* COPD event

*a COPD exacerbation managed with antibiotics and/or oral corticosteroids

3C Time to First Severe**^** COPD event

^ a COPD exacerbation which also resulted in emergency department presentation or hospitalization

FIG 4 Forest Plot of Subgroup Analyses

Supplementary Files Figures

Figure S1

Study withdrawal rate

FIGURE 1

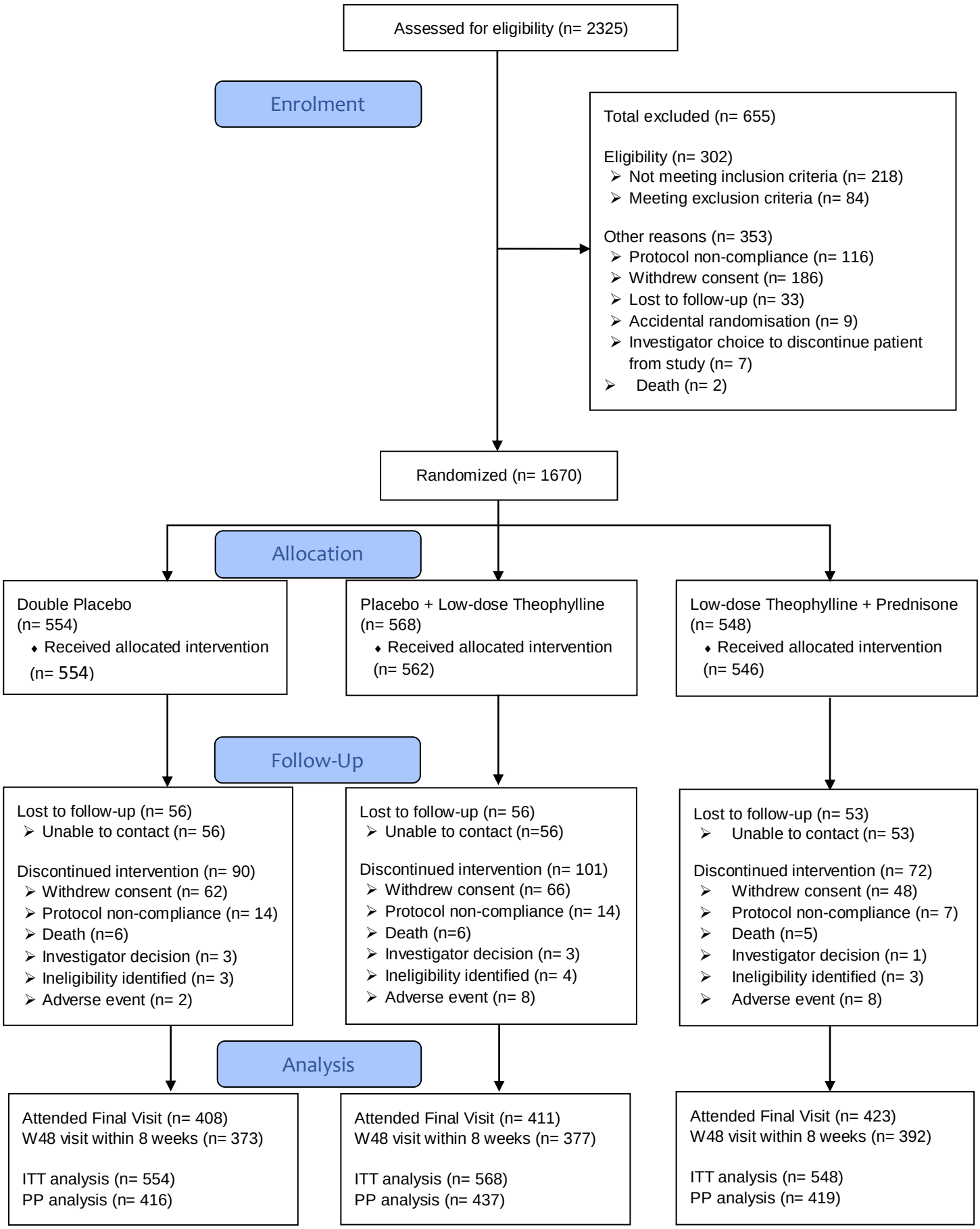
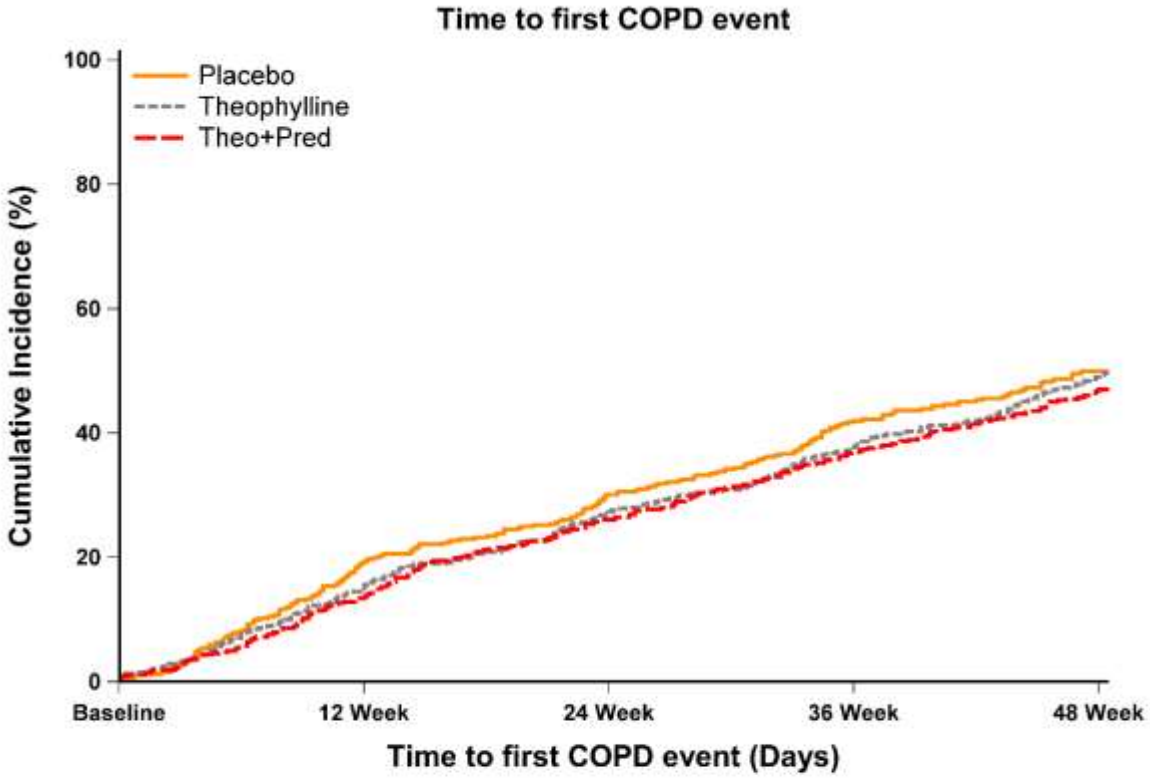
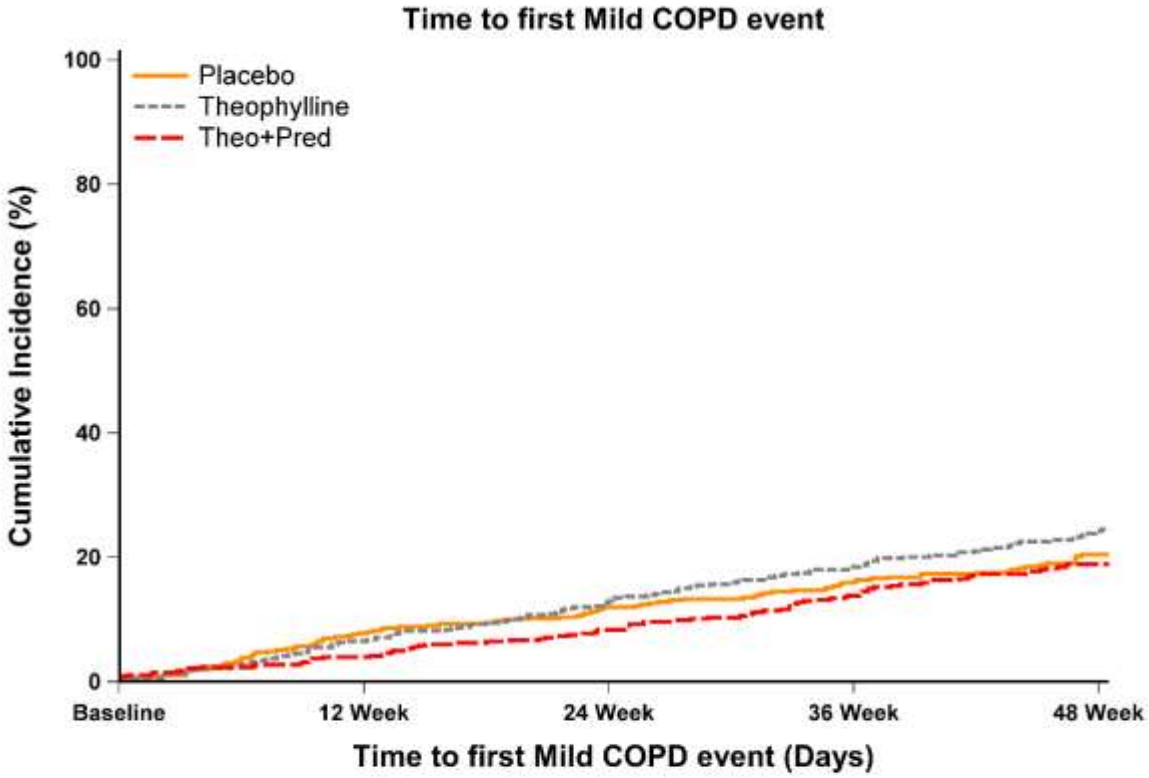

