Beneficial Impact of Switching from Cigarette Smoking to Tobacco Heating System Use on Biomarkers of Potential Harm in a Randomized Trial

Christelle Haziza (Christelle.Haziza@pmi.com)
Philip Morris International (Switzerland)
Paul S. Hession
Philip Morris International (Switzerland)
Morgane David
Philip Morris International (Switzerland)
S. Michael Ansari
Philip Morris International (Switzerland)
Nicolas Blanc
Philip Morris International (Switzerland)
Guillaume de La Bourdonnaye
Philip Morris International (Switzerland)
Sandrine Pouly
Philip Morris International (Switzerland)
Manuel C. Peitsch
Philip Morris International (Switzerland)
Annie Heremans
Philip Morris International (Switzerland)

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Abstract

Background: Smoking cessation reduces the risk of developing smoking-related diseases. Although smoking prevalence has declined, many smokers continue smoking cigarettes. Switching to less harmful smoke-free alternatives such as the Tobacco Heating System (THS), a non-combustible tobacco-based product, is an approach to reduce the harm caused by cigarettes.

Methods: We conducted a 12-month clinical study with 984 adult smokers randomized to either continue smoking or to use THS. We assessed the trajectories of biomarkers of potential harm (BoPH) known to be reversible upon smoking cessation, as one measure of different pathways involved in the pathogenesis of cardiovascular or respiratory diseases, and carcinogenicity. Beneficial impact on 8 key BoPHs was used as a proxy to evaluate harm reduction.

Results: At 12 months, comparison of the 8 BoPH levels between the predominant THS use and cigarette smoking groups showed differences in favor of THS switching when contextualized to the changes reported for smoking cessation.

Conclusions: Our results likely indicate a further decrease in carcinogenicity and relative risk of developing cardiovascular or respiratory diseases for smokers switching to THS compared to those who would continue smoking. These results provide additional evidence of the harm reduction potential of predominant THS use.

Trial Registration

clinicaltrials.gov Identifier: NCT02649556

Date of registration: 07/01/2016 (dd/mm/yyyy)

(https://clinicaltrials.gov/ct2/show/NCT02649556)

Introduction

Smoking cessation is the best choice for reducing the risk of developing cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and lung cancer. Despite the growing number of tobacco control measures implemented in recent decades, [1, 2] which reduced the prevalence of smoking, less than 10% of smokers successfully quit every year in the United States (US) [3]. For those who decide to continue to smoke, an approach is needed for reducing the risk of smoking-related diseases.

In principle, tobacco harm reduction can be achieved when cigarettes are replaced by substantially less harmful nicotine delivery systems [4, 5]. According to the Institute of Medicine (IOM), “a product is harm-reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants” [6]. The risk–benefit balance for smokers to replace cigarettes with potentially harmless alternatives such as heated tobacco products, e-cigarettes, or

snus is recognized as an approach to tobacco harm reduction by some authorities [7–9]. However, it remains controversial from a public health perspective [10–12]. This is partly because of the complexity of assessing their impact owing to: (i) the large variety of alternatives available, (ii) their recent market introduction, (iii) the absence of a framework for assessing the long-term reduced risk associated with their use in the intended population (smokers) without epidemiological evidence, (iv) the potential dual or poly-use of products including cigarettes, and (v) their impact on non-intended users (for example, nonsmokers, or youth).

The Tobacco Heating System (THS; brand name *IQOS*™) is a heat-not-burn tobacco product developed by Philip Morris International (PMI). In 2020, FDA authorized IQOS to be marketed as a Modified Risk Tobacco Product with exposure modification orders [13]. Other heat-not-burn tobacco products include Glo [14] and Ploom TECH [15].

PMI has been conducting a comprehensive scientific assessment program for evaluating the reduced risk potential of THS [16–27]. The decrease in harmful and potentially harmful constituent (HPHC) emissions (including carcinogens, cardiovascular, reproductive, developmental, and respiratory toxicants) in THS aerosol relative to cigarette smoke is well documented [21, 28–30]. In coherence with the chemistry findings, smokers switching from cigarettes to ad libitum THS use are less exposed to HPHCs [31–37]. Because chronic exposure to HPHCs alters patho-mechanisms and the function of multiple organs, it is likely that switching completely from cigarettes to THS results in a meaningful reduction of future disease risk.

Morbidity and mortality data from epidemiological studies would provide the ultimate evidence of the relationship between long-term switching to THS use and prevention or minimization of harm to smokers. However, at least a decade is needed to obtain meaningful data from a large population of users. As THS has been commercially marketed since 2014, epidemiological data are not available. It is nevertheless critical to get insights into the health risk profile of THS use versus cigarette smoking. According to the IOM, a set of biomarkers of potential harm (BoPH), to monitor the early beneficial changes in biological and physiological functions underlying the development of clinical symptoms and disease, could be used as a proxy to evaluate further disease risk modification in smokers without diagnosis of diseases compared to continued smoking [6, 38]. This approach has been suggested for assessing the cardiovascular risk associated with the use of smoke-free alternatives to cigarettes [39].

Clinical and epidemiological data on the short- to long-term health effects of smoking cessation and the association with reduced risk of disease is extensively documented [40]. Comparison of the short-term beneficial changes in BoPHs, characterized for smoking cessation, could be used as a benchmark to estimate the reduction in risk associated with THS use against continuing smoking [41]. If the trajectory of changes is comparable to those observed with smoking cessation, a modification of the relative health risk profile associated with THS could be substantiated.

With that in mind, this publication describes the beneficial changes in BoPHs observed over 12 months in adult smokers who switched to THS in comparison to those who continued smoking. This study aimed at providing additional scientific evidence of the long-term potential for THS to reduce the risk of disease in smokers who would otherwise continue smoking.

