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Assessment Approach and Results from a 3 Month Reduced Exposure Study in Japan of the Tobacco Heating System (THS2.2), a Philip Morris International Candidate Reduced Risk Product (RRP)

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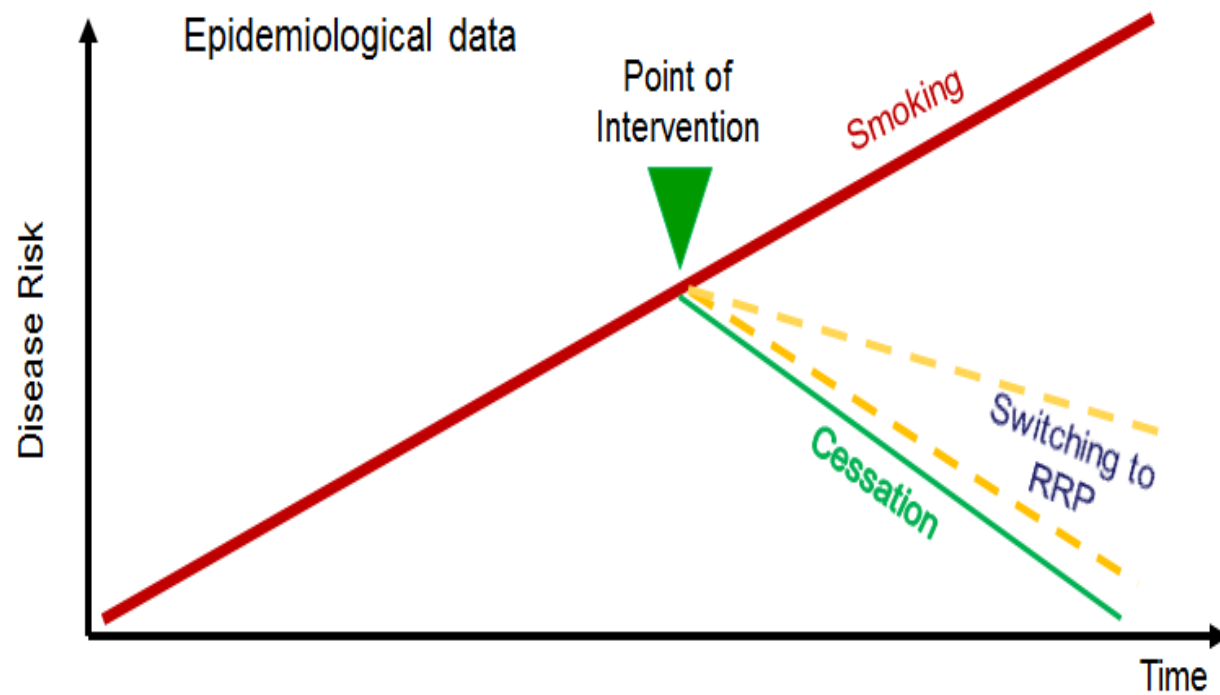
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Reduced-Risk Products (“RRPs”) is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. PMI’s RRP’s are **in various stages of development and commercialization**, and we are conducting **extensive and rigorous scientific studies** to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when **compared to smoking cigarettes**.

Before making any such claims, we will **rigorously evaluate the full set of data** from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims **may also be subject to government review and authorization** as is the case in the US today.

Comparison with Continued Smoking and Smoking Cessation

Based on epidemiological evidence it is abundantly clear and quantified, that cigarette smoking causes serious chronic diseases and premature death and cessation is the least risky alternative.



To date, there is a gap of epidemiological evidence concerning the impact of our RRP with regard to the health risks of conventional cigarette (CC) smokers who choose switching to RRP compared to CC smoking and smoking cessation.

The U.S. Institute of Medicine (“IOM”), called smoking cessation the “*gold standard*” for the assessment of an RRP, providing “*an aspirational goal for risk and exposure.*”

PMI's Reduced Risk Product Portfolio

Heated Tobacco Products



P1 - THS

- Heated tobacco
- Main unit & holder
- Specially designed tobacco product

Commercialized



P2

- Heated tobacco
- No device
- Closest to the conventional cigarette

Product development
ongoing

Nicotine Containing Products



P3

- Technology acquired from the Nicorette (NRT patch) inventors
- Chemical reaction of a weak acid with nicotine



