TOBACCO HEATING SYSTEM 2.2 IN MILD TO MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE SUBJECTS: AN EXPLORATORY ANALYSIS

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Introduction and Objectives

The Tobacco Heating System (THS) is a product that electronically heats tobacco at temperatures significantly lower (<350°C) than that required for combustion of cigarettes (CC), producing substantially (on average 95%) lower levels of harmful and potentially harmful constituents, while providing nicotine sensorial experience that approaches that of CC.

Introduction and Objectives

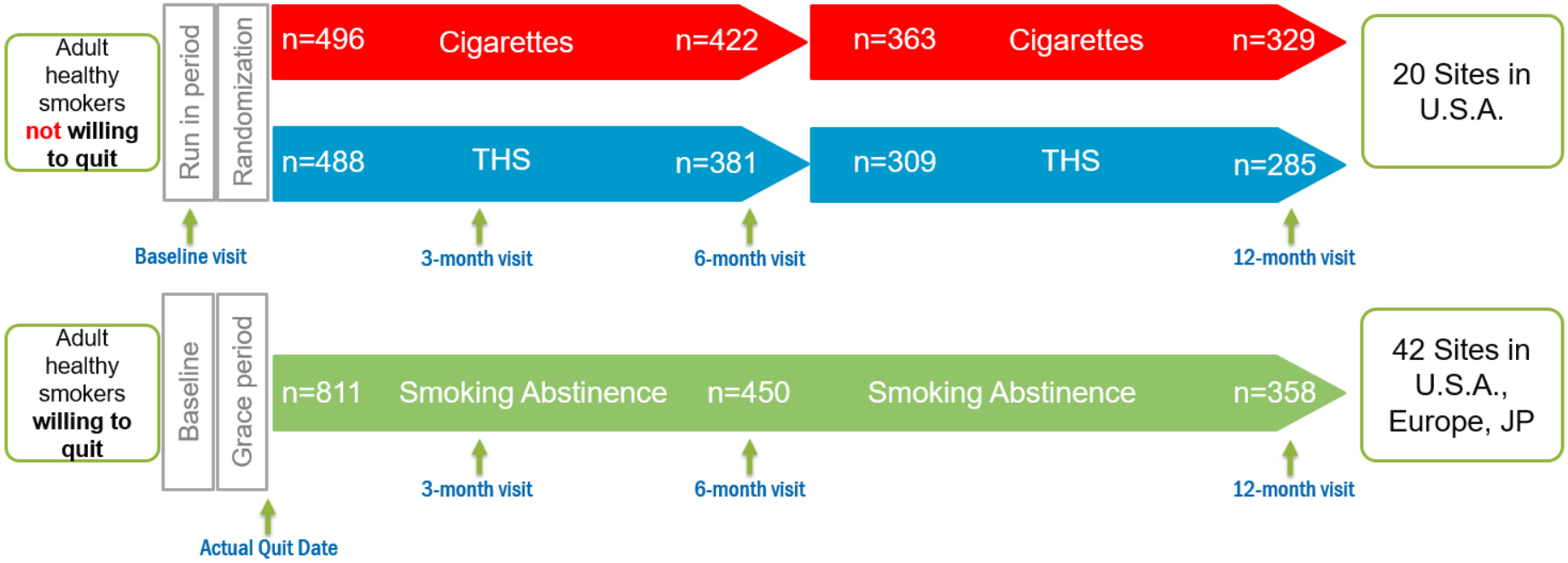
A randomized, two-arm parallel group, multicenter "Exposure Response Study"[1] (ERS) conducted in the USA (NCT02396381) demonstrated statistically significant favorable changes in five of eight biomarkers of effect (BoEff) at 6 months among adult smokers (not willing to quit smoking) switching to THS 2.2 relative to those who continued smoking, with all BoEffs moving in the direction of smoking cessation (SC). The study was extended for additional 6 months (NCT02649556) for the selected BoEffs.

In parallel, a 12-month Smoking Cessation Response Study (SCR) was conducted in smokers willing to quit smoking in the USA, Europe, and Japan (NCT02432729). All studies were conducted in accordance with the ICH GCP guidelines

[1]Ludicke F, et al. Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. Cancer Epidemiol Biomarkers Prev 2019;28:1934–43

Introduction and Objectives

This analysis explored the health effects of switching to THS 2.2 compared with continued smoking in a subgroup of smokers with mild to moderate chronic obstructive pulmonary disease (COPD) enrolled in the ERS study relative to those enrolled in the SCR.