Materials And Methods

Study Design

This study consisted of an initial 6-month randomized, controlled, two-arm “exposure response” study conducted in an ambulatory setting in the US (clinicaltrials.gov: NCT02396381, 23/03/2015 [42]), followed by a 6-month extension study (clinicaltrials.gov: NCT02649556, 07/01/2016). The initial study enrolled a total of 984 adult healthy smokers who were not willing to quit smoking and randomized them (1:1 ratio) into 2 groups:

- to smoke their own cigarettes *ad libitum* (496 participants; cigarette arm), or
- to use THS (non-menthol variant) *ad libitum* (488 participants; THS arm).

The method used to calculate the sample size was reported in a separate publication [42]. Randomization was performed during the initial study through an interactive voice and web response system. Stratified randomization ensured that each sex was represented by at least 40% of the subjects. A quota ensured that the White race did not represent more than 75% of the randomized subjects.

One site was closed for noncompliance with the principles of Good Clinical Practice (GCP); the data from this site were reported for safety purposes, and the subjects did not participate in the extension study.

Subjects from the 19 remaining sites who completed the initial study (381 in the THS arm and 422 in the cigarette arm) were asked to participate for an additional 6 months according to their initial randomization arm. The Midlands Independent Review Board (Overland Park, KS, USA) approved the study, and all subjects provided written informed consent prior to screening. Recruitment to the extension study started in September 2015, and the last subject completed the study in March 2017.

Together, the two studies covered a 12-month period, including a baseline visit when all subjects smoked cigarettes, a run-in period of 8 ± 2 days during which the subjects used THS for familiarization, a visit for randomization, subsequent visits at 3, 6, and 12 months, and monthly visits for safety checks. A 28-day safety follow-up period was scheduled after the 12-month visit or after discontinuation. All data were collected in electronic case report forms.

Products

The product tested, THS, comprises a holder that heats a tobacco stick and a charger that is used to recharge the holder [23]. The sponsor provided THS to the subjects because it was not marketed in the US at the time of the study. The tobacco sticks were provided on demand during or between site visits. Their

content, including nicotine, has been reported in a separate publication [43]. Cigarettes, used as a comparator, were purchased by subjects.

Subjects

The initial study enrolled adults with 10 years of smoking history who had smoked at least 10 nonmenthol cigarettes per day over the year prior to screening. They were at least 30 years old and not willing to quit. The study excluded subjects with stage II to IV COPD [44], pregnant or breastfeeding women, and subjects with body mass index (BMI) < 18.5 or ≥ 35 kg/m^2.

All subjects from the initial study were eligible to enroll in the extension study, unless they had made a quit attempt in the previous study, had medical conditions that would jeopardize their participation, or were breastfeeding or pregnant.

The subjects were instructed to continue using their allocated product exclusively without restrictions.

Any subject who wanted to quit using tobacco-containing products during the study was encouraged to do so and referred to appropriate services. Such subjects were not discontinued; they were encouraged to attend scheduled visits for assessment.

Compensation was provided, as per IRB approval and according to a predefined payment schedule, irrespective of actual product use.

Procedures

A detailed schedule of assessments is provided in Supplementary Table 1.

Over 12-months, the subjects recorded their daily use of tobacco or nicotine-containing products. All subjects received information on the risks of smoking and advice on smoking cessation during the study and were briefed that THS should not be considered a lower risk than cigarettes.

For assessment of urinary BoPHs and biomarkers of exposure (BoExp), subjects started urine collection at home on the morning preceding their visit and stopped the collection 24 h later.

Blood was collected from the subjects to measure BoPH levels in serum and plasma.

Spirometry was carried out, following the American Thoracic Society and European Respiratory Society guidelines [45], with predicted values standardized to the National Health and Nutrition Examination Survey III-predicted set [46]. All post-bronchodilator spirometry testing was performed 15–30 min post-administration of around 400 µg of salbutamol (equivalent to 4 puffs, assuming 100 µg/puff).

Body height, body mass, waist circumference, and blood pressure were recorded.

Biomarkers of potential harm and biomarkers of exposure

In the initial study, a set of 8 relevant and mutually supportive BoPHs with evidence of a robust relationship with CVD, COPD, or carcinogenicity, and a known beneficial impact within 12 months following smoking cessation, was *a priori* selected from a review of published studies [42]. The BoPHs included: white blood cell count (WBC); high-density lipoprotein cholesterol (HDL-C); forced expiratory volume in 1 s %predicted post bronchodilator (FEV_1%pred pBD); soluble intercellular adhesion molecule-1 (s-ICAM-1); 11-dehydro-thromboxane B2 (11DTXB2); 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$); carboxyhemoglobin (COHb); and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) [42]. Respectively, they are one measure of inflammation, lipid metabolism, lung function, endothelial function, oxidative stress, oxygen transport, platelet activity, and carcinogenicity, representing some of the main patho-mechanisms underlying CVD, COPD, and cancer, as described by the US Surgeon General's report on smoking cessation [40]. These BoPHs were tested as primary objectives in the initial study, for which results have been published [42]. These BoPHs were measured in the extension study, together with supportive BoPHs (the complete list is provided in **Supplementary Table 2**) to derive complementary information. The supportive BoPH were known to be indicative of the same pathways but not necessarily known to be beneficially influenced by smoking cessation within 1 year. In addition, BoExps to the following HPHCs were measured: total *N*-nitrosonornicotine, acrylonitrile, nicotine, and carbon monoxide. The formula used to obtain nicotine equivalent (NEQ) values is provided in the Supplementary Material (**Supplementary Method 1**).

All urinary BoPH and BoExp levels were adjusted to urinary creatinine concentration and analysed by Covance Central Laboratories Services, Inc., Indianapolis, IN, USA, or Celerion, Inc., Lincoln, NE, USA. These laboratories used methods validated in accordance with the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) standards or the Bioanalytical Method Validation guidance for Industry, from the US Food and Drug Administration (2018) [47].