Assessed for eligibility (n= 2325)
Enrolment
Total excluded (n= 655)
Eligibility (n= 302)
Not meeting inclusion criteria (n= 218)
Meeting exclusion criteria (n= 84)
Other reasons (n= 353)
Protocol non-compliance (n= 116)
Withdrew consent (n= 186)
Lost to follow-up (n= 33)
Accidental randomisation (n= 9)
Investigator choice to discontinue patient from study (n= 7)
Death (n= 2)
Randomized (n= 1670)
Allocation
Double Placebo (n= 554)
Received allocated intervention (n= 554)
Placebo + Low-dose Theophylline (n= 568)
Received allocated intervention (n= 562)
Low-dose Theophylline + Prednisone (n= 548)
Received allocated intervention (n= 546)
Follow-Up
Lost to follow-up (n= 56)
Unable to contact (n= 56)
Discontinued intervention (n= 90)
Withdrew consent (n= 62)
Protocol non-compliance (n= 14)
Death (n=6)
Investigator decision (n= 3)
Ineligibility identified (n= 3)
Adverse event (n= 2)
Lost to follow-up (n= 56)
Unable to contact (n=56)
Discontinued intervention (n= 101)
Withdrew consent (n= 66)
Protocol non-compliance (n= 14)
Death (n=6)
Investigator decision (n= 3)
Ineligibility identified (n= 4)
Adverse event (n= 8)
Lost to follow-up (n= 53)
Unable to contact (n= 53)
Discontinued intervention (n= 72)
Withdrew consent (n= 48)
Protocol non-compliance (n= 7)
Death (n=5)
Investigator decision (n= 1)
Ineligibility identified (n= 3)
Adverse event (n= 8)
Analysis
Attended Final Visit (n= 408)
W48 visit within 8 weeks (n= 373)
ITT analysis (n= 554)
PP analysis (n= 416)
Attended Final Visit (n= 411)
W48 visit within 8 weeks (n= 377)
ITT analysis (n= 568)
PP analysis (n= 437)
Attended Final Visit (n= 423)
W48 visit within 8 weeks (n= 392)
ITT analysis (n= 548)
PP analysis (n= 419)

