Evaluation of Biological and Functional Changes in Healthy Smokers after Switching from Cigarettes to Tobacco Heating System (THS) 2.2 for 6 Months

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Introduction and Objectives

The most effective way for cigarette smokers to reduce their risk of smoking-related diseases, resulting from long-term exposure to harmful and potentially harmful constituents (HPHCs) in cigarette smoke, is to quit smoking.

Tobacco harm reduction, replacing cigarettes with less harmful tobacco products, is a complementary approach for smokers who would otherwise continue smoking. THS is a novel tobacco product that electrically heats tobacco at temperatures lower than cigarettes,producing substantially lower HPHC levels, while providing a taste, sensory experience, nicotine delivery that parallels smoking. Previous clinical studies demonstrated reduced exposure to HPHCs (approaching levels of smoking abstinence) for smokers who switched to THS for up to 3 months (NCT01989156; NCT01970995).

This study was designed to further substantiate the harm reduction potential in smokers switching to THS, confirming similar changes in biological and physiological health effects (clinical risk endpoints [CREs]) to those observed in smokers who stop smoking.

The study, registered on ClinicalTrials.gov (NCT02396381), was approved by an Institutional Review Board for each of the participating sites and respected the ICH-GCP principles.

Methods

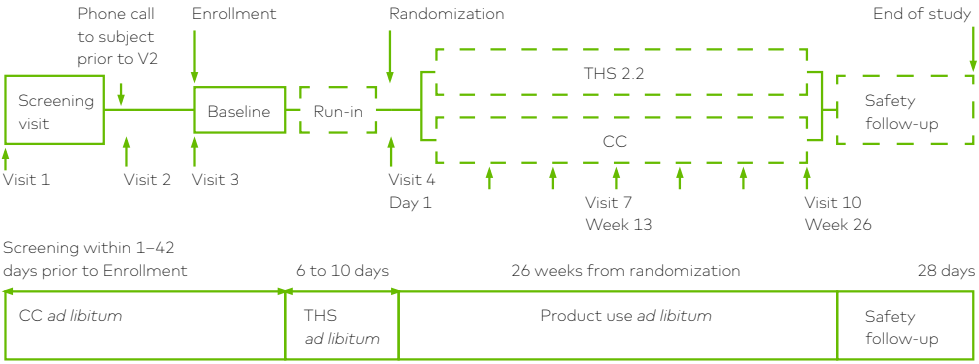
Design

This was a randomized, controlled, two-arm parallel group, multicenter US study in healthy adult smokers, not willing to quit smoking, who switched from CC to THS 2.2 relative to continuing to smoke CC over 6 months (Figure 1). The primary objective was to demonstrate statistically significant favorable changes (comparable to smoking cessation) in THS switchers for at least 5 out of the 8 CREs tested (Table 1). These CREs are linked to smoking-related diseases, representative of multiple pathomechanistic pathways that are sensitive to smoking and reversible within 1 year of smoking cessation in the literature.

Participants — main eligibilty criteria

① Subjects understood study information and signed the Informed Consent Form.
② Subjects were healthy and had no disorders or conditions that would jeopardize the subjects' safety or study result validity as judged by the Investigator.
③ Subjects (minimum age of 30), smoked ≥10 CC (non-menthol) per day for the last 12 months and had been smoking for ≥ 10 years.
④ Female subjects were not pregnant or breast feeding.
⑤ Subjects were not planning to quit smoking within the next 6 months.

Figure 1



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

Statistics

The population (FAS-EX) used for analysis of CREs, biomarkers of exposure (BoExp) to HPHCs and to nicotine, included all subjects with at least one THS 2.2 or CC use post-randomization and a valid value for at least one co-primary CRE at baseline and post-randomization. Subjects were analyzed according to these product use categories:

① THS-use: >70% use and more than 50% of days THS use
② Dual-use: <70% use or less than 50% of days
③ CC-use: < 1% THS use
④ Other-use: E-cigarette, quitters, other products

At Month 6, each CRE tested in the primary objective was analyzed for THS-use vs CC-use category comparison using a mixed-effect model repeated measurements approach adjusting for sex, Caucasian origin, timepoint (Month 3 and Month 6), the Baseline value and its interaction with timepoint, product use category and its interaction with timepoint, and other Baseline covariates relevant for each specific CRE. Site was included as a random effect.