6-Month + 6-Month Exposure Response and Smoking Cessation Response Studies.

Methods

The analysis included mild to moderate COPD subjects (GOLD 1 & 2[2]) from the ERS, which was broadened to include airway obstruction defined by FEV_1/FVC <0.75 (previous ATS guidelines[3]), described as characteristic of COPD subjects, as per the Lung Health Study[4]. The results from a subset of subjects with mild COPD from the SCR, using the same definition for airway obstruction as in the ERS, were used as the reference.

[2]Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018
[3]Gardner R, et al. Standardization of spirometry—1987 update: official statement of the American Thoracic Society. Am. Rev. Respir. Dis. 136:1285–1298. 1987
[4]Scanlon P, et al. Smoking Cessation and Lung Function in Mild-to-Moderate Chronic Obstructive Pulmonary Disease -The Lung Health Study. Am J Respir Crit Care Med; 161, No. 2; 2000

Methods

Original Study Population

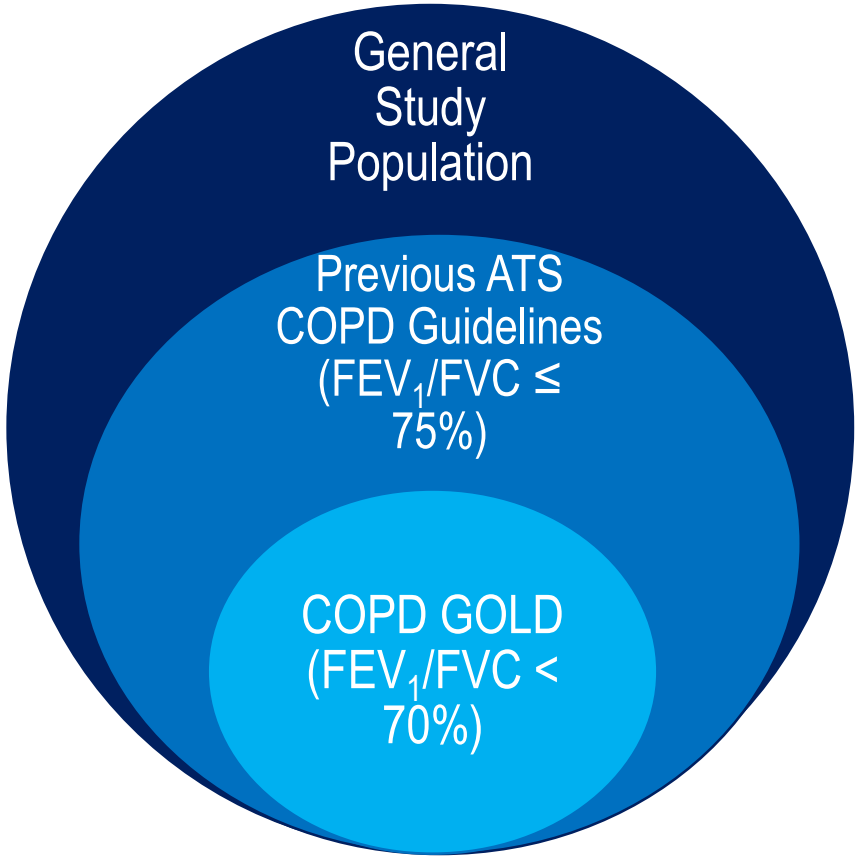
- All subjects in the main analysis set of the 12-month exposure study and SCR subjects for 12 months

COPD (previous ATS)

- Subjects with $FEV_1/FVC < 0.75$[3]

COPD GOLD

- Subjects with $FEV_1/FVC \leq 0.70$[2]



[2]Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018
[3]Gardner R, et al. Standardization of spirometry—1987 update: official statement of the American Thoracic Society. Am. Rev. Respir. Dis. 136:1285–1298. 1987
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Methods

Data from the subset of COPD subjects randomized to the THS 2.2 or CC arm from the ERS and subjects from the SCR were analyzed at 6 and 12 months. The selected respiratory and cardiovascular BoEffs in this subgroup analysis were: forced expiratory volume in 1 second (FEV_1), white blood cell (WBC) count, soluble intercellular adhesion molecule-1 (sICAM-1) level, and 8-epi-prostaglandin F2α (8-epi-PGF2α) level.