Cough Questionnaire

For evaluating cough symptoms, the subjects were asked if they had experienced a regular need to cough within the previous 24 h; they indicated the intensity of the cough by completing a visual analogue scale (VAS) and answered 3 Likert scale questions (**Supplementary Table 7**). These questions assessed the cough intensity, frequency, and the amount of sputum production.

Safety

The safety population consisted of all enrolled subjects with at least one safety assessment. Safety was monitored under the responsibility of the Investigator supervising each site (**Supplementary Table 1**). The following tests were performed: medical interview to check health status, physical examination, vital sign measurements, electrocardiogram, and safety laboratory (hematology, blood biochemistry, and urine analysis). Adverse events (AE) were recorded and assessed for seriousness and relatedness to product or study.

Population Analysis Sets and Statistical Analyses

Subjects enrolled at the site terminated for noncompliance with GCP were excluded from the full analysis set but not from the safety population.

The full analysis set included all randomized subjects with recorded product use, baseline values, and at least one post-randomization value for one of the 8 BoPHs.

To reflect the realistic use of THS, subjects were classified into four groups (as exposed) according to their product use pattern. The groups were defined *a priori* for the safety population and the full analysis set based on self-reported product use (cigarettes and tobacco sticks) over the 12 months post-randomization (**Supplementary Table 9**). Predominant THS use (predTHS) was defined as ≥ 70% of daily tobacco stick use (THS use) on average (on at least 50% of the days over 12 months). Dual use was defined as 1% to < 70% THS use. Cigarette smoking (cig) was defined as < 1% THS use. All subjects who did not meet these criteria were included in the “other” use group. The study was not powered to demonstrate effects.

Each BoPH was analyzed (**Supplementary Table 2**)—between the predTHS and cig groups and the dual and cig groups—by using a mixed-effects model for repeated measurements (MMRM), adjusting for sex, Caucasian origin, time, value at baseline and its interaction with time, product use group, and other relevant baseline covariates. Site was included as a random effect.

The least squares (LS) means and estimate of the difference, along with 95% confidence intervals (CI) and 2-sided p-values, were presented for HDL-C, WBC, and FEV_1%pred. For sICAM1, 11DTXB2, 8epi$PGF_{2\alpha}$, COHb, and total NNAL, values were analyzed on the log-scale, and the results were back-transformed in the original scale as a ratio as well as % reduction relative to cigarette smoking (that is, predTHS:cig ratio or dual:cig ratio).

Odds ratios for need to cough (Yes/No) between predTHS and cig users were derived from a mixed effects logistic regression model with visit, baseline value and its interaction with visit, sex, Caucasian origin, age, smoking intensity, and product use group and its interaction with time as fixed-effect factors and site as a random effect.

Considering the limited accuracy of self-reported product use, a post-hoc analysis of predTHS was performed to explore the magnitude of effects according to the intensity of cigarette smoking concomitant to THS use [48]. For each timepoint, this analysis determined the levels of the 8 BoPHs according to each cyanoethyl mercapturic acid (2CyEMA) quartile. 2CyEMA is a BoExp to acrylonitrile (an HPHC generated in cigarette smoke from tobacco combustion at > 400°C [49]) and exhibits a linear relationship with the number of cigarettes smoked [50]. The half-life of 2CyEMA has been estimated at up to 8–9 hours [51, 52]. In previous studies, acrylonitrile levels were reduced by over 99% in THS aerosol relative to cigarette smoke [21], and urinary 2CyEMA levels in smokers switching to THS exclusively for 5 days were decreased by approximately 80% relative to smokers who continued smoking [16, 53]. In that context, the present study used 2CyEMA as an objective chemical marker for evaluating the degree of cigarette smoking in the predTHS group.

All analyses were performed with Statistical Analysis Software (SAS) version 9.2 (SAS Inc., Cary, NC, USA).

Results

Population Analysis Set and Demographics

Figure 1 summarizes the subject flow through the initial 6-month “Exposure Response Study” and the 6-month extension study.

Subjects who completed the initial study (excluding subjects from the terminated site) were asked to participate in the extension study. In the THS and Cigarette arms, 81% and 86% of subjects, respectively, from the initial study extended their participation and of those 285 and 329 subjects, respectively, completed the study.

The safety population consisted of 940 subjects classified according to product use: predTHS (241 subjects), dual use (159 subjects), cigarette (434 subjects), and other (106 subjects) groups.

The full analysis set consisted of 857 subjects classified according to product use: predTHS (230 subjects), dual use (152 subjects), cigarette (424 subjects), and other (51 subjects) groups. Of the 230 subjects in the predTHS category, 136 subjects (59%) were classified as being exclusive users (≥ 95% use of THS).

The baseline characteristics of the subjects (Table 1) in the full analysis set were balanced across the four groups including, age, sex, race, smoking history, BMI, pack-year smoking history, and daily cigarette consumption. Their cigarette consumption ranged between 18 and 20 cigarettes per day and smoking history was of 25–27 years on average. Pulmonary function was normal in 92.6%, 93.4%, 91.4%, and 92.2% of the predTHS users, cigarette smokers, dual users, and other users, respectively. Across the groups, some subjects were classified as having COPD stage I and II according to the GOLD guidelines [44].