The primary objective was to demonstrate statistically significant favorable changes in at least 5 of 8 co-primary CRE, with THS-use vs CC-use effect evaluated for each CRE using a 1-sided test with the Hailperin–Rüger adjusted type I error (a=1.5625%).

Table 1

Endpoints of the primary objective	Mechanistic pathways linked to smoking-related diseases
HDL-C	Lipid metabolism
WBC Count	Inflammation
sICAM-1	Endothelial dysfunction
11-DTX-B_2	Clotting
8-epi-PGF_{2a}	Oxidative stress
COHb	Acute effect
FEV_1	Respiratory function
Total NNAL	Genotoxicity

Results

Demographics

A total of 984 subjects were randomized to CC (n=496) or THS 2.2 (n=488) arms. The demographic characteristics for FAS-EX set are presented in Table 2.

Table 2: Summary of demographic data (FAS-EX)

Variable		Statistic	THS-use (N=245)	Dual-use (N=142)	CC-use (N=428)	Other-use (N=42)	Overall (N=857)
Sex	Male	n (%)	151 (61.6)	79 (55.6)	246 (57.5)	28 (66.7)	504 (58.8)
	Female	n (%)	94 (38.4)	63 (44.4)	182 (42.5)	14 (33.3)	353 (41.2)
Age (years)		Mean (SD)	44.2 (9.64)	43.8 (9.77)	45.2 (9.55)	44.2 (8.14)	44.6 (9.55)
Race	White	n (%)	195 (79.6)	113 (79.6)	341 (79.7)	30 (71.4)	679 (79.2)
	Black or African American	n (%)	42 (17.1)	25 (17.6)	74 (17.3)	10 (23.8)	151 (17.6)
	American Indian or Alaska native	n (%)	2 (0.8)	2 (1.4)	2 (0.5)	0	6 (0.7)
	Asian	n (%)	2 (0.8)	0	5 (1.2)	1 (2.4)	8 (0.9)
	Native Hawaiian or other Pacific islander	n (%)	1 (0.4)	0	2 (0.5)	0	3 (0.4)
	Other	n (%)	3 (1.2)	2 (1.4)	4 (0.9)	1 (2.4)	10 (1.2)
Weight (kg)		Mean (SD)	80.9 (16.8)	80.4 (15.4)	81.0 (15.6)	81.0 (18.9)	80.9 (16.1)
10–19 cig/day		n (%)	116 (47.3)	64 (45.1)	180 (42.1)	17 (40.5)	377 (44.0)
>19 cig/day		n (%)	129 (52.7)	78 (54.9)	248 (57.9)	25 (59.5)	480 (56.0)

Figure 2: Distribution of randomized subjects by product use categories (FAS-EX) over 6 month

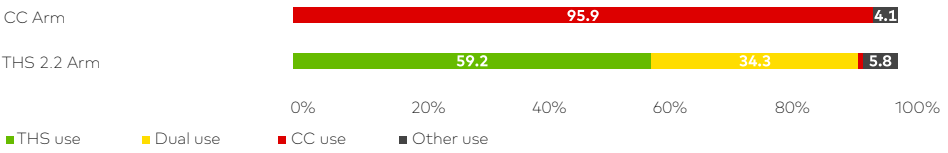


Table 3

Average Daily Products Used Within Product Use Category (FAS-EX)

Timeperiod	Product	THS-use mean (95% CI)	Dual-use mean (95% CI)	CC-use mean (95% CI)
Baseline	CC	18.5 (17.6, 19.4)	19.5 (18.2, 20.8)	19.5 (18.7, 20.2)
Post-randomization	THS 2.2	16.5 (15.3, 17.6)	7.58 (6.72, 8.44)	<0.01 (0, <0.01)
	CC	1.95 (1.65, 2.25)	9.99 (9.02, 11.0)	16.8 (16.1, 17.4)
	Overall Tobacco	18.5 (17.3, 19.6)	17.6 (16.3, 18.9)	16.9 (16.2, 17.5)

The overall tobacco use in the THS-use category was similar to the reported Baseline CC use, with mean of approximately 16.5 THS/day and 2CC/day. In the Dual-use and CC-use categories, the overall tobacco use during the randomized period was lower compared to the reported baseline CC use.

