



Tobacco harm reduction: The potential to reduce the risk from smoking: a six-month exposure response study on switching from cigarettes to tobacco heating system (THS)

Smanjenje štete od duvana: Potencijal za smanjenje rizika od pušenja: šestomesečna studija reakcije na prelazak sa cigareta na sistem zagrevanja duvana (*Tobacco heating system - THS*)

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Abstract

The primary goal of the Exposure Response Study (ERS) was to generate direct evidence that actual use of Philip Morris International's smoke-free alternative to cigarettes, Tobacco Heating System (THS), can reduce smokers' risk of harm compared to continuing to smoke cigarettes. In the study eight biomarkers of potential harm (BoPH) were measured, to provide further evidence on effects of current adult smokers switching to THS. Each of the BoPH were selected because they are associated with smoking-related diseases, are negatively impacted by smoking and are reversible following smoking cessation. Given the study hypothesis, that the eight BoPH which cover eight different pathways of disease would change favorably, similarly to what is reported in the literature following smoking cessation. Therefore all eight BoPH were included and tested as co-primary endpoints.

In total 984 smokers were randomized to either switch to THS use, or continue to smoke cigarettes. The eight BoPH were assessed over a period of six months in an ambulatory setting. The results showed that when smokers switched to THS, all eight BoPH showed a changes similar to what is seen following smoking cessation, and five of the eight BoPH were statistically significant better in smokers who switched to THS than smokers who continued to smoke cigarettes. This led to the conclusion that switching from cigarettes to THS-use likely reduces a smoker's risk of tobacco-related disease and may present less risk of harm compared to continued smoking.

Key words: tobacco heating system (THS), biomarkers of potential harm (BoPH), smoke-free products, tobacco harm reduction

Apstrakt

Primarni cilj Studije reakcije na izloženost (*Exposure Response Study - ERS*) bio je generisanje direktnih dokaza da stvarna upotreba alternativna za cigarete, sistema za zagrevanje duvana (THS) kompanije Philip Morris International može da smanji rizik štete od pušenja u poređenju sa nastavljanjem pušenja cigareta. U studiji je izmereno osam biomarkera potencijalne štete (*Biomarkers of Potential Harm - BoPH*) kako bi se obezbedili dodatni dokazi o efektima kod trenutnih punoletnih pušača koji su prešli na THS. Svaki BoPH je izabran jer je povezan sa bolestima povezanim sa pušenjem, pušenje negativno utiče na njih i reverzibilni su nakon prestanka pušenja. Uzimajući u obzir hipotezu studije, da će se osam BoPH koji pokrivaju osam različitih puteva bolesti povoljno promeniti, slično onome što se navodi u literaturi nakon prestanka pušenja, svih osam BoPH je uključeno i testirani su kao ko-primarne krajnje tačke.

Ukupno je 984 pušača nasumično odabrano da ili pređu na upotrebu THS-a ili da nastave da puše cigarete. Osam pomenutih BoPH procenjeno je tokom šest meseci u ambulantom okruženju. Rezultati su pokazali da je, kada su pušači prešli na THS, došlo do promena kod svih osam BoPH, promena sličnih onima koje se vide nakon prestanka pušenja, a pet od osam BoPH statistički su značajno bolji kod pušača koji su prešli na THS u odnosu na pušače koji su nastavili da puše cigarete. Ovo je dovelo do zaključka da prelazak sa cigarete na upotrebu THS-a verovatno smanjuje rizik pušača od bolesti povezane sa duvanom i može predstavljati manji rizik od štete u poređenju sa nastavkom pušenja.

Ključne reči: sistem za zagrevanje duvana (THS), biomarkeri potencijalne štete (BoPH), proizvodi bez dima, smanjenje štete prouzrokovane duvanom



Introduction

The best choice that a smoker can make for their health is to stop using tobacco and nicotine containing products all together. But, despite the reduction in smoking prevalence globally, and the known risks of developing smoking-related diseases such as lung cancer, COPD, and cardiovascular disease, it is still estimated that over 1 billion people will continue to smoke by 2025 (1). It is important that we continue to reduce the number of smokers (reduce initiation and increase cessation), but this can be complemented by strategies that explore ways to reduce the risk of harm for existing smokers. Today there are newer tobacco products, that are able to deliver nicotine, but which much lower levels of the toxicants that cause smoking-related diseases. These products are less harmful alternatives to cigarettes and can be a replacement for cigarettes to achieve tobacco harm reduction. Philip Morris International is developing, assessing, and commercializing a portfolio of these products, smoke-free alternatives to cigarette, that have the potential to reduced risk of harm compared to smoking cigarettes.