Results — Baseline Characteristics

Variable	THS Use		CC Use		SC	
	General Population (n = 230)	Obstruction Subset (n = 52)	General Population (n = 424)	Obstruction Subset (n = 97)	General Population (n = 358)	Obstruction Subset (n = 53)
Male: n (%)	143 (62.2)	35 (67.3)	244 (57.5)	63 (64.9)	181 (50.6)	28 (52.8)
Female: n (%)	87 (37.8)	17 (32.7)	180 (42.5)	34 (35.1)	177 (49.4)	25 (47.2)
Age (years): Mean (SD)	43.8 (9.68)	48.5 (10.3)	45.2 (9.54)	52.0 (10.1)	43.8 (9.21)	49.8 (8.91)
Caucasian: n (%)	168 (73.0)	38 (73.1)	312 (73.6)	78 (80.4)	203 (56.7)	39 (73.6)
Not Caucasian: n (%)	62 (27.0)	14 (26.9)	112 (26.4)	19 (19.6)	155 (43.3)	14 (26.4)
BMI (kg/m^2): Mean (SD)	27.0 (4.06)	26.2 (4.08)	27.1 (4.13)	25.9 (3.65)	24.8 (3.75)	25.2 (3.14)
Smoking duration (years): Mean (SD)	25.6 (9.48)	30.8 (9.62)	26.7 (10.1)	33.0 (11.3)	22.8 (8.76)	28.4 (8.57)
Smoking intensity over the past year (cig/day): Mean (SD)	18.4 (6.88)	18.7 (5.69)	19.5 (7.87)	18.6 (6.87)	16.6 (5.27)	16.8 (5.92)
COPD (Previous ATS)*: n (%)	35 (15.2)	35 (67.3)	69 (16.3)	69 (71.1)	35 (66.0)	35 (66.0)
GOLD 1: Mild n (%)	14 (6.1)	14 (26.9)	24 (5.7	24 (24.7)	18 (34.0)	18 (34.0)
GOLD 2: Moderate n (%)	3 (1.3)	3 (5.8)	4 (0.9)	4 (4.1)	0	0

Note: THS use refers to THS 2.2 use of 70% or more; CC use refers to THS 2.2 use of less than 1%; SC refers to continuous smoking abstinence from the actual quit date to month 12 in the SCR.

ATS = American Thoracic Society

*COPD subjects with $0.70 < FEV_1/FVC < 0.75$, according to the previous ATS guidelines for obstruction.

GOLD 2018 COPD Guidelines[1]

Results — Pre-Bronchodilator Spirometry

THS Use – CC Use Difference	LS Mean	95% CI
Pre-BD FEV_1 (%pred)		
Month 6		
General Study Population	0.99	-0.02, 2.00
COPD (Previous ATS)*	1.47	-0.52, 3.46
COPD (GOLD 2018) subjects	0.71	-2.97, 4.39
Month 12		
General Study Population	1.16	-0.06, 2.39
COPD (Previous ATS)*	1.92	-0.49, 4.32
COPD (GOLD 2018) subjects	3.48	-1.12, 8.07
Pre-BD Best FEV_1 (mL)		
Month 6		
General Study Population	30.1	-6.99, 67.1
COPD (Previous ATS)*	46.4	-27.5, 120
COPD (GOLD 2018) subjects	11.1	-125, 147
Month 12		
General Study Population	40.7	-2.15, 83.5
COPD (Previous ATS)*	60.2	-27.9, 148
COPD (GOLD 2018) subjects	71.8	-101, 244

