Changes in Clinical Risk Endpoints Linked to Cardiovascular and Other Smoking-Related Diseases after Switching from Cigarettes to the Tobacco Heating System (THS) 2.2 for Six Months

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Introduction and Objectives

Background

Tobacco harm reduction, by substituting less harmful tobacco products for cigarettes, is a complementary approach to smoking prevention and cessation and solely intended for smokers who would otherwise continue to smoke. The Tobacco Heating System (THS) 2.2 is a novel tobacco product with the potential to present less risk of harm compared with continued smoking. It heats a tobacco plug in a controlled manner, never allowing the temperature to exceed 350°C, preventing combustion and thereby producing substantially lower levels of toxicants while providing nicotine, taste, ritual, and sensory experiences that closely parallel those of cigarettes (CC).

Main Objectives

- Demonstrate statistically significant changes in five out of eight clinical risk endpoints (CRE) for smokers switching from CC to THS compared with continued smoking for six months.
- All eight CREs must move directionally toward the changes reported upon smoking cessation in the literature.

Several completed clinical studies have demonstrated reduced exposure to selected toxicants for smokers who switched to THS for up to three months (e.g., NCT01989156, NCT01970995) compared with continued smoking of cigarettes. This study was designed to further substantiate the harm reduction potential of THS 2.2 by demonstrating that changes in CREs are comparable in magnitude and direction to those observed when smokers stop smoking. The CREs are linked to smoking-related diseases, representative of multiple pathophysiological pathways that are sensitive to smoking, and reversible upon smoking cessation.

Disease Pathways	Clinical Risk Endpoints
Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	s-ICAM-1
CO acute effect	COHb
Inflammation	WBC
Oxidative stress	8-epi-$PGF_{2\alpha}$
Airway impairment	FEV_1
DNA adducts formation	Total NNAL

Study Conduct

The study was approved by an Institutional Review Board and initiated in March 2015. The study was conducted according to the principles of International Conference on Harmonisation Good Clinical Practice and registered on ClinicalTrials.gov (NCT02396381).

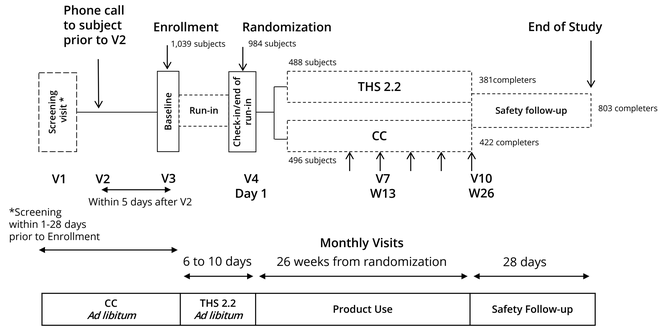
Clinical risk endpoint abbreviations:

High-density lipoprotein cholesterol (HDL-C); 11-dehydrothromboxane B2 (11-DTX-B2); soluble intercellular adhesion molecule-1 (sICAM-1); carboxyhemoglobin (COHb); white blood cell count (WBC); 8-epi-Prostaglandin F2α (8-epi-$PGF_{2\alpha}$); forced expiratory volume in 1 second (FEV_1); total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol (Total NNAL).

Methods

Study Design

This was a randomized, controlled, two-arm parallel group, multicenter U.S. study in adult smokers who switched from CCs to THS compared with those who continued to smoke CCs over six months. The primary objective was to demonstrate significant changes in THS users (≥ 70%) for at least five out of the eight CREs. 984 subjects were randomized to CC (n = 496) or THS (n = 488). Additional biomarkers of exposure and CREs of inflammation, lipid metabolism, endothelial function, platelet function, oxidative stress, and lung function were evaluated in the study.



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V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Safety follow-up
Screening		Enrollment /Baseline	Day 1	Week 4	Week 9	Week 13	Week 17	Week 22	Week 26	28 days

Statistical Analysis

Success Criteria:

To establish that the risk profile of IQOS is modified compared to cigarettes

1. <u>All</u> co-primary endpoints shift in the direction of cessation
2. ≥ 5 out of 8 clinical risk endpoints are statistically significant (Hailperin-Rüger Approach)
3. Majority of the smoking cessation effect is preserved

Primary Analysis: Predominant users of IQOS > 70%

Establish Modification of Risk

Smokers' Health Profile
Study-wise α=0.05
Test-wise α=0.031

If Modification of Risk is Established

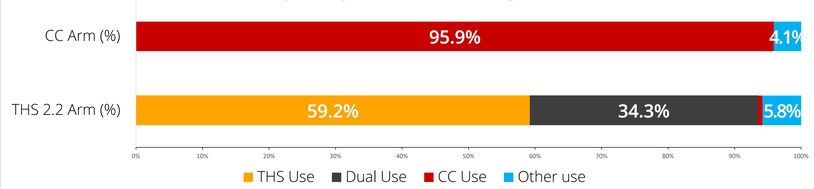
≥ 5/8 significant clinical risk endpoints*

Results of the study can be verified with the effects measured for smoking cessation

*Using a 1-sided test with the Hailperin-Rüger adjusted α level for multiple testing (1.5625%)

Results

Distribution of Randomized Subjects by Product Use Categories



Changes in Clinical Risk Endpoints

Endpoint	Change from CC Use	Observed Change LS Mean Difference/Relative Reduction	Hailperin-Rüger Adjusted 96.875% CI	1-Sided *p*-value (0.0156)	THS 2.2 Directional Change vs. SA (literature)
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	< 0.001*	✓ significant
WBC Count	Difference	−0.420 Gl/L	−0.717, −0.123	0.001*	✓ significant
sICAM-1	% Reduction	2.86%	−0.426, 6.04	0.030	✓
11-DTX-B2	% Reduction	4.74%	−7.50, 15.6	0.193	✓
8-epi-$PGF_{2\alpha}$	% Reduction	6.80%	−0.216, 13.3	0.018	✓
COHb	% Reduction	32.2%	24.5, 39.0	< 0.001*	✓ significant
FEV_1 %pred	Difference	1.28 %pred	0.145, 2.42	0.008*	✓ significant
Total NNAL	% Reduction	43.5 %	33.7, 51.9	< 0.001*	✓ significant

Conclusions

The Exposure Response Study was designed to answer important regulatory questions on the effects of THS as it is actually used by adult smokers.

We evaluated biological and functional changes in healthy, adult smokers who switched to THS compared with continued CC smoking. The study demonstrated that all CREs moved in the same direction as the smoking cessation effect observed in the literature. Five out of eight endpoints showed significant favorable changes after switching to THS vs. continued smoking, notwithstanding up to 30% of cigarette smoking in the primary analysis population.

The results obtained through this study further substantiate the harm reduction potential of THS while providing information on product use and acceptance of THS by smokers.

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