Smoke-free alternative

THS is composed of three distinct components: a novel tobacco stick made of processed tobacco, an electronically controlled holder into which the tobacco stick is inserted, and a charger to recharge the holder.

The THS holder contains a heating blade that directly heats the tobacco but also monitors and controls the temperature of the tobacco, ensuring that the tobacco stays under 350°C which is below the ignition temperature of tobacco (~400°C). By avoiding the burning the tobacco, the aerosol that is emitted from THS is fundamentally different in composition than cigarette smoke. Heating tobacco produces an aerosol with significantly lower levels of harmful and potentially harmful constituents (HPHCs) than are in cigarette smoke (3).

Scientific assessment strategy

The Company Philip Morris International developed a scientific assessment approach to assess smoke-free alternatives to understand the relative risk profile compared to continuing to smoke cigarettes, but also understanding how the risk profiles compare to smoking cessation, which is the gold standard for reducing the risk of smoking-related diseases (4).

The thorough systematic scientific assessment program includes: 1) platform development, where we analyze the levels of HPHC formation, but also look at the levels relative to cigarettes. 2) Toxicological assessment, verifying that the reduction in toxic emissions leads to a reduced toxicity and that this then leads to

a reduction of risk of smoking-related diseases in laboratory models. 3) Clinical assessment, demonstrating that smokers who switch to these products have a reduced exposure to HPHCs and that the reduced exposure is associated with favorable changes in biological, functional, clinical endpoints (i.e., BoPH) that are used as an indicator for the potential of longer term risk reduction in smoking-related diseases. 4) Perception and behavior assessment assesses in a pre-market setting, how the products may be used and how consumers may transition to these products over time, this is important as these products are for smokers who would otherwise continue to smoke cigarettes. 5) Post market surveillance and studies is a program designed to assess the real-world impacts and use of these products. It includes safety monitoring, as well as short and longer-term assessment in consumers, to evaluate the prevalence and patterns of use of the product, the safety of the products, and the impacts of these products on consumers – their contribution to harm reduction. This five step assessment program is further outlined in Smith *et al.*'s publication on THS (5).

The Exposure Response Study design

The ERS was designed to provide direct evidence that the switching to THS as it is actually used can reduce smokers' risk of harm compared to continuing to smoke cigarettes. In the study eight BoPH (referred as clinical risk endpoints) are assessed as part of the primary objective to be an indicator of how the risk profile of smoking may change when switching from cigarettes to THS. The study was designed to complement the already available evidence on THS's effects by providing clinical evidence on the harms. The eight BoPH were selected based on a predefined set of criteria looking at the literature from clinical and epidemiological studies on the health effects of smoking and smoking cessation.

Criteria for BoPH Selection: 1 – epidemiological evidence of a robust relationship between the BoPH and at least one of the major smoking-related diseases; 2 – clinical evidence linking cigarette smoking to negative impact on the BoPH (consistent with the epidemiological evidence); 3 – clinical evidence linking positive changes in BoPH following smoking cessation (within the 6 month timeframe of the study) and, 4 – availability of fit-for purpose and validated analytical methods.

The study was a six-month randomized, controlled, two-arm study in an ambulatory setting, where participants were randomized into one of two groups: smokers who continued to smoke cigarettes (496 participants), and smokers who switched to THS (488 participants). It was not expected that smokers randomized to THS, would immediately switch to exclusive use of THS. The participants in this study were smokers who

Table 1. List of Clinical Risk Endpoints tested in the primary objective.