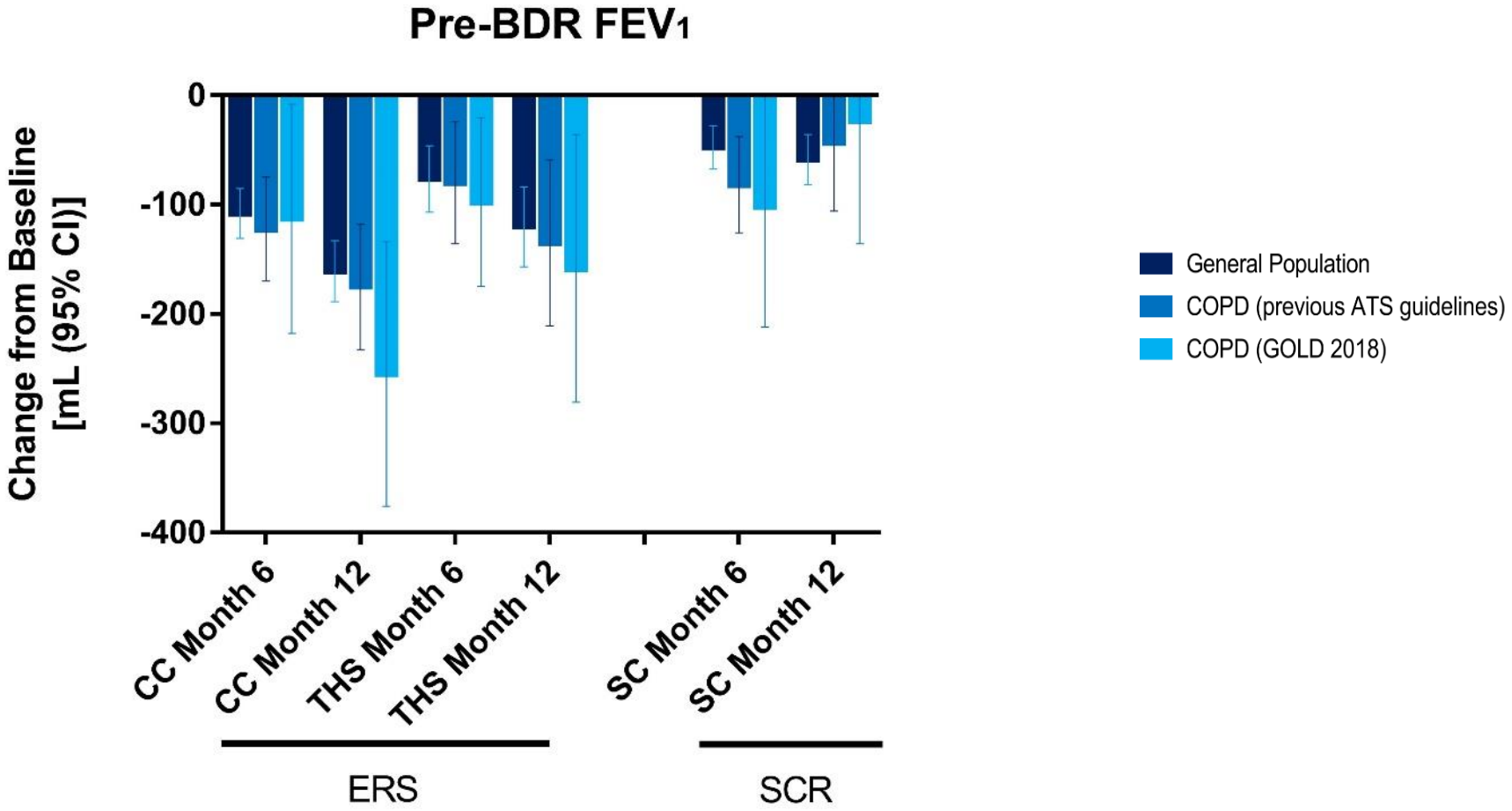
Note: Adjusted least squares (LS) means and confidence intervals (CIs) from a mixed model analysis conducted on original values with visit, baseline value and its interaction with visit, sex, Caucasian race, product-use pattern category and its interaction with visit, and baseline smoking intensity as fixed-effect factors and site as a random-effect factor. BD = bronchodilator, short-acting beta agonist

Spirometry endpoints were adjusted for diet; no age adjustment of FEV_1 parameters as %pred.

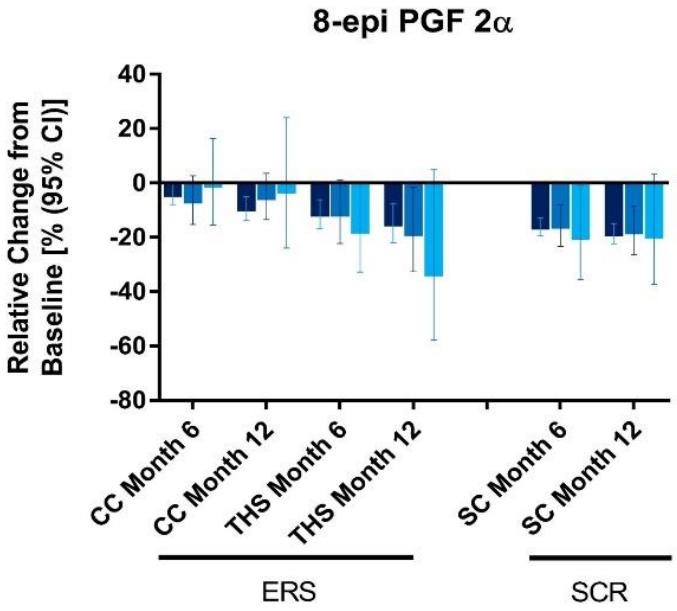
General Population encompasses the study population of the exposure-response studies.

