Supplementary Files

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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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

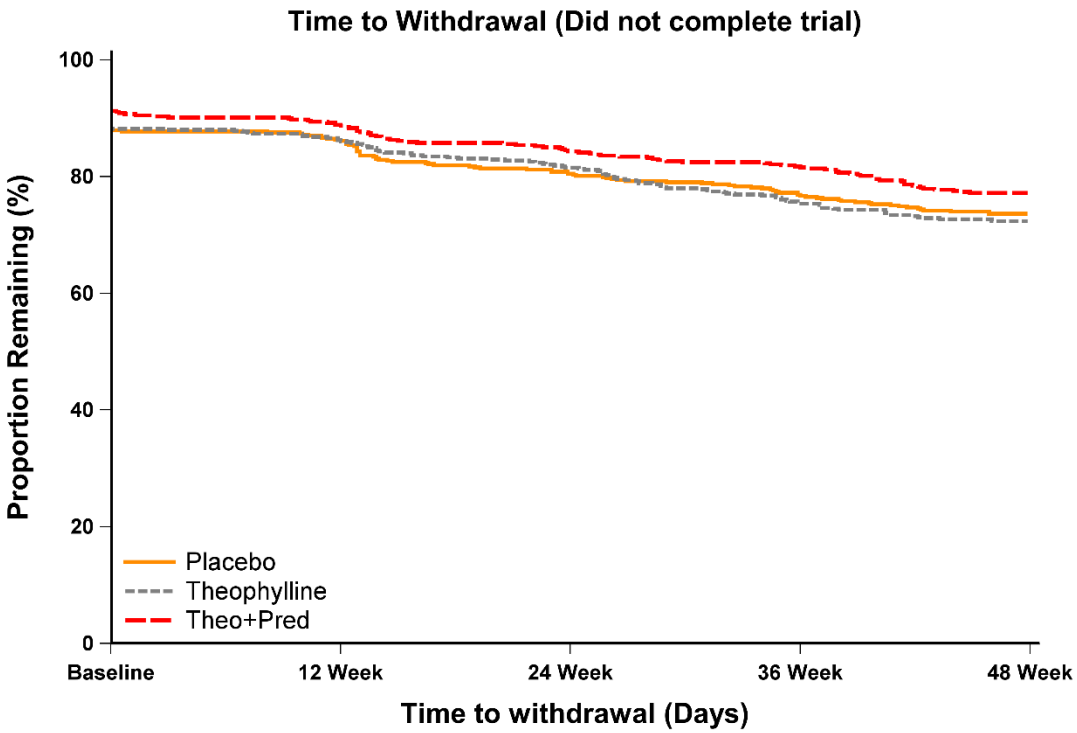
The Theophylline and Steroids in COPD Study (TASCS) Centres and Investigators

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
Theophylline :	568	492	464	430	377
Theo+Pred :	548	489	463	449	392