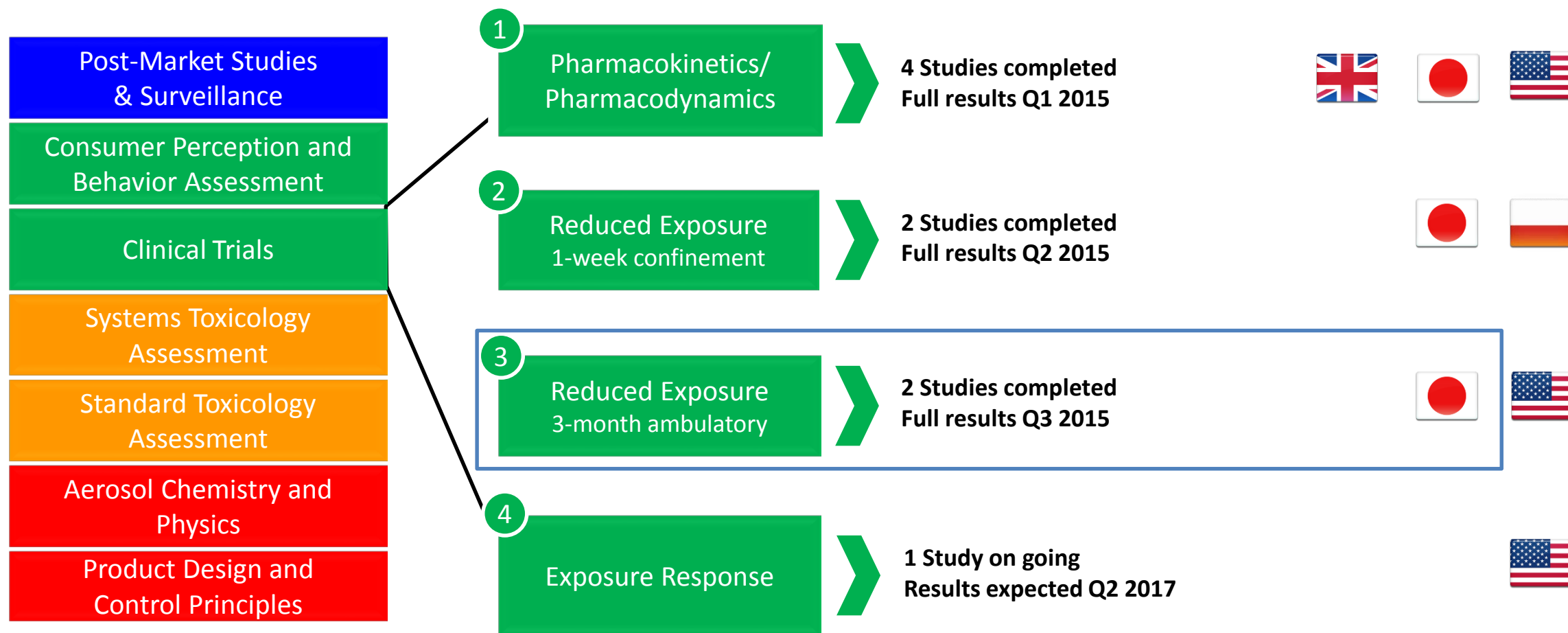
P4

- e-Cigarette
- Differentiation through design features, quality and brand building

Commercialized

The RRP's depicted are subject to ongoing development and therefore the descriptions are illustrative and do not necessarily represent the latest stages of product development.

Clinical Assessment Program





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Heat-not-Burn

THS-Specific Science and Results to Date





Study Title and Primary Objective

Study Title:

- A randomized, controlled, open-label, 3-arm parallel group, multi center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the THS or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting.

Primary Objective:

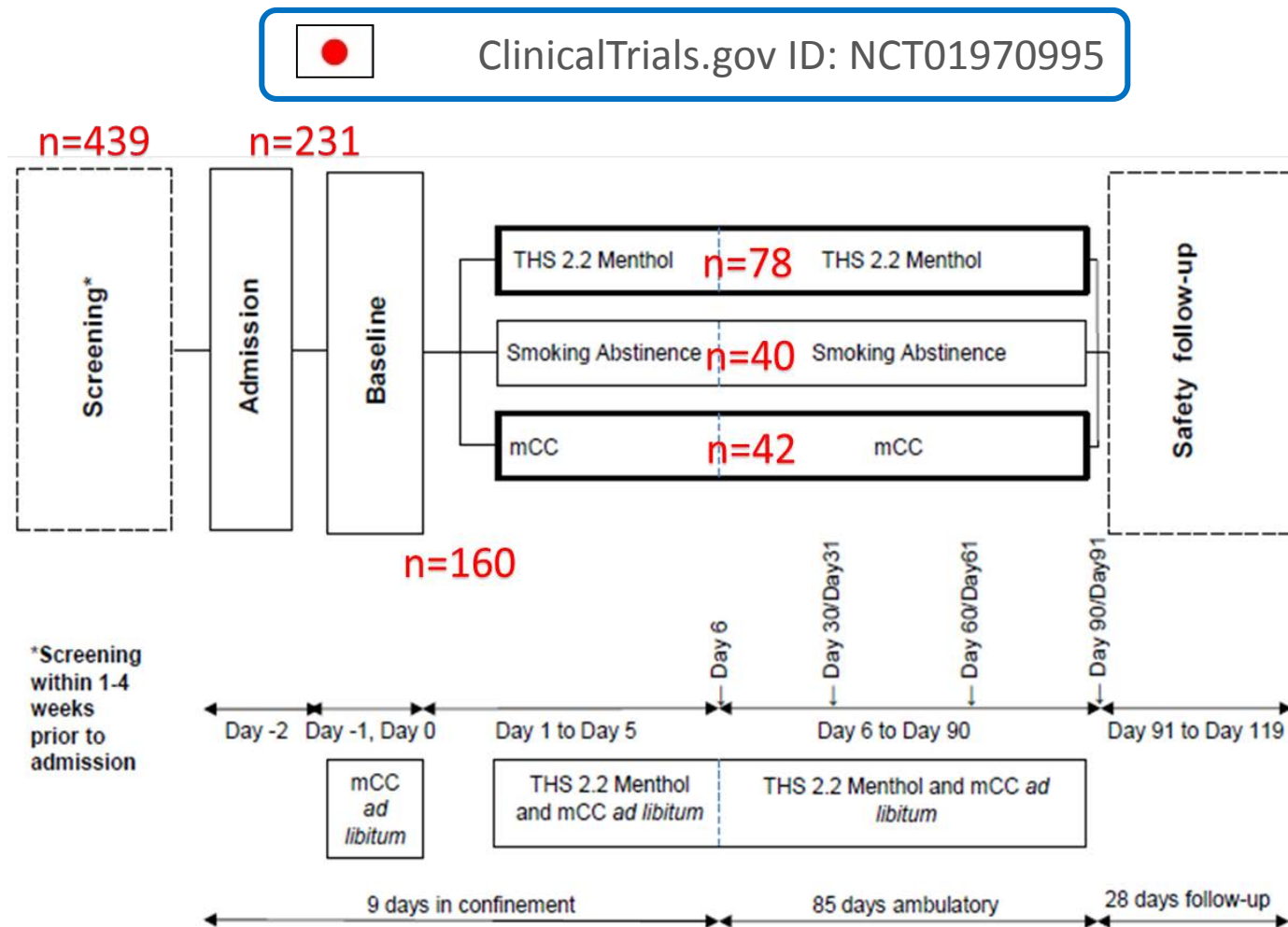
- To demonstrate the reduction of biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) in smokers switching from CC to THS compared to smokers continuing to smoke CC.



THREE-MONTH REDUCED EXPOSURE STUDY



Study Design and Disposition



2 Sites in Tokyo:

- Tokyo Heart Center (TOK)
- Seishukai Clinic (SEI)

First subject screened:

01 August 2013

Last subject last visit:

02 July 2014

Abbreviations: mCC = Menthol conventional cigarette(s); THS = Tobacco Heating System; Figure not to scale.