Table 1
Summary of demographic data and smoking-related characteristics at baseline; full analysis by product use group

Variables	Statistics	THS use (n = 230)	Dual use (n = 152)	Cig use (n = 424)	Other use (n = 51)
Sex					
Male	n (%)	143 (62.2)	85 (55.9)	244 (57.5)	32 (62.7)
Female	n (%)	87 (37.8)	67 (44.1)	180 (42.5)	19 (37.3)
Age (years)	n	230	152	424	51
	Mean (SD)	43.8 (9.68)	44.2 (9.76)	45.2 (9.54)	44.5 (8.21)
Race					
White	n (%)	182 (79.1)	123 (80.9)	338 (79.7)	36 (70.6)
Black or African American	n (%)	41 (17.8)	25 (16.4)	73 (17.2)	12 (23.5)
Others [a]	n (%)	7 (3.0)	2 (1.3)	13 (3.0)	3 (5.8)
Height (cm)	n (%)	230 (100)	152 (100)	424 (100)	51 (100)
	Mean (SD)	173 (10.3)	172 (8.97)	173 (9.57)	172 (10.2)
Weight (kg)	n (%)	230 (100)	152 (100)	424 (100)	51 (100)
	Mean (SD)	81.4 (17.0)	80.0 (15.3)	81.2 (15.6)	79.1 (18.1)
BMI (kg/m^2)	n (%)	230 (100)	152 (100)	424 (100)	51 (100)
	Mean (SD)	27.0 (4.06)	26.9 (4.25)	27.1 (4.13)	26.6 (4.91)
Underweight	n (%)	1 (0.4)	0	0	0
Normal weight	n (%)	77 (33.5)	55 (36.2)	142 (33.5)	17 (33.3)
Overweight	n (%)	88 (38.3)	57 (37.5)	163 (38.4)	19 (37.3)
Obese	n (%)	64 (27.8)	40 (26.3)	119 (28.1)	15 (29.4)
Waist circumference (cm)	n (%)	230 (100)	152 (100)	422 (99.5)	50 (98.0)
	Mean (SD)	94.6 (16.6)	96.2 (15.3)	94.5 (14.8)	93.3 (12.0)

[a]Others include American Indian or Alaska Native, Asian, and Native Hawaiian, or other Pacific Islander

[b]Average daily cigarette consumption over the last year

SD = standard deviation; cm = centimeters; kg = kilograms; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = global initiative for chronic obstructive lung disease

Variables	Statistics	THS use (n = 230)	Dual use (n = 152)	Cig use (n = 424)	Other use (n = 51)
COPD stage					
Normal	n (%)	213 (92.6)	139 (91.4)	396 (93.4)	47 (92.2)
GOLD1: Mild	n (%)	14 (6.1)	9 (5.9)	24 (5.7)	4 (7.8)
GOLD2: Moderate	n (%)	3 (1.3)	4 (2.6)	4 (0.9)	0
Others	n (%)	0	0	0	0
Smoking duration	n (%)				
	Mean (SD)	25.6 (9.48)	25.6 (10.0)	26.7 (10.1)	25.7 (10.2)
Smoking intensity [b]	Mean (SD)	18.4 (6.88)	19.5 (7.82)	19.5 (7.87)	20.5 (11.0)
Pack year smoking history	Mean (SD)	22.7 (12.3)	23.3 (14.1)	25.0 (15.9)	23.4 (14.6)
[a]Others include American Indian or Alaska Native, Asian, and Native Hawaiian, or other Pacific Islander					
[b]Average daily cigarette consumption over the last year					
SD = standard deviation; cm = centimeters; kg = kilograms; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = global initiative for chronic obstructive lung disease					

Product Use

Over 12 months, the predTHS users reported a mean daily use of 16.5 THS tobacco sticks and 1.6 cigarettes per day (**Supplementary Table 8**); the dual users reported a mean use of 8.1 THS tobacco sticks and 9.2 cigarettes per day, and the cigarette smokers reported a mean use of 16.5 cigarettes per day.

The baseline NEQ levels were similar across the predTHS, dual, and cig groups, with overlapping CIs ranging from 9.1 to 11.8 mg/g creatinine; these levels were maintained throughout the 12 months (8.47–9.73 mg/g creatinine).

The average product consumption and exposure to nicotine were stable over the study irrespectively of the timepoint.

BoPHs

Comparison between the predTHS and cig groups showed a beneficial impact on the majority of BoPH across the study in favor of switching to THS, when contextualized to the changes reported for cessation (Fig. 2). The changes from baseline were overall in line with the results of the inferential analyses. The

BoPH results are summarized below and provided in full, at baseline, 3, 6, and 12 months, in **Supplementary Table 3**.

All the comparisons below are described against the cig group.

Lipid metabolism

The levels of HDL-C were 1.6, 3.1, and 1.8 mg/dL higher at 3, 6, and 12 months in the predTHS group respectively. Concomitantly, the levels of Apo A1 were 0.5, 3.7, and 2.1 mg/dL respectively. The LDL-C and Apo B levels were lower at 3 and 6 months in the predTHS group with no notable difference in Apo B levels at 12 months while a slight increase was observed for LDL-C.

Endothelial dysfunction and platelet activation

The levels of s-ICAM-1 and 11DTXB2 in the predTHS group were slightly reduced across the study, starting from 3 months. The mean reductions ranged from − 1.9% to -3.2% and from − 3.3% to -4.5%, respectively. No meaningful changes were observed in platelet or fibrinogen levels.

Lung function

FEV_1%pred values were slightly higher in the predTHS group across the study, starting from 3 months. The mean differences ranged from 0.8–1.3%. FVC %pred, FEV_1/FVC ratio, and FEF_{25-75}%pred were consistently higher in the predTHS group.

Inflammation and oxidative stress

The WBC count was lower in the predTHS group across the study, starting from 3 months. The mean differences ranged from − 0.47 GI/L to -0.41 GI/L. In line with this result, the myeloperoxidase (MPO) and high-sensitivity C-reactive protein (hs-CRP) levels were reduced by at least − 12.8% and − 7.8% in the predTHS group, starting from 3 months. In contrast, the homocysteine levels were slightly increased (from 2–4%) in the predTHS group. The mean reductions in the levels of 8-epi-$PGF_{2\alpha}$ ranged from − 5.9% to -7.5% over the study, starting from 3 months.

