Background
Cigarette smoking is causally linked to the development of cardiovascular disease (CVD). Cigarette smoke (CS) contains 54 chemicals categorized as harmful and potentially hazardous constituents (HPHCs) by the U.S. Food and Drug Administration. Twelve HPHCs have been identified as cardiotoxic: the HPHCs, inorganic arsenic, and carbon-nanotube nanoparticles (cbNPs) contained in CS are mediators of endothelial dysfunction and other pathophysiological changes underlying atherosclerosis and CVD. To reduce the risk of CS and other smoking-related diseases, Philip Morris International has developed the Tobacco Heating System (THS) 2.2, which heats a tobacco plug in a controlled manner, reduces combustion, and reduces exposure to CS, preventing the combustion process from taking place, thereby generating an aerosol containing no cbNPs and significantly reduced levels of HPHCs (cardiotoxic tobacco tar is reduced by ~50% in THS 2.2 aerosol vs. CS).

Our assessment program aims to demonstrate that switching to THS 2.2 has the potential to reduce the risk of smoking-related diseases vs. continued smoking. This program includes toxicology tests that follow Organization for Economic Co-operation and Development guidelines, Good Laboratory Practice, a systems toxicology approach, and randomized, controlled clinical studies following Good Clinical Practice.

PMI has completed 17 non-clinical studies and 9 clinical studies, including the studies presented here. The totality of evidence available to date, from non-clinical and clinical studies, indicates that switching to THS 2.2 has the potential to reduce the risk of smoking-related diseases vs. continued smoking.

Methods

Clinical Study — Clinical Risk Endpoints in THS Switchers
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 CS, to demonstrate favorable changes in THS 2.2 users (~70%) in eight co-primary endpoints representative of pathogenic pathways (e.g., of inflammation, lip metabolism, endothelial function, platelet function, and oxidative stress involved in CVD). 984 subjects were randomized to CC (n = 492) or THS 2.2 (n = 492) for the six-month study period.

Adhesion of Monocytes to Human Coronary Arterial Endothelial Cells (HCAEC), a Critical Stage in Atherosclerosis.Thys et al. [13] showed that switching to THS 2.2 aerosol, compared with conventional cigarettes, halts the progression of CS-induced atherosclerotic changes. THS 2.2 aerosol had minimal adverse effects in the ApoE-/- mouse study.

In Vivo Study to Investigate Atherosclerotic Plaque in the Aortic Arch
This study examined the development of the hallmarks of CVD in ApoE-/- mice chronically exposed to THS 2.2 aerosol (matched to the nicotine concentration in THS 2.2, 2.2 mg nicotine/mL), or filtered air (n = 7 per group). At the end of the study, mice were sacrificed, and THS 2.2 exposure dose corresponded to ~30 cigarettes per day in THS 2.2 aerosol (switching), filtered air (cessation), or continued smoking (control group). This study examined the development of the hallmarks of CVD in ApoE-/- mice chronically exposed to THS 2.2 aerosol (matched to the nicotine concentration in THS 2.2, 2.2 mg nicotine/mL), or filtered air (n = 7 per group). At the end of the study, mice were sacrificed, and THS 2.2 exposure dose corresponded to ~30 cigarettes per day in THS 2.2 aerosol (switching), filtered air (cessation), or continued smoking (control group).

In Vivo Model: Atherosclerotic Plaque in the Aortic Arch Data from µCT at Month 7

Clinical Study — Changes in Clinical Risk Endpoints

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

Results

Conclusions

References
4. Aorta plaque volume (mm3); Aorta plaque surface area (mm2); Aorta mean occlusion (%).