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Reduced Exposure

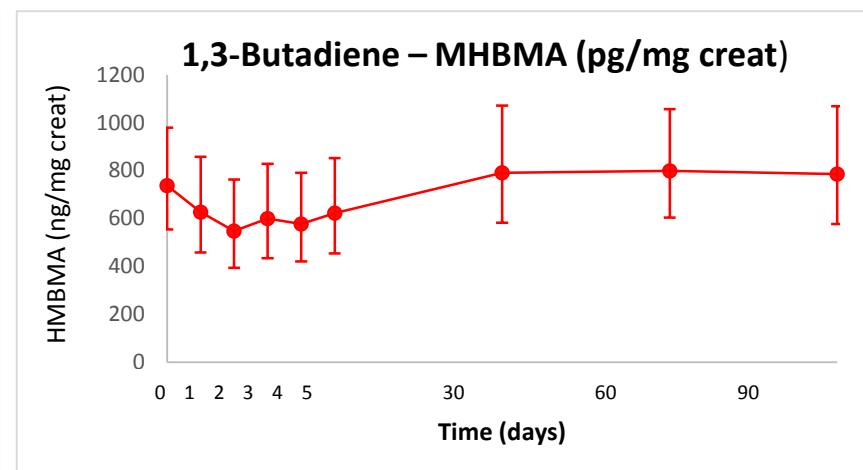
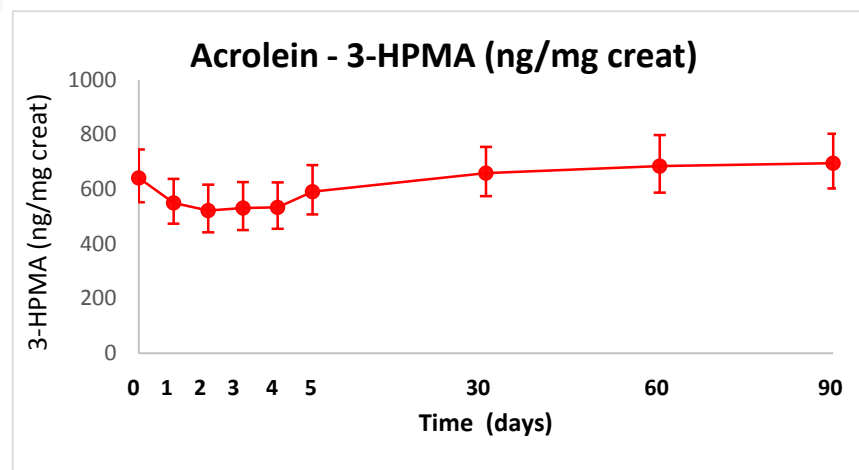
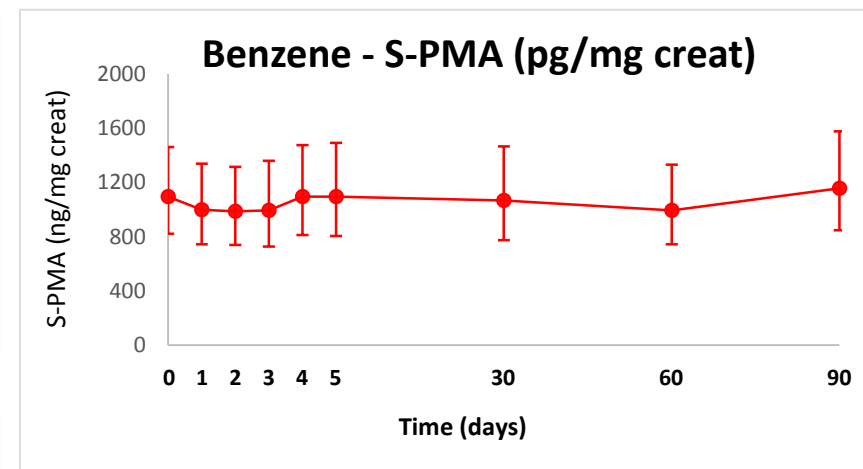
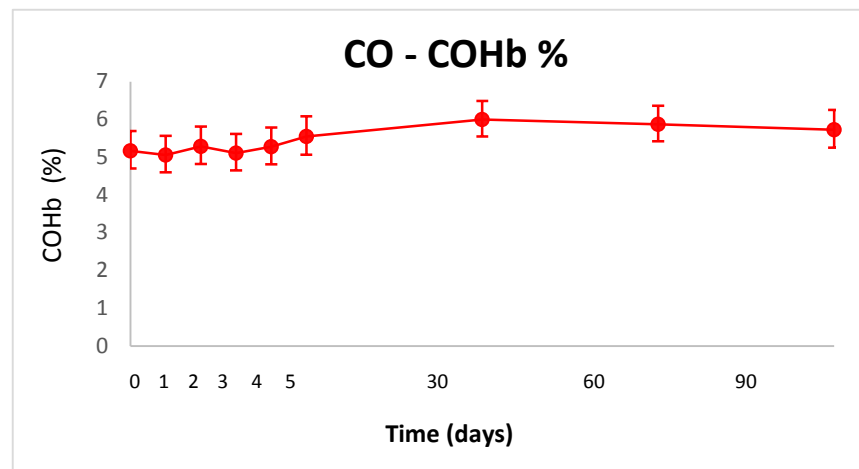
Clinical
Assessment

Adult smokers
used the products
ad libitum

Adult smokers
randomized to
cigarettes or THS
were free to use the
product as often as
they wished, in
confinement
(5 days) and then
ambulatory
(85 days)