Oxygen transport and carcinogenicity

The mean reductions in COHb and total NNAL levels in the predTHS group ranged, respectively, from − 31.2% to -32.0% and − 42.1–46.3% across the study.

Impact of Dual Use

In the comparison between the dual and cig groups, the trajectories of the BoPHs in the dual group were similar to those in the predTHS group, although the magnitude of effect in the former group was much lower (**Supplementary Table 3)**.

In the *post hoc* analysis carried out in the predTHS group according to 2CyEMA quartiles **(Supplementary Table 5)**, except for HDL-C, the magnitude of beneficial effects on BoPHs over 12 months was higher when exposure to 2CyEMA was reduced (the lowest intensity of cigarette smoking) (Fig. 3**)**. As an example, this favorable effect on most BoPHs was the highest at 12 months and higher in the first quartile (1st) than in the third quartile (3rd), with the following mean values: sICAM-1 level, -4.77 vs. -2.83; 11-DTX-B2 level, -8.53% vs. -2.11%; WBC count, -0.576 vs. -0.345; FEV_1%pred pBD, 1.45% pred. vs 0.711% pred; 8-epi-$PGF_{2\alpha}$ level, -17.8% vs. -3.36%; COHb level, -53.5% vs. -21.85%; and total NNAL level, -68.8% vs. 35.9%. Inversely, the lowest favorable effect on HDL-C levels was observed in the first quartile (-0.192 vs. 2.43 mg/dL in quartiles 1 and 3, respectively (**Supplementary Table 4**).

Exposure to HPHCs

In addition to total NNAL and COHb, the following HPHCs showed relative reductions in the predTHS group versus the cig group consistently across the study, starting from 3 months: total NNN level (*N*-nitrosonornicotine; LS mean relative reduction, 26–39%), 2CyEMA level (LS mean relative reduction, 47.6–51.5%), and exhaled CO level (LS mean relative difference, -5.46 to -7.90 ppm). Dual users showed a markedly inferior reduction in BoExp levels (**Supplementary Table 6**). NEQ levels were comparable across the study to baseline irrespective of the product use group.

Cough

The proportion of subjects who reported a regular need to cough was lower in the predTHS group than in the cig group. The mean odds ratio for the need to cough (predTHS use:cig) was consistent across the study, starting with 0.65 (95% CI, 0.43–1.01) at month 3 and moving to 0.59 (0.37–0.92) at month 6 and 0.60 (0.36–1.01) at month 12.

Safety

There were no serious AEs (SAE) related to THS use, while 3 SAEs reported by 3 randomized subjects were considered related to continued cigarette smoking. No randomized subject was discontinued because of AEs related to THS or cigarettes.

Among the predTHS group, 151 (62.7%) reported 371 AEs, in contrast to 278 (64.1%) in the cig group who reported 705 AEs; a total of 33 AEs in the two product use groups were classified as severe by the investigators. The incidence of product use-related AEs was comparable between the predTHS group (8/241 subjects; 3.3%) and cig group (13/434 subjects; 3.0%). The incidence of product use-related AEs in the dual group was higher (11/159 subjects; 6.9%). The most frequent AEs were upper respiratory tract infection (predTHS, 21/241 subjects [8.7%]; cig, 40/434 subjects [9.2%]), hypertension (predTHS, 9/241 subjects [3.7%]; cig, 26/434 [6.0%]), and increased blood triglyceride levels (predTHS, 10/241 subjects [4.1%]; cig, 26/434 subjects [6.0%]).

There were very few clinically relevant findings in the clinical laboratory, vital signs, or ECG data, with comparable changes from baseline to month 6 and month 12 between the predTHS group and cig group.

Discussion

We used a panel of 8 patho-mechanistically relevant BoPHs to estimate the long-term risk reduction of switching to THS on the development of the main smoking-related diseases (CVD, COPD, and lung cancer) compared to continued smoking over a period of 12 months.

If predominant switching to THS use has the potential to reduce the occurrence of adverse health outcomes and disease risk relative to continued smoking, it should impact the selected BoPHs in the same direction as reported in the literature following smoking cessation.

The primary analysis was performed in subjects classified as predTHS users as the potential benefit from switching to THS is assumed only if cigarette consumption is reduced to an absolute minimum. However, it was expected that some smokers randomized to use THS would not be completely adherent as product satisfaction is a critical component of adherence.

In the THS randomized arm, 55.6% of subjects were classified as predTHS users and 44.4% as dual users (THS and cigarettes). The reduction in exposure to HPHCs in the predTHS group compared to the cig group was lower compared to previous publications including an independent review [28, 54]. This is likely related to the allowance of up to 30% concomitant use of cigarettes. Despite the substantial reduction from baseline in the daily cigarette consumption of the predTHS group, subjects reported an average consumption of 1.6 cigarettes per day. In the dual use group (an average of 9.2 cigarettes per day), if the exposure was decreased relative to the cig group, it was lower than in the predTHS group. (Self-reported product use is provided in **Supplementary Table 8.).**

Our results in predTHS users substantiate the beneficial impact of THS use versus cigarette smoking, with most of the changes in the BoPHs (increases or decreases) in line with those reported upon 1 year of smoking cessation.

Lipid metabolism was improved, as reflected by higher levels of HDL-C and Apo A1 across the study. The absence of a clear or consistent decrease in LDL-C or Apo B levels was expected [55–57].

In coherence with the lipid metabolism evidence, BoPHs for endothelial dysfunction and platelet activation (s-ICAM-1 and 11-DTX-B2), inflammation and oxidative stress (WBC and 8-epi-$PGF_{2\alpha}$), and oxygen transport impairment (COHb) were all consistently reduced in predTHS users in a similar manner as observed following smoking cessation.