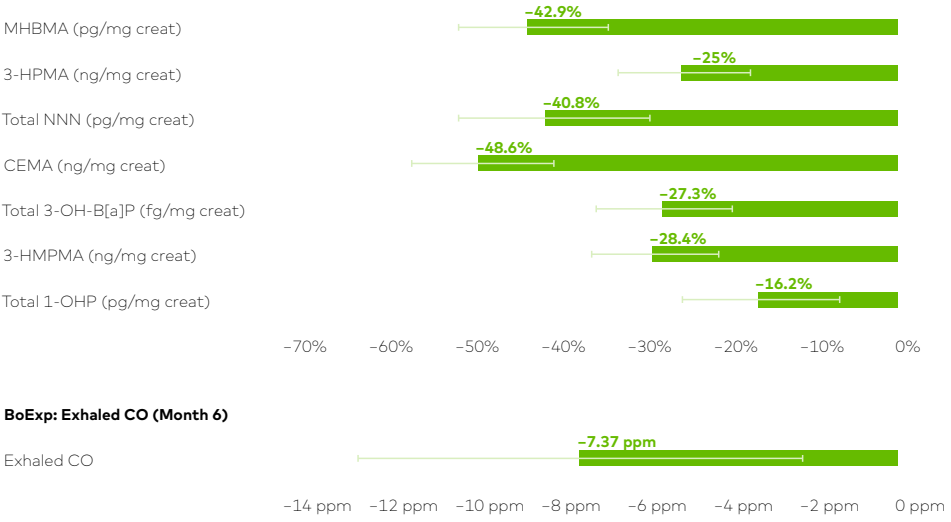
Table 4: Primary analysis of «Smokers' Health Profile» endpoints between THS-use and CC-use categories at month-6 (FAS-EX)

Endpoint	Change from CC-use	LS mean difference / Relative reduction	96.875% CI	1-sided p-value
HDL-C	Difference	3.09 mg/dl	1.10, 5.09	<0.001*
WBC count	Difference	−0.420 Gl/L	−0.717, −0.123	0.001*
sICAM-1	% reduction	2.86%	−0.426, 6.04	0.030
11-DTX-B_2	% reduction	4.74%	−7.50, 15.6	0.193
8-epi-PGF_{2a}	% reduction	6.80%	−0.216, 13.3	0.018
COHb	% reduction	32.2%	24.5, 39.0	<0.001*
FEV_1 % pred	Difference	1.28%pred	0.145, 2.42	0.008*
Total NNAL	% reduction	43.5%	33.7, 51.9	<0.001*

* Denotes significant p value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

Exposure to nicotine, as measured by urinary nicotine equivalents, nicotine and cotinine in plasma, was comparable between THS-use and CC-use categories.

Figure 3: Analysis of the BoExp: Comparison Between THS-use and CC-use Categories at Month 6



Safety

In the safety population, 19 SAEs were reported by 13 Subjects (1.3%); 8 SAEs in 6 subjects (1.3%) in the THS 2.2 arm; 11 SAEs in 7 subjects (1.4%) in the CC arm. Among these SAEs, the seriousness criteria were fatal in 2 SAEs, life threatening for 1 SAE, hospitalization for 17 SAEs, and 1 SAE was classified as an important medical event. In 2 of the 19 SAEs, more than 1 seriousness criteria was selected. There were no SAE related to THS or CC reported by any randomized subjects, and no randomized subjects were discontinued due to AEs related to THS or CC. Overall, THS was well tolerated by study participants.

Conclusions

This study demonstrated that switching to THS 2.2 results in favorable changes in CREs representative of pathomechanistic pathways underlying the development of smoking-related diseases. These results indicate a lower risk profile in smokers switching from CC to THS 2.2, an alternative candidate modified risk tobacco product.

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Competing financial interest

The research described in this brochure was sponsored by the Philip Morris International group of companies

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June 14–16, 2018
Warsaw, Poland