FIGURE 2



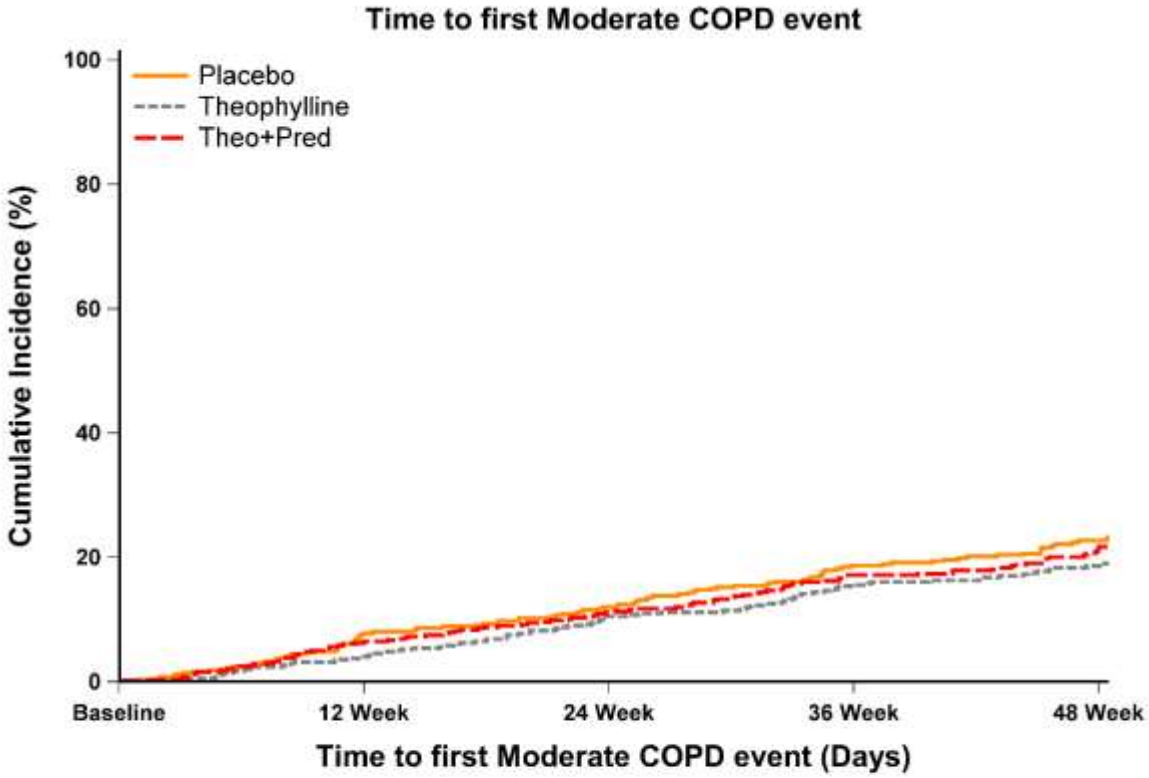
No. at risk :					
Placebo :	554	390	315	251	176
Theophylline :	568	425	343	272	172
Theo+Pred :	548	428	346	288	187

FIGURE 3(A)