No intergroup differences were noted in platelet count, albumin, or fibrinogen levels. This is consistent with the findings in the literature, as changes in fibrinogen levels may take over 2–5 years to develop [58, 59], and findings on changes in platelet count are controversial [60–62]. In the present study, a consistent reduction in hs-CRP level was observed within 12 months of switching to THS, although this change is usually reported following 2–5 years of cessation [63].

Homocysteine levels are reported to decrease upon smoking cessation [64], but the predTHS group in the present study showed a slight increase in these levels. This was possibly due to their concomitant use of cigarettes [64]. It may also be related to diet, which could be another confounding factor. For example, a diet relatively low in fruits, vegetables, and dairy products may raise homocysteine levels [65].

The results from the predTHS group overall, are characteristic of a lower atherogenic profile that could indicate a reduction in cardiovascular risk, particularly when considering that HDL-C levels [66, 67], WBC count, and 8-epi-$PGF_{2\alpha}$ and s-ICAM-1 levels are reported to be predictive of decreased future adverse cardiovascular outcomes [68].

Predominant use of THS had a beneficial and consistent impact on respiratory function, with a lesser decline in FEV_1%pred, FVC %pred, FEV_1/FVC ratio, and FEF_{25-75}%pred in the predTHS group over 12 months, as well as a decrease in regular coughing versus smokers. Together with the decrease in inflammation and oxidative stress, this could indicate a reduction in risk for respiratory diseases such as COPD. This inference is supported by the findings of other studies: (i) improvement in mucociliary clearance in smokers [69]; (ii) in a 1-year cohort, *IQOS* users showed improvement from baseline in total COPD assessment (40%), ability to walk longer, and spirometry outcomes [70]; (iii) a substantial decrease in annual exacerbations in COPD patients who used *IQOS* for 3 years versus those who continued smoking [71].

Similarly, the reduction in exposure to total NNAL in predTHS users, a carcinogenic suggested as a risk marker for lung cancer [72], is another propitious indicator for smokers to switch to THS.

Dual users showed modifications in BoPHs but to a much lower extent. This result is coherent with the lower reduction of exposure versus predominant THS use. The impact of cigarette smoking was verified in predTHS users when we evaluated the magnitude of changes in the 8 key BoPHs by using 2CyEMA exposure to quantify cigarette smoking intensity. We observed that lower exposure to 2CyEMA was associated with a higher beneficial impact on the BoPHs, except in the case of HDL-C, which presented a different profile. At this stage, no plausible explanation can be found for the difference in the HDL-C profile.

Overall, the data clearly indicates an inverse dose response between the number of cigarettes smoked per day and the magnitude of the beneficial effects when switching to THS. Using THS exclusively in place of cigarette is critical to further reduce disease risk and achieve harm reduction. In the real-world—where smokers choose to try the product and continue if they have a satisfactory experience—the adherence is likely to be higher, and the beneficial impact on BoPHs could be more pronounced.

The improvement in the levels of BoPH observed in smokers who switch to THS are consistent with the findings from a review of heat-not-burn products [54] and 2 studies on THS [73, 74]. One observational, cross-sectional, study reported an increase of 13.9% in HDL-C levels and a decrease of 12.4% in sICAM-1, 17.4% in WBC, 32.6% in 11-DTX-B2, and 28.9% in 8-epi-PGF2α levels in exclusive Ploom TECH users versus continued smokers over an average of 1.2 years [73]. The differences between Ploom TECH users

and never smokers in this study were not significant. Similarly, the authors observed a difference of 8.5% in FEV_1%pred between Ploom TECH users and smokers in favor of the heat-not-burn users. The beneficial effects of using this alternative to cigarettes were of a lower magnitude than observed in never smokers. In a previous 1-year study, where smokers were randomized to continue smoking or switched to exclusive use of the Glo heated tobacco product, similar beneficial changes were reported [74]. It is likely that up to 30% concomitant use of cigarettes by the predTHS users (as self-reported) in our study explains the lower magnitude of effects on BoPHs than those reported in these previous publications.

One of the strengths of our study was the large sample size, along with the measurement of multiple BoPHs over 12 months of THS use. These BoPH indicated the impact of THS on various patho-mechanisms on the causal pathway to smoking-related diseases. When compared with the effect of smoking cessation over the same timeframe, this approach is valuable to provide early insights into the long-term risk reduction associated with alternatives to cigarettes, such as THS, in the absence of epidemiological data.

This study has some limitations. Self-reported product use has limited accuracy. Despite the balance in demographic characteristics across the 4 groups of product use at baseline, our “per-exposure” analysis instead of per randomization arm could have introduced an imbalance at the end of the study. We also observed high variability in some BoPHs. Moreover, the study does not provide insights on clinical outcomes. A study to detect a difference in clinical outcomes would have necessitated a much longer-term follow-up, particularly in smokers without a disease diagnosis.

In smokers who switched from cigarettes to predominant THS use, our study shows reduction of exposure to HPHCs and favorable changes on multiple BoPH, indicative of lipid metabolism, endothelial dysfunction, platelet activation, lung function, oxygen transport, carcinogenicity, inflammation, and oxidative stress. This data brings additional scientific evidence of the potential of THS to further reduce the risk of the main smoking-related diseases, in smokers who would otherwise continue to smoke cigarettes.

Declarations

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Author Contributions

Christelle Haziza, Guillaume de La Bourdonnaye, Sandrine Pouly, Nicolas Blanc and S. Michael Ansari were responsible for the accuracy of the scientific content and interpretation. Morgane David and Paul Hession contributed to the creation of tables and figures and to ensure the quality control of the

manuscript. Manuel C. Peitsch, and Annie Heremans reviewed the manuscript. The manuscript was written by Christelle Haziza and reviewed by all the authors prior to submission. Paul Hession provided writing and editorial support. All contributors were involved or knowledgeable in the design and the reporting of the clinical study described in this publication.