	Endpoint	Abbreviation	Disease Pathway	Units
Co-Primary CRE	High density lipoprotein cholesterol	HDL-C	Lipid Metabolism	mg/dL in serum
	White blood cell total count	WBC	Inflammation	GI/L in blood
	Soluble intercellular adhesion molecule 1	sICAM-1	Endothelial Dysfunction	ng/mL In serum
	8 epi prostaglandin F _{2α}	8-epi-PGF _{2α}	Oxidative Stress	pg/mg creat In urine ¹
	11 dehydrothromboxane B ₂	11-DTX-B ₂	Clotting	pg/mg creat In urine ¹
	Carboxyhemoglobin	COHb	Acute Effect	% In blood
	Forced expiratory volume in 1 second	FEV ₁	Airway Impairment	% predicted ²
	Total 4 (methylnitrosamino) 1 (3 pyridyl) 1 butanol	Total NNAL	Genotoxicity	pg/mg creat In urine ¹

Notes: 1) concentration adjusted for creatinine. 2) post bronchiodilator.

were planning to continue to smoke cigarettes, therefore we understood that they would likely go through an adaptation to the new product, which takes time because it is a change to their long existing habits. However, to maximize the harm reduction potential of THS, it is important to minimize (or eliminate) concomitant use of cigarettes with THS. Therefore, to be able to properly interpret the study results, it was important to analyze the eight BoPH as a function of the product(s) that were actually used during the study. Subjects were classified into four categories: THS-use (allowing up to 30% concomitant cigarette use), dual-use, cigarette use, and other use.

The primary objective was to demonstrate favorable changes across the set of eight co-primary BoPH representative of mechanistic pathways involved in the development of smoking-related diseases as listed in Table 1. This approach is based on the principle that favorable changes (similar to cessation) observed across a set of BoPH that are known to be linked to smoking-related disease could provide, in the short term, evidence of risk of harm and an indication of the potential for longer term risk of disease as reported in epidemiological data for smoking cessation. Given that a reduction in disease risk is well established in former smokers (6), with the risk decreasing progressively over time with increasing number of years of smoking cessation and the BoPH evaluated in the ERS are known to be favorably changes upon smoking cessation (7-9).

The study was designed to see that smokers who switch to THS show an improvement in all eight BoPH (improve similarly to smoking cessation) and that the majority (at least five) demonstrate a statistically significant improvement compared to continuing to smoke cigarettes. The BoPH were assessed at the beginning of the study to capture the baseline when everyone was smoking cigarettes and then at 3 and 6 months after switching to THS.

Results

The study results provided evidence that smokers who switch from smoking to THS, have a reduction in exposure to toxicants that directly translate to favorable biological and functional changes over time. All eight of the BoPH shifted in the same direction following the switch to THS as is seen in the literature for smoker following smoking cessation. Further to this, there were favorable changes observed in all of the BoPH following the switch to THS compared to continuing to smoke, and these changes were statistically significant for five of the eight BoPH (i.e., high density lipoprotein cholesterol, white blood cell total count, carboxyhemoglobin, forced expiratory volume in 1 second and total 4 (methylnitrosamino) 1 (3 pyridyl) 1 butanol), as seen in table 1. Thus demonstrating a risk profile that characterizes a reduced risk of harm (10).

Conclusion

This ERS demonstrates that switching from smoking cigarettes to using THS results in favorable changes in a number of BoPH that are indicative of disease pathways leading to smoking-related diseases. In other words, smokers who switch from smoking cigarettes to THS are likely to reduce the risks of harms which has the potential to lead to a reduction in smoking-related diseases than if they continued to smoke cigarettes. The results of this study are coherent and concordant and complement the evidence generated to date on the THS risk profile, with all the studies pointing in the direction of a beneficial effect from switching to THS compared to continuing to smoke cigarettes.

This was the first study to evaluate the effect of the reduction in exposure to toxicants for smokers who switch from cigarette to THS on biological and functional markers over a 6 month period in a large number of smokers.

The study showed that approximately 60% of the smokers who would have otherwise continued to smoke cigarettes when randomized to THS, switched with less than 30% concomitant cigarettes use, which is in line with our experience in markets where THS is commercialized. The total tobacco consumption (cigarette and THS) was comparable to the cigarette consumption at baseline, meaning that smokers were able to replace cigarettes with THS. Exposure to

HPHCs was reduced in smokers who switched to THS (even with up to 30% concomitant use of cigarettes) compared those who continued smoking cigarettes -- though those results have not been discussed in this overview. And this reduction in exposure led to statistically significant favorable changes in BoPH in smokers who switched to THS relative to those who continued smoking cigarettes.

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