Assessing the Impact of Switching to the Tobacco Heating System on Cardiovascular Events: Translating Basic Science Into Clinical Benefit

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Introduction and Objectives

Cigarette Smoke (CS) is causally linked to the development of cardiovascular disease (CVD) through different pathophysiologic pathways, which include endothelial injury and dysfunction, oxidative stress, a proinflammatory status, inflammation, and an abnormal lipid profile, all contributing to the development of atherosclerosis.

Tobacco harm reduction, by virtue of substituting cigarettes with less harmful products, is a complementary approach to current tobacco control strategies for smokers who would otherwise continue to smoke. The Tobacco Heating System (THS) 2.2 is a novel tobacco product that heats tobacco instead of burning it, never allowing the temperature to exceed 350°C, thereby preventing the combustion process from occurring and producing substantially lower levels of toxicants (on average, <80%) than CS. In particular, the levels of eight cardiovascular toxicants (aerolene, benzene, benzanthracene, benzo(k)fluoranthene, hydrogen cyanide, lead, phthalate, and propionaldehyde) are lower by on average >92% in THS aerosol than in CS. Furthermore, THS aerosol does not contain the solid carbon-based nanoparticles (CBNP) that are generated by combustion.

![Figure 1: The THS generates an aerosol that does not contain carbon-based nanoparticles (CBNP).](image)

Philip Morris International's (PMI) assessment program aims to demonstrate that switching to THS has the potential to reduce the risk of smoking-related diseases versus continued smoking. The program includes in vivo toxicology testing methods that follow OECD guidelines, Good Laboratory Practice, a systems toxicology approach, and randomized, controlled clinical studies that follow the principles of Good Clinical Practice.

Methods

Adhesion of Monocytes to Human Coronary Arterial Endothelial Cells (HCAEC), a Critical Stage in Atherosclerosis — THS 2.2 vs CS (In Vitro Adhesion Assay)

In Vivo Study to Investigate Atherosclerotic Plaque of the Aortic Arch

This study examined the development of the hallmarks of CVD in ApoE−/− mice chronically exposed to 3R4F, THS 2.2 aerosol (matched to the nicotine concentration in 3R4F [30 μg/ml], or filtered air for three hours per day, five days per week, for up to eight months (approximately 40% of lifetime). After two months of exposure to 3R4F, mice were switched to THS 2.2 aerosol (switching), filtered air (cessation), or continued exposure to 3R4F. The exposure dose corresponded to ~30 cigarettes per day in human comparison.

![Figure 2: Groups and exposures.](image)

Variance analyses (ANOVA) were used to determine significant differences between the groups. The significance level was set at p < 0.05. The data are presented as mean ± standard error (SEM) of the mean.

Results

In Vitro Model: Adhesion Assay

![Figure 3: Effects of THS 2.2 and 3R4F aerosol extracts on the adhesion of MM6 cells to HCAECs following indirect, direct, and fresh direct treatments of HCAECs.](image)

A randomized, controlled, two-arm parallel group, multicenter U.S. study was conducted over six months in adult smokers who switched from cigarettes to THS 2.2, compared with those who continued to smoke cigarettes, to demonstrate favorable changes in THS 2.2 users (>70%) in eight co-primary endpoints representative of pathomechanistic pathways leading to atherosclerosis (e.g., inflammation, lipid metabolism, endothelial function, platelet function, and oxidative stress). 984 subjects were randomized to continued cigarette smoking (n=496) or THS 2.2 (n=488).

Conclusions and Discussion

The results of the THS 2.2 assessment program demonstrate that:

- THS 2.2 aerosol contains no CBNPs. Additionally, the levels of cardiovascular toxicants are reduced by on average >92%.
- Adhesion of mononuclear cells to HCAECs in vitro is significantly lower following THS 2.2 treatment than after exposure to 3R4F CS.
- Switching to THS 2.2 halted the progression of CS-induced atherosclerotic changes in vivo.

In humans, all co-primary endpoints representative of different pathophysiological pathways leading to atherosclerosis shifted favorably, in the same direction as the smoking cessation effect reported in the literature, after 6 months of switching from cigarettes to THS 2.2.

PMI has completed 18 non-clinical and 10 clinical studies, including those presented here. The evidence available to date indicates that switching to THS presents less risk of harm and has the potential to reduce the risk of smoking-related diseases, such as CVD.

As a next step, PMI will complement its THS assessment program with cardiovascular outcome studies intended to demonstrate the clinical benefits of switching to THS (e.g., reduction in the risk of cardiovascular death, myocardial infarction, and stroke) over continued smoking.

References


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