—●— Combustible Cigarette





Reduced Exposure

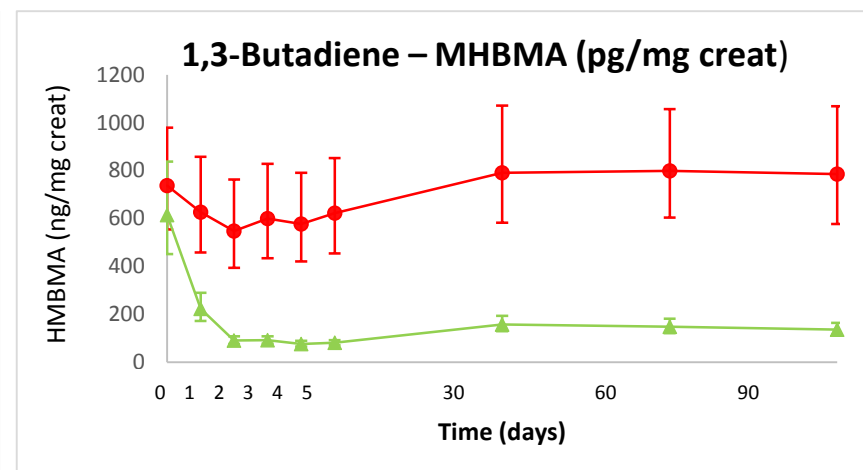
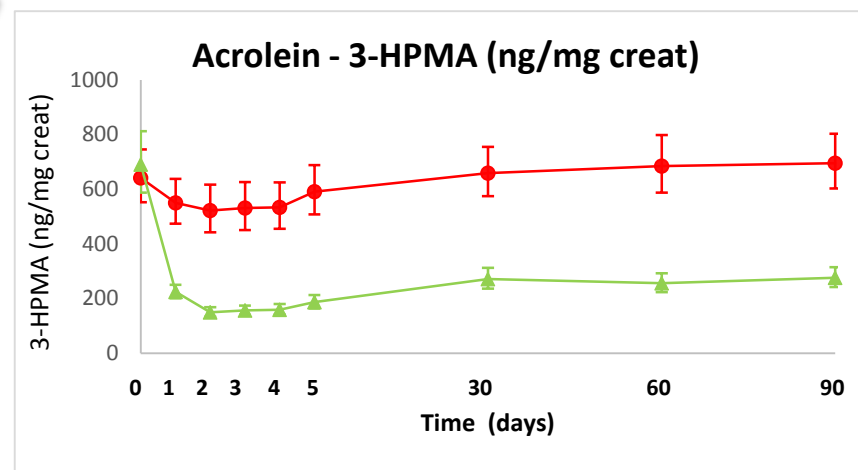
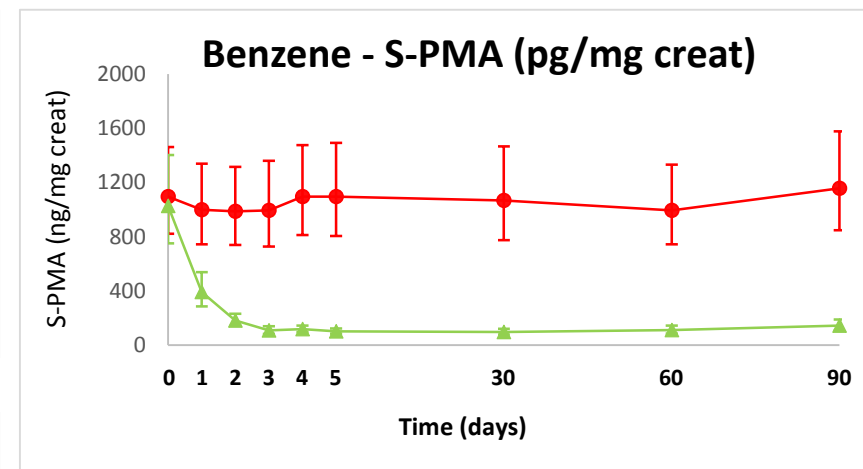
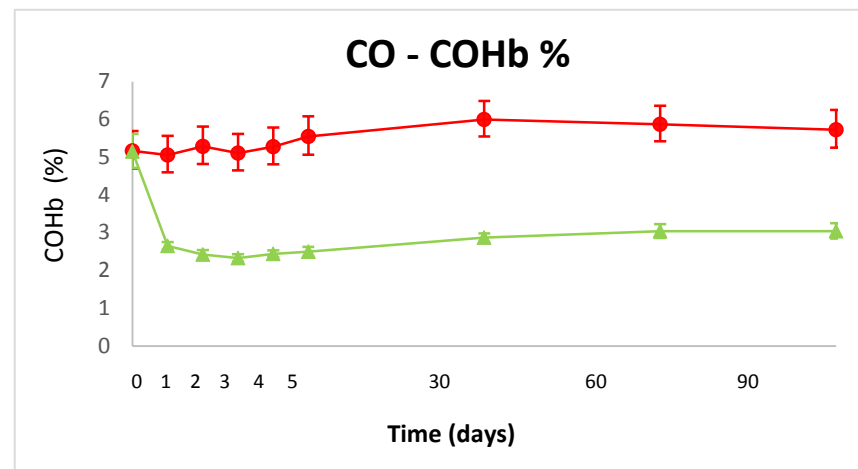
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—●— Combustible Cigarette —▲— Cessation



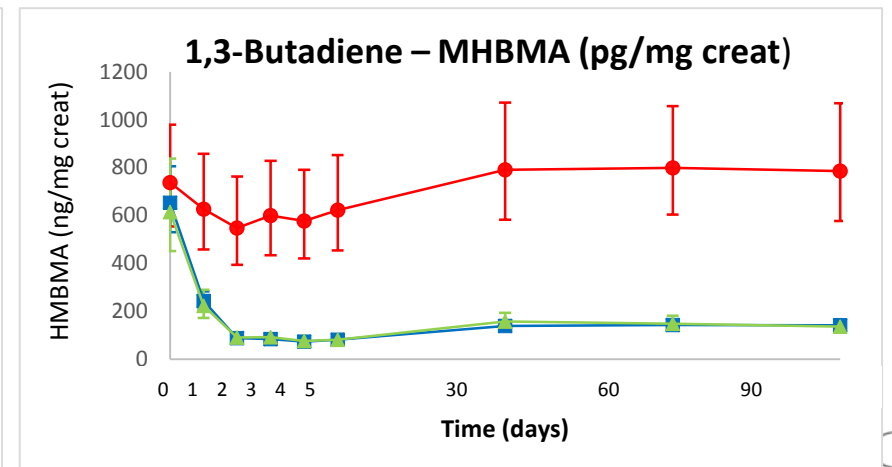
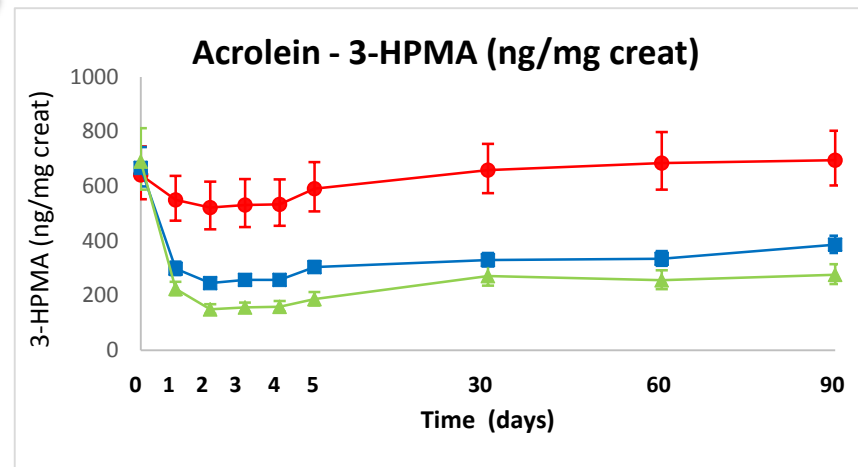
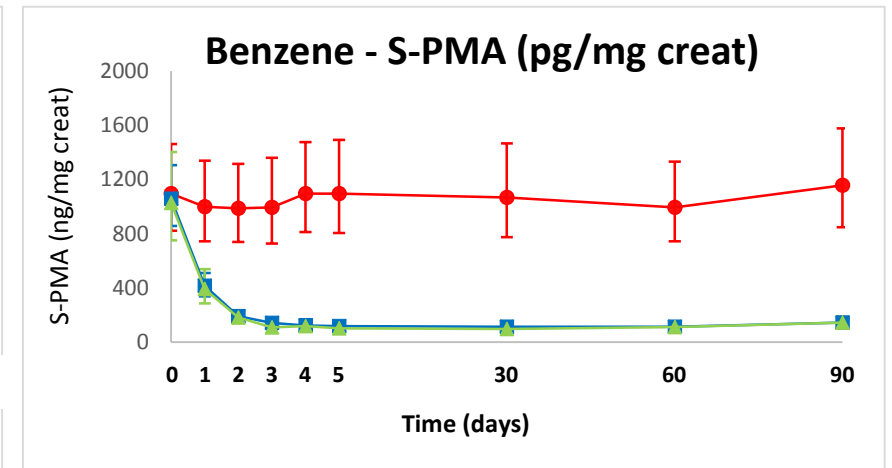
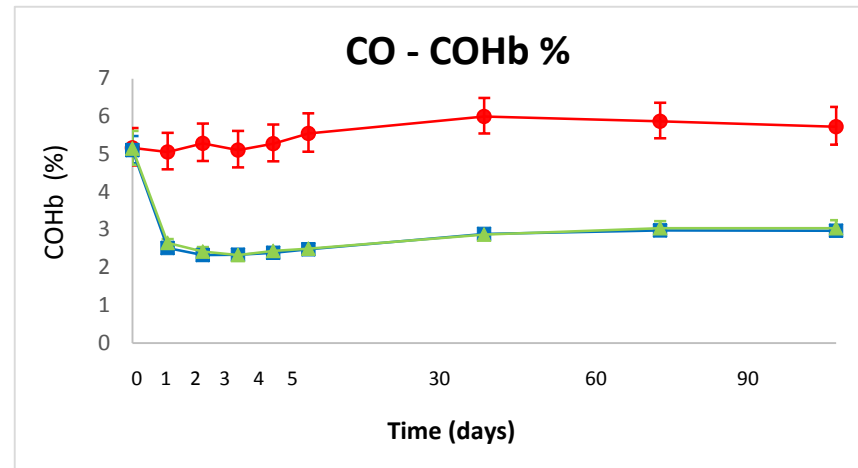
Reduced Exposure