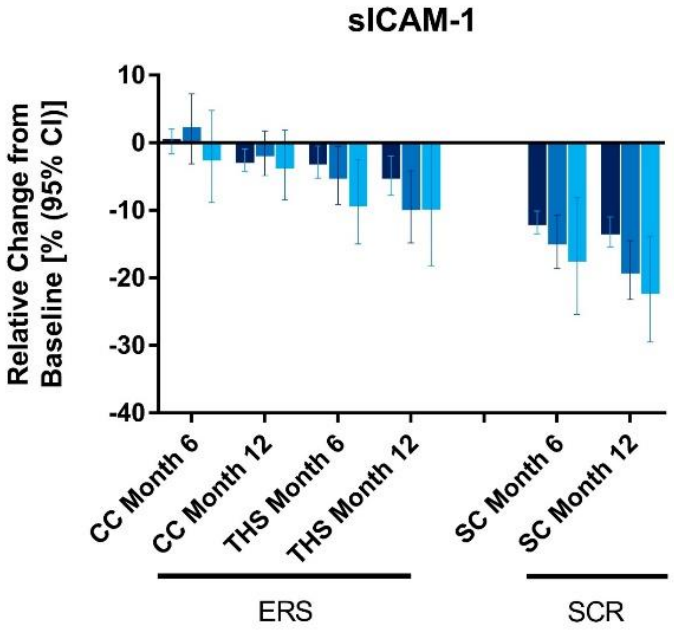
*Previous ATS Guidelines for obstruction with $FEV_1/FVC < 0.75$.

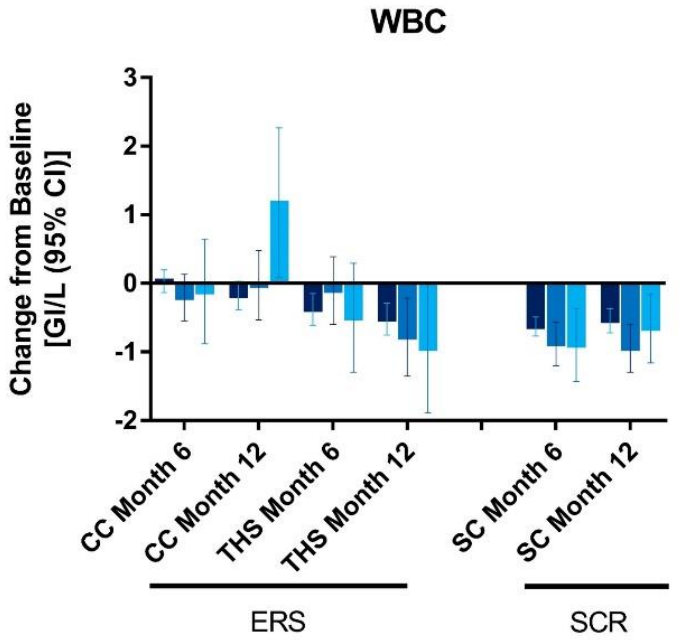
Results — Respiratory Biomarkers of Effect in the COPD Subset



Results — Respiratory and Cardiovascular Biomarkers of Effect in the COPD Subset







General Population
COPD (previous ATS guidelines)
COPD (GOLD 2018)

Conclusions

- The results indicated a favorable THS–CC difference of 72 mL in FEV_1 among COPD subjects after 12 months.
- They also indicated a reduction of 1.95 GI/L in WBC count, 6.8% in sICAM-1 level, and 28% in 8-epi-PGF2α level for THS relative to CC.
- After 12 months of follow-up, most of the BoEffs in subjects with COPD who used the THS showed favorable shifts in the direction of the changes observed with SC.
- The magnitude of these shifts was more pronounced than those observed in the ERS, which included a majority of healthy subjects.
- The results of this preliminary analysis are consistent with the findings of the main ERS and suggest a reduced harm potential for THS relative to smoking in subjects with mild to moderate COPD.