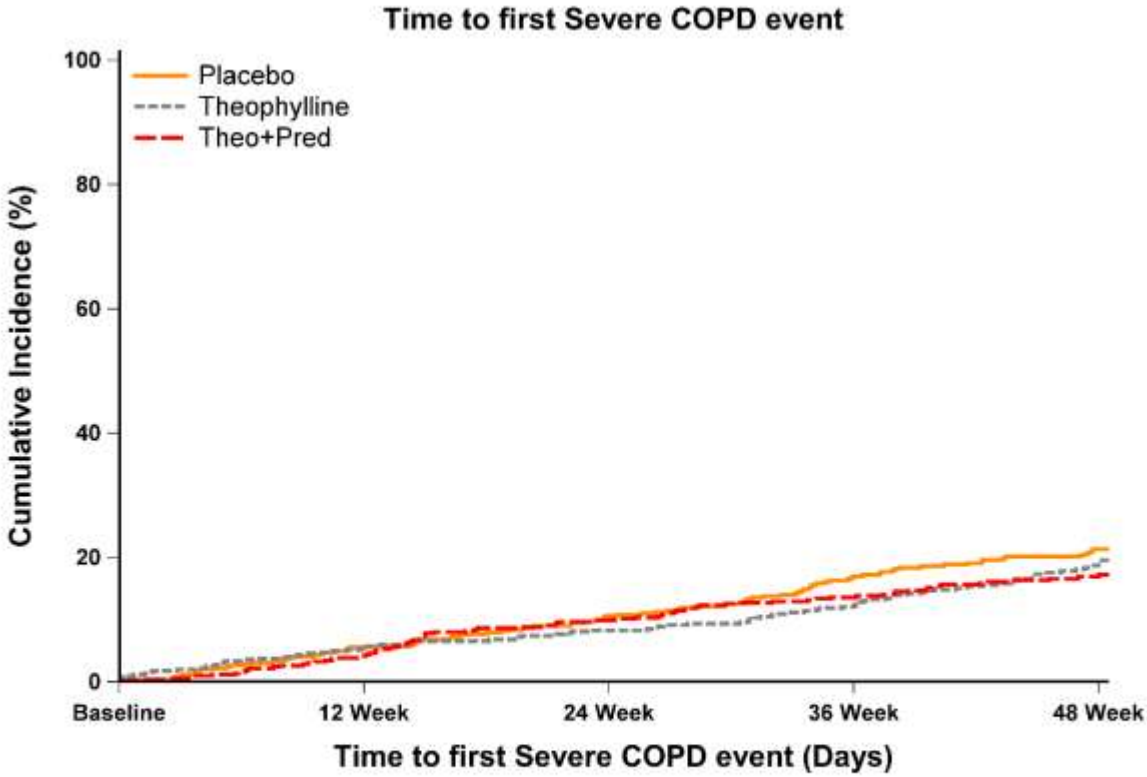
No. at risk :					
Placebo :	554	442	395	359	280
Theophylline :	568	462	408	353	256
Theo+Pred :	548	471	428	390	282

FIGURE 3(B)



No. at risk :					
Placebo :	554	444	394	348	261
Theophylline :	568	476	416	361	271
Theo+Pred :	548	459	411	371	262

FIGURE 3(C)