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—■— THS —●— Combustible Cigarette —▲— Cessation

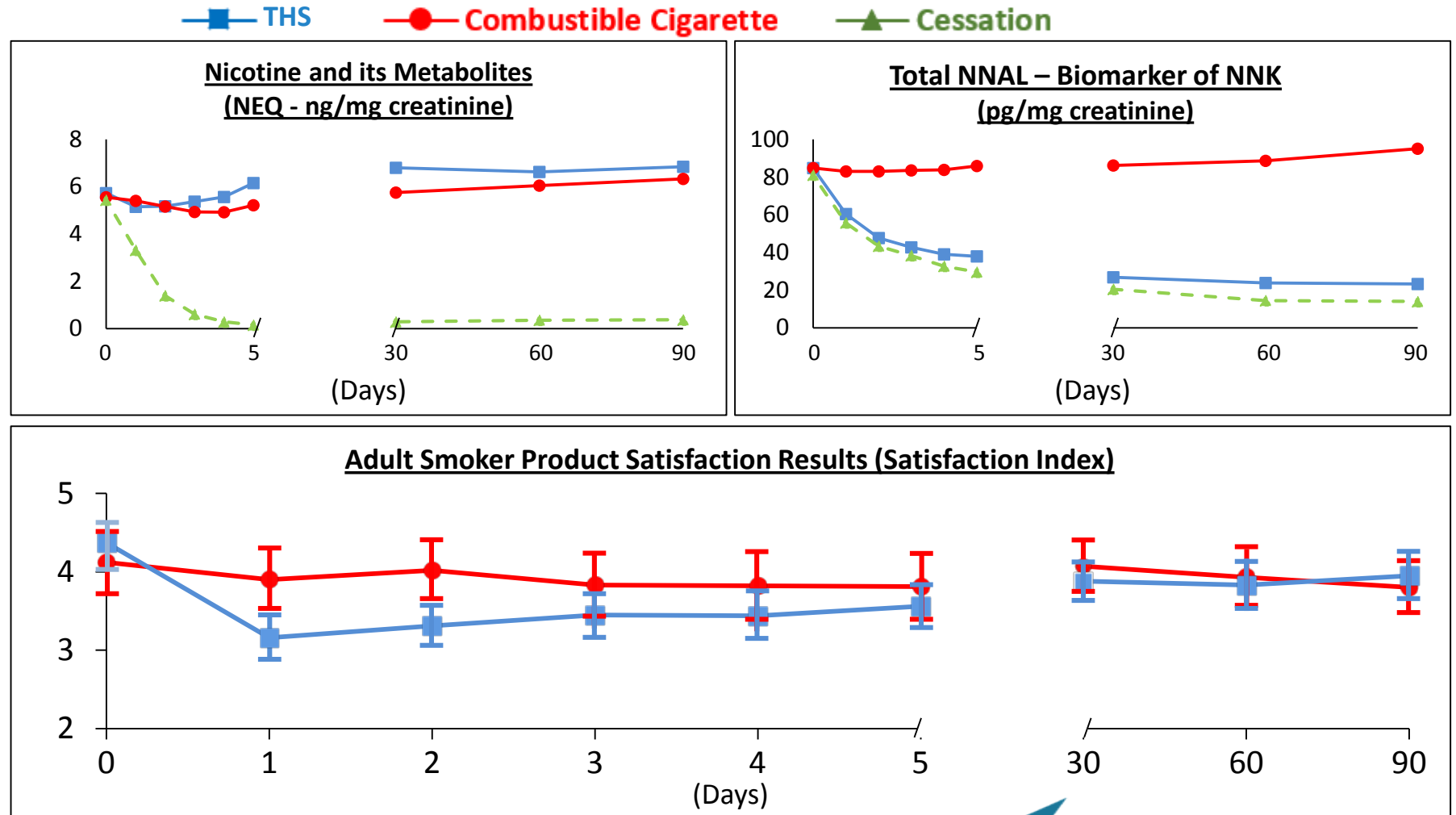


Reduced Exposure

Clinical Assessment

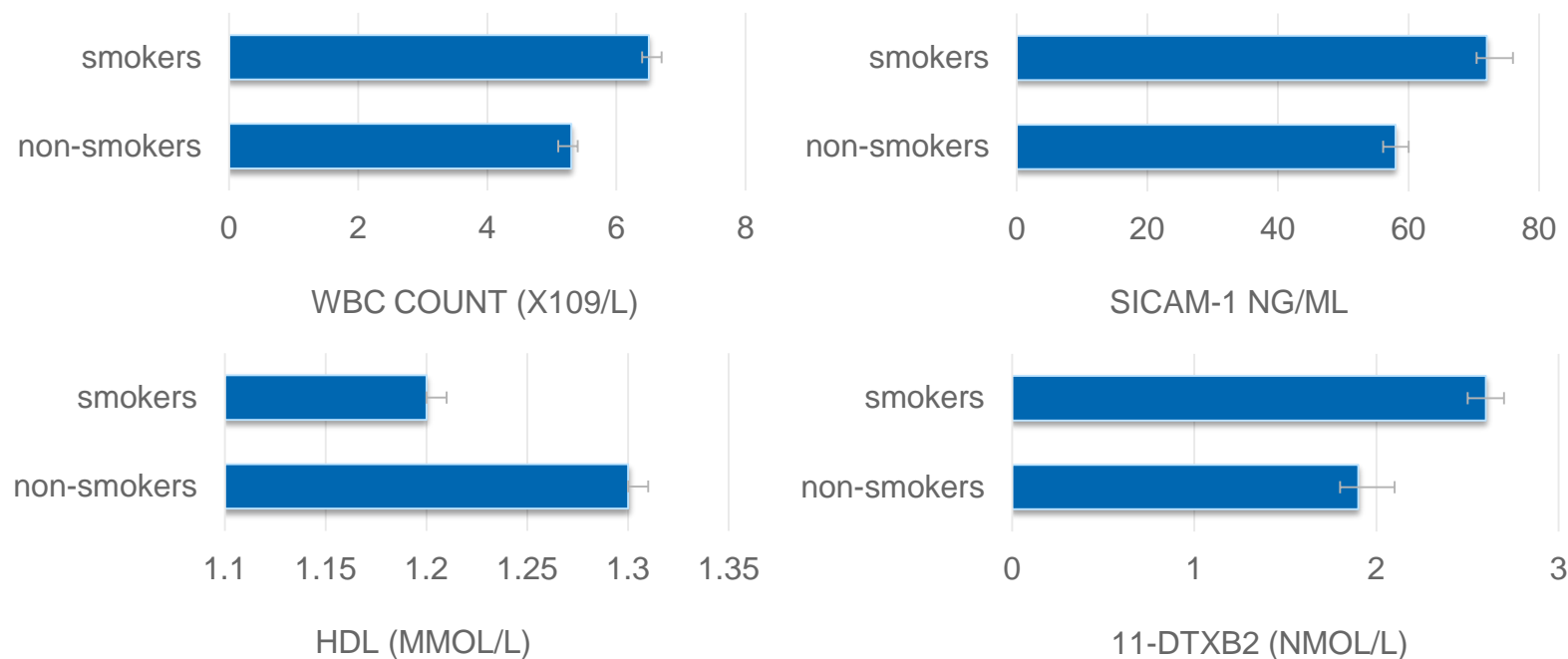
Adult smokers used the products *ad libitum*

Adult smokers randomized to cigarettes or THS were free to use the product as often as they wished, in confinement (5 days) and then ambulatory (85 days)



Biomarkers Related to Cardiovascular Disease

Differences in Biomarkers Related to Cardiovascular Disease between Japanese Smokers and Non-Smokers



Lüdicke et al.: A Japanese Cross-sectional Multicentre Study of Biomarkers Associated with Cardiovascular Disease in Smokers and Non-smokers. Submitted for publication.

Multicentric cross-sectional study conducted in 2007 in six Japanese cities in N=1026 smokers and non-smokers (both sexes)

Clinical Studies Demonstrate Favorable Changes in Smoker's Health Profile

Clinical Assessment

Disease Mechanisms	Expected Change	Effect of Cessation	Effect of Switching to THS	Direction of Change
Lipid Metabolism (HDL-C)	Increase	6.4 mg/dL ↑	4.5 mg/dL ↑	Same direction as cessation
Inflammation (WBC)	Decrease	-0.40 10 ⁹ /L ↓	-0.57 10 ⁹ /L ↓	Same direction as cessation
Endothelial Dysfunction (sICAM-1)	Decrease	10.9 % ↓	8.7 % ↓	Same direction as cessation
Oxidative Stress (8-epi-PGF2α)	Decrease	5.9 % ↓	12.7 % ↓	Same direction as cessation
Clotting (11-DTX-B2)	Decrease	19.4 % ↓	9.0 % ↓	Same direction as cessation
Lung Function (FEV1)	Increase	1.9 %Pred ↑	1.9 %Pred ↑	Same direction as cessation

These studies measured the levels of 6 clinical risk endpoints.

Measurements of these markers in smokers who switched to THS showed that the majority of beneficial effects that were seen in the smoking cessation arm were preserved.

Note: These data alone do not represent a claim of reduced risk.
Source: PMI R&Dt; Clinicaltrials.gov: NCT 01970995



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Source: Philip Morris International R&D

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