Data Availability

The data generated in this study are not publicly available but are available upon reasonable request from the corresponding author. The study protocol and study results are disclosed on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02649556).

Additional Information

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Competing interests

All authors are employees of Philip Morris Products S.A. or worked for Philip Morris Products S.A. under contractual agreements.

Ethical approval

The study was approved by the Midlands Independent Review Board, Overland Park, KS, USA. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Figures

Figure 1

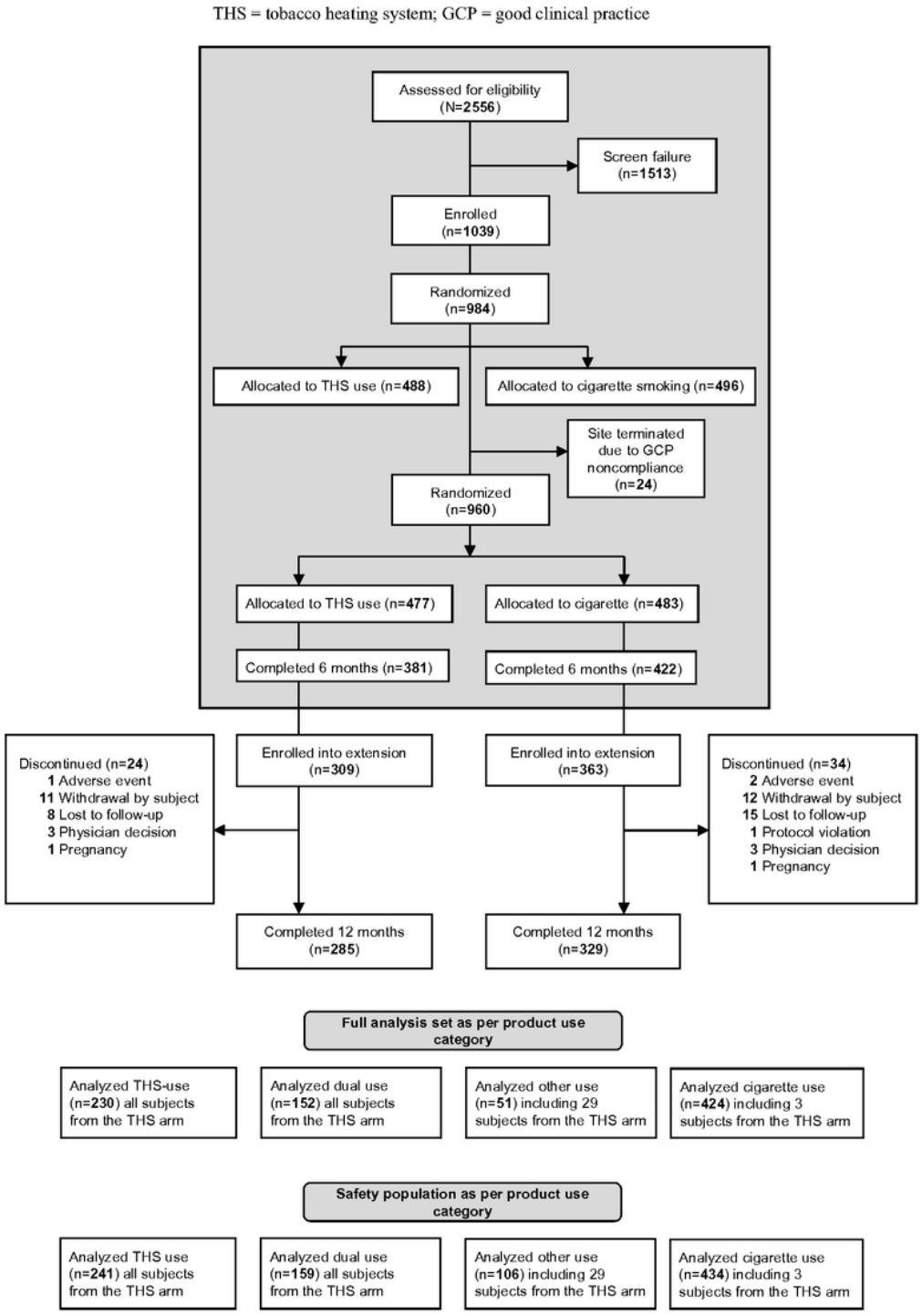

Figure 1

Flow of participants through the “Exposure Response Study” and study extension.