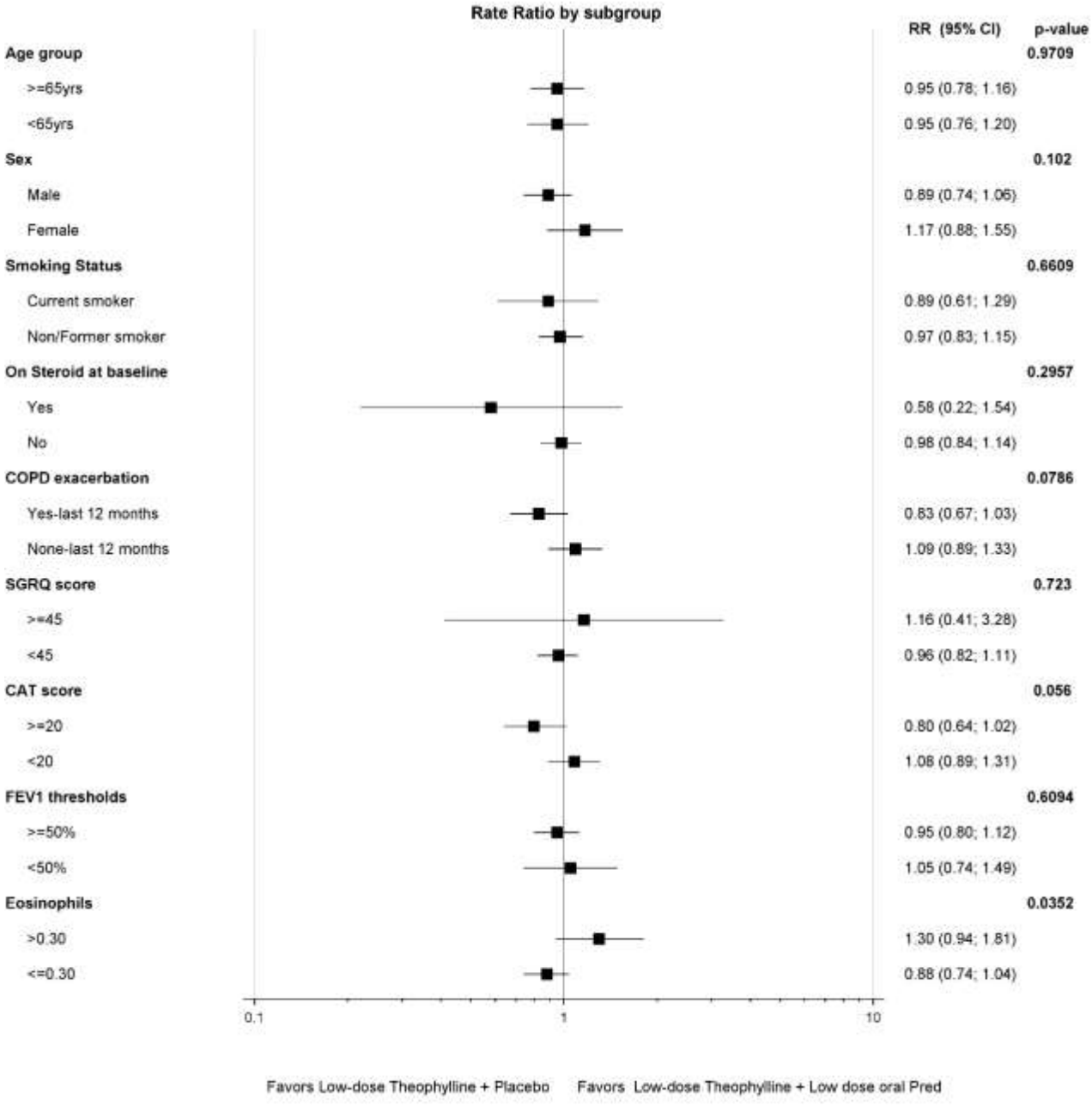


No. at risk :					
Placebo :	554	455	402	360	267
Theophylline :	568	470	430	383	276
Theo+Pred :	548	474	420	393	291

FIGURE 4

Forest Plot showing Rate ratios by Subgroup with 95% CI

Model has been adjusted for Hospital Region, History of Smoking, Sex, Exacerbation in the year prior to randomisation and post-bronchodilator percent FEV1 at screening



Supplementary Files

The Effect of Low Dose Corticosteroids and Theophylline on the Risk of Acute Exacerbations of COPD. The TASCS Randomised Controlled Trial

Christine R. Jenkins[1], Fu-Qiang Wen[2], Allison Martin[1], Peter J. Barnes[3], Bartolome Celli[4], Nan-Shan Zhong[5], Jin-Ping Zheng[5], Anish Scaria[1], Gian-Luca Di Tanna[1], Thomas Bradbury[1], Norbert Berend[1], on behalf of the TASCS study investigators.

1. The George Institute for Global Health, Sydney and UNSW Sydney, Australia

2. West China Hospital, Sichuan University, Chengdu, China

3. National Heart & Lung Institute, Imperial College, London UK

4. Brigham and Women's Hospital, Boston MA, USA

5. State Key Laboratory of Respiratory Disease, National Clinical Research Centre for Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China.

Contents

Supplementary Note 1

Additional statistical comments

We initially planned to recruit 2400 patients, in order to have 90% power to detect a 20% risk reduction for exacerbations in the theophylline plus prednisone arm versus placebo, but our recruitment rate in the first 12 months suggested we could not meet this target with our allocated funding. We therefore reduced the power to 80%, noting this was the case for several published randomised controlled trials with COPD exacerbations as a primary outcome.

