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CARDIOVASCULAR EFFECTS OF THE TOBACCO HEATING SYSTEM (THS) COMPARED WITH CONTINUED SMOKING

Fribourg, Switzerland

Dr. Patrick Picavet, M.D., on behalf of:
Baker, Gizelle; Haziza, Christelle; Hoeng, Julia; Ivanov, Nikolai; Luedicke, Frank; Maeder, Serge; Peitsch, Manuel; Phillips, Blaine; Poussin, Carine; Vanscheeuwijck, Patrick

Philip Morris International
XX March 2019

Creating a New Category: Reduced-Risk Products

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Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

We have a range of RRPs in various stages of development, scientific assessment, and commercialization.

Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

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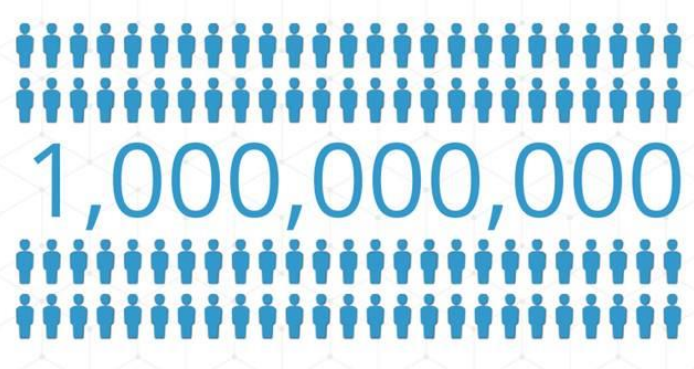
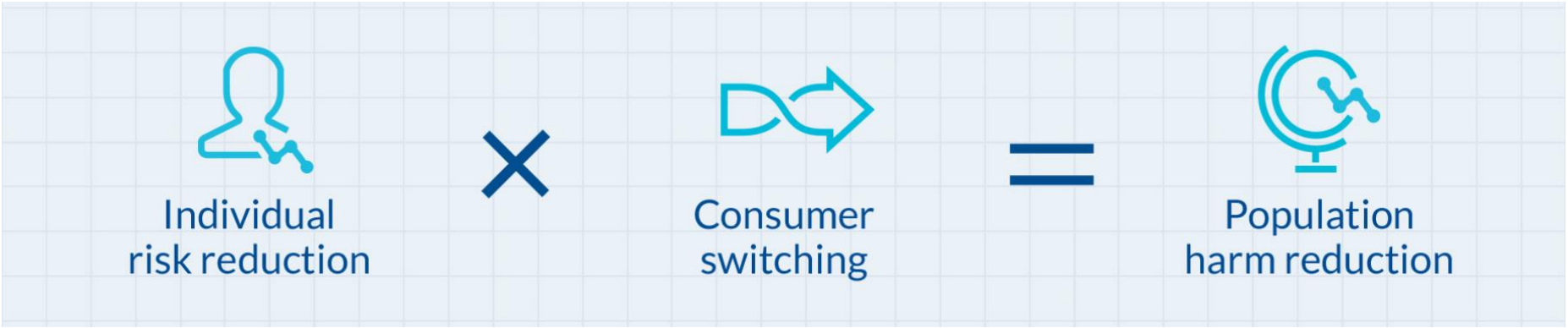
Tobacco Harm Reduction

What Is the Objective of Harm Reduction?

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies





Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products they can fully switched to, should they decide not to quit.

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking.

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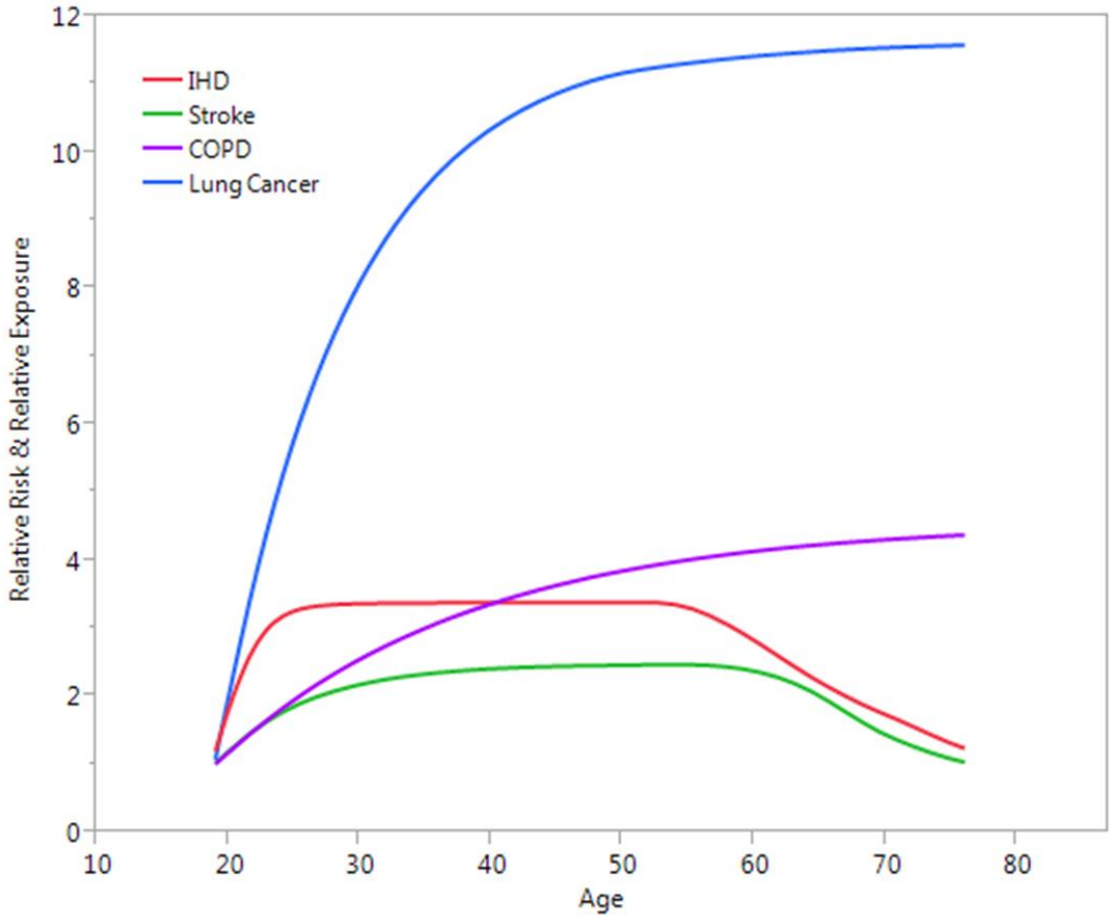
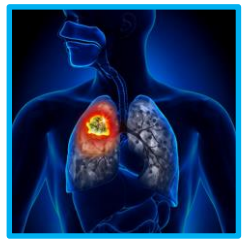
Excess Risk of Smoking-Related Disease

Disease-Specific Relative Risk [1] (by age) *Relative risk of IHD, Stroke, COPD, and LC for an adult cigarette smoker*





Source: Relative risk: Lung Cancer (Lee 2012), COPD (Forey 2011), IHD and Stroke (Lee 2016)

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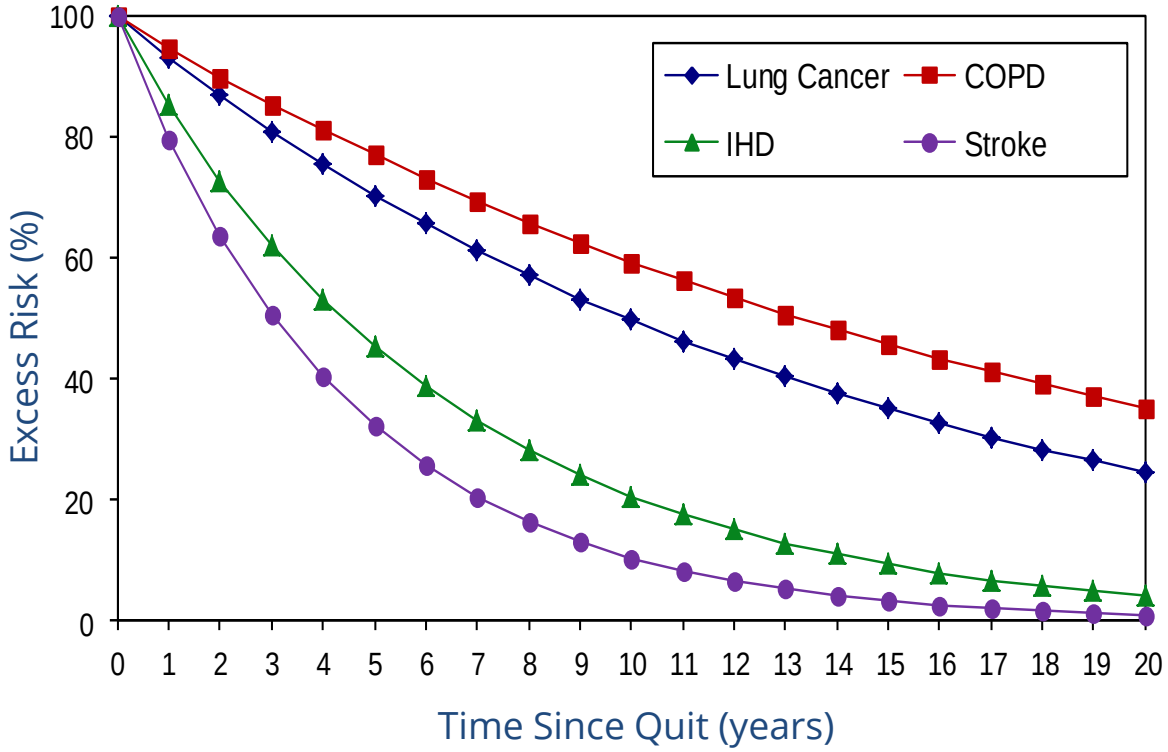
Excess Risk of Smoking-Related Disease

Reduction in Excess Risk Over Time



Disease Risk Half-Life (The time at which half of the Excess risk associated with cigarette smoking has disappeared)				
Age (*a*)	Lung Cancer	IHD	Stroke	COPD
Any age	-	-	4.78	13.32
to 49	6.98	1.47	-	-
50 to 59	10.39	5.22	-	-
60 to 69	10.60	7.48	-	-
70 to 79	12.99	13.77	-	-

[1] Sources for relative risk: Lung Cancer (Lee 2012), COPD (Forey 2011), IHD and Stroke (Lee 2016)
[2] Sources for half-life of risk: Lung Cancer (Fry 2013), COPD (Lee 2014), IHD (Lee 2012), Stroke (Lee 2014)

Source: Half-life of risk: Lung Cancer (Fry 2013), COPD (Lee 2014), IHD (Lee 2012), Stroke (Lee 2014)

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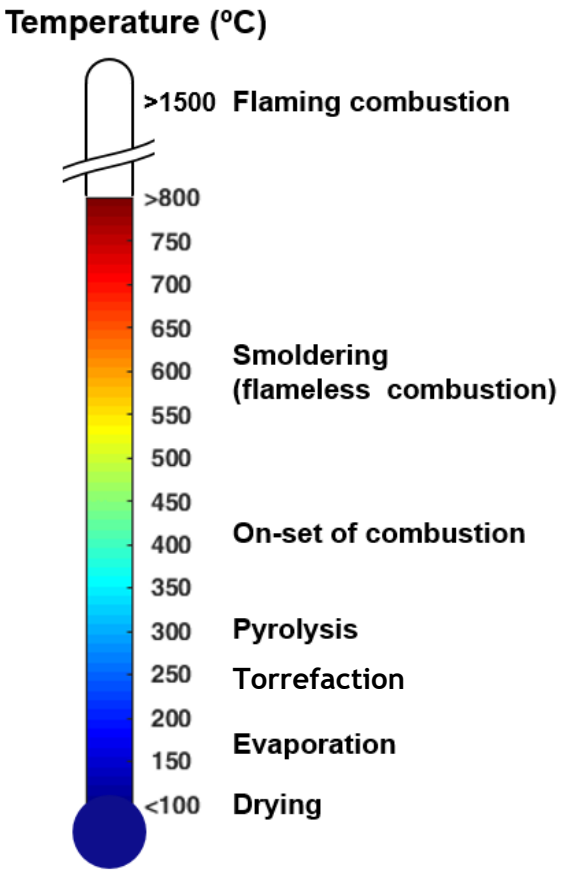
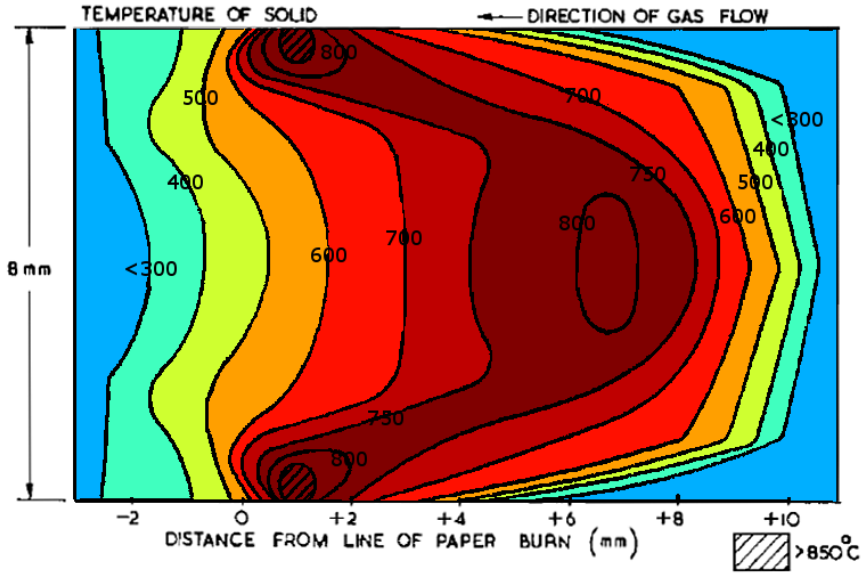
Combustion