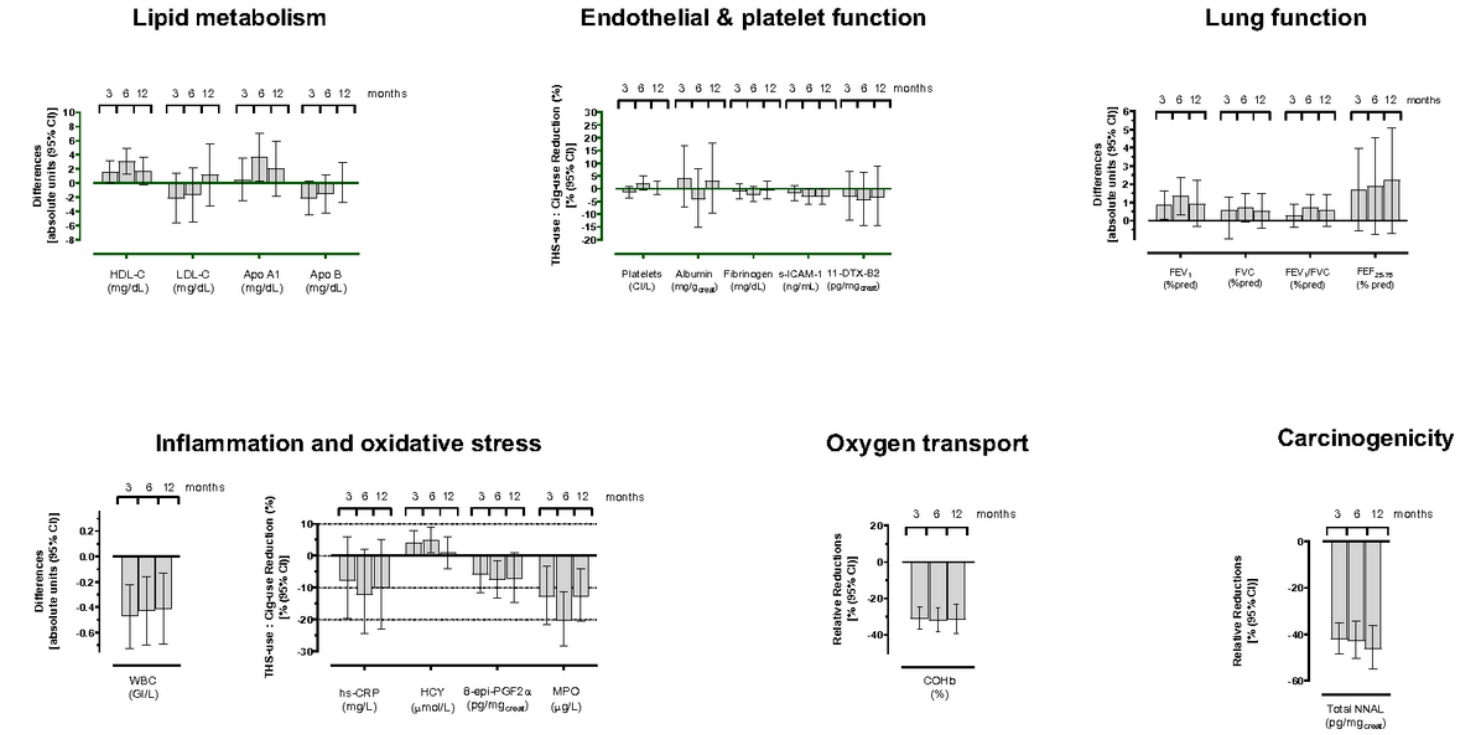

Figure 2

Mean relative difference or reduction (and 95% confidence intervals) between the predTHS and cig groups after 3, 6, and 12 months of product use.

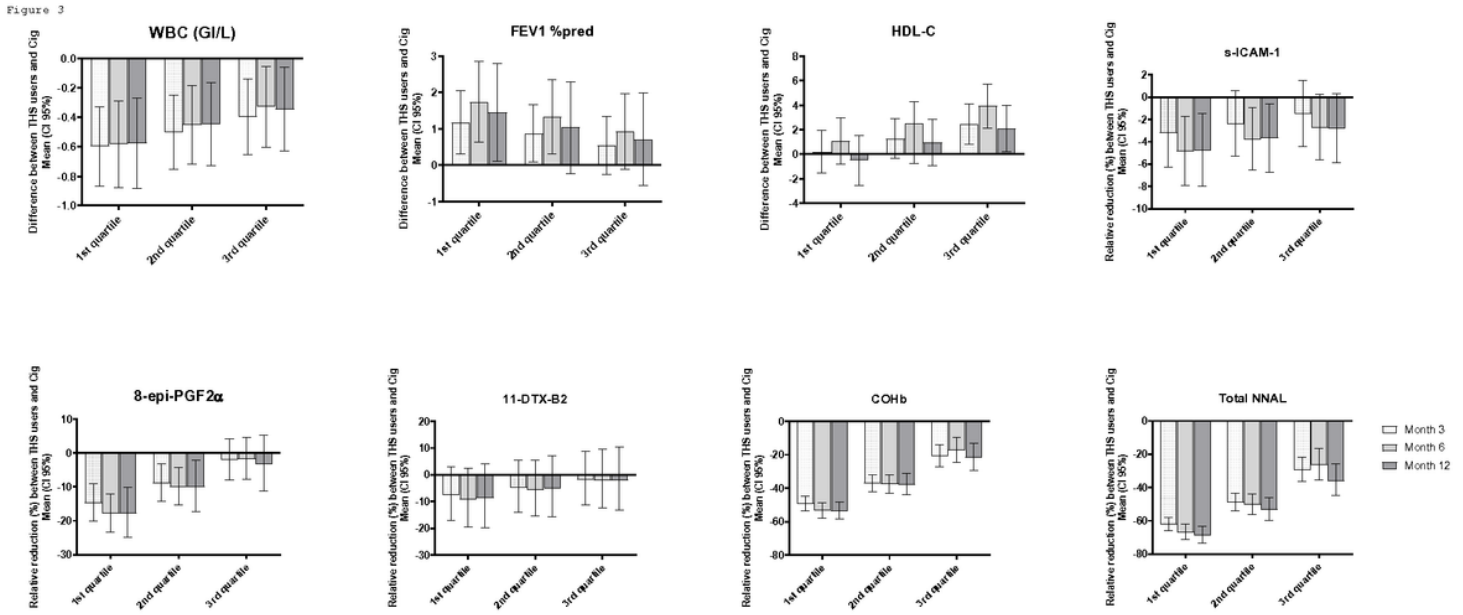

Figure 3

Mean relative difference or reduction (and 95% confidence intervals) between predTHS and versus cigarette smokers according to 2CyEMA quartile distribution for the set of eight BoPHs after 3, 6, and 12 months of product use

Supplementary Files

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