Based on a negative binomial distribution of COPD exacerbations with a dispersion parameter of 0.8, we estimated that 1650 patients would be required to detect a 20% relative risk reduction (80% power, 2-tailed alpha) for comparison of low dose theophylline (LDT) and low dose prednisone versus placebo for the primary outcome, the number of COPD exacerbations per patient over 48 weeks, annualised to 12 months in a 3-arm trial. In the primary outcome analysis, we pooled the placebo/placebo and LDT/placebo groups vs LDT and low dose prednisone, as detailed in the pre-specified statistical analysis plan.

The rationale for this was because the goal of the study was to see if LDT, for which there is an in vitro rationale for enhancing the benefit of corticosteroids, is effective in doing so in vivo. The pooling of Placebo + LDT data can be justified on the basis that there were data to show that LTD by itself is ineffective in reducing AECOPD vs Placebo, which we also found in TASCS. This change was made at the time of the reduced target recruitment and restriction to a China-only study. It was prespecified in the Statistical Analysis Plan (SAP). In it we wrote “To overcome the potential issue of multiple testing among three treatment groups, the primary comparison is pre-specified as the treatment group of low-dose theophylline and low dose oral prednisone versus combination of other two groups (low-dose theophylline along and placebo group)”. In the SAP we had also specified a hierarchical process where, if the primary comparison was found as statistically significant, the comparison between the two treatment groups versus placebo group separately would have been conducted.

For completeness and exploratory purposes, we have calculated the following Rate Ratios:
Low-dose Theophylline + placebo vs placebo: 0.866, 95% CI 0.728; 1.029, p=0.101 and
Low-dose Theophylline + Low dose oral Prednisone vs placebo : 0.895, 95% CI 0.755; 1.061, p=0.201

Supplementary Note 2

Participants randomised with no follow up visit

If participants provided any follow-up time, they were included in the Intention to Treat (ITT) analysis. A sensitivity analysis was performed where those participants who had zero follow-up were not included in the analysis to ensure that the results did not differ from the PP analysis. No (multiple) imputation procedure has been employed.

Supplementary Note 3

Study Oversight

An international steering committee of investigators was responsible for broad oversight of the TASCS trial and met face to face twice yearly during the study. The study team, based at The George Institute for Global Health (TGI) met weekly or more often with the study team in Beijing throughout the study. A Data Safety Monitoring Committee (DSMC), independent of the trial investigators and sites, performed an ongoing review of the predefined safety parameters and overall study conduct. The DSMC was comprised of experts in clinical trials, bio-statistics and respiratory medicine and reviewed unblinded data on participant characteristics and AEs at 12 monthly intervals during the study. The DSMC reported back formally to the study investigators with a recommendation to continue or discontinue the study, or requesting further information. Principal outcomes monitored by the DSMC included deaths, hospitalizations, exacerbations and SAEs of interest.

Supplementary Note 4

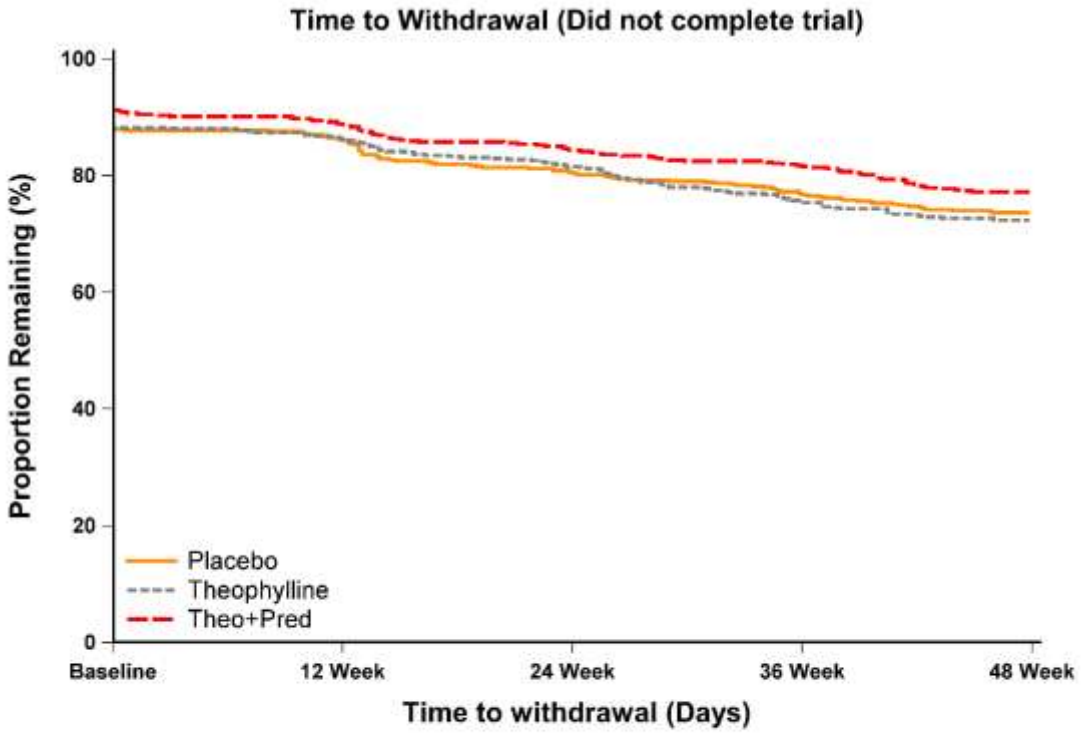
The Theophylline and Steroids in COPD Study (TASCS) Centres and Investigators

Site No.	Site Name	Site Principal Investigator
001	West China Hospital of Sichuan University	WEN Fuqiang
002	The First Affiliated Hospital of Guangzhou Medical College	ZHONG Nanshan
004	Beijing Chao-yang Hospital, Capital Medical University	Lin Yingxiang
010	Daping Hospital, 3rd Military Medical University Cui	Shehuai
012	The Military General Hospital of Chengdu PLA	Xiao Zhenliang
014	First Hospital of Jilin University	Li Dan
019	People's Hospital of Henan Province	MA Lijun
025	The First Affiliated Hospital of Guangxi Medical University	ZhongXiaoning
026	Jiangsu Provincial Hospital of State Organ	Liu Jiannan
029	The First Affiliated Hospital of Nanchang University	Zhang Wei
033	The Fouth Hospital of China Medical University	Wang Xiaoge
035	The First Affiliated Hospital of Baotou Medical College	HE Huijie
036	Hejian Municipal People's Hospital	DU Baoliang
038	Yutian County Hospital, Hebei Province	WANG Jinchao
039	The First People’s Hospital of Zunyi	LIU Daishun
040	Leshan People's Hospital	Wei Maogang
041	Neijiang First People's Hospital	Zhang Yong
042	Chengdu Second People's Hospital	Yan Hao
044	Bazhong Central Hospital	Zhang Shiguo
045	Affiliated Hospital of North Sichuan Medical College	Chen Shaoping
046	Third People’s Hospital of Mianyang	Wang Kailv
047	Chengdu Fifth People's Hospital	Wang Jun
048	The Nuclear Industry 416 Hospital	Xiong Shuguang
049	The first people's hospital of liangshan state	LI LI
051	Sichuan Mianyang 404 Hospital	Wang Limin
052	Suining Central Hospital	He Zhengguang
053	Dazhou Central Hospital	Wang Hongjun

Site No.	Site Name	Site Principal Investigator
057	Chinese and Western medicine Hospital of Panzhihua	Hu Qiang
058	Yuxian People's Hospital	Guo Dongshuang
059	Pengzhou People's Hospital	Weng Bangqiong
060	Traditional Chinese Medicine Hospital Affiliated to Luzhou Medical College	Ao Suhua
061	People’s hospital Changji Hui Autonomous Prefecture, Xinjia	Guo Yang
063	Chengdu Qingbaijiang People's Hospital	Liu Zehui
064	Wendeng Municipal hospital	Zhao Jinguo
065	Dong'e people's hospital, Shan Dong Province	Cui Jiadong
066	Henan Dancheng County People's Hospital	Yang Yuwang
067	Jiangyou People’s Hospital	Wang Jun

Supplementary FIGURE S1

Time to Withdrawal



No. at risk :					
Placebo :	554	479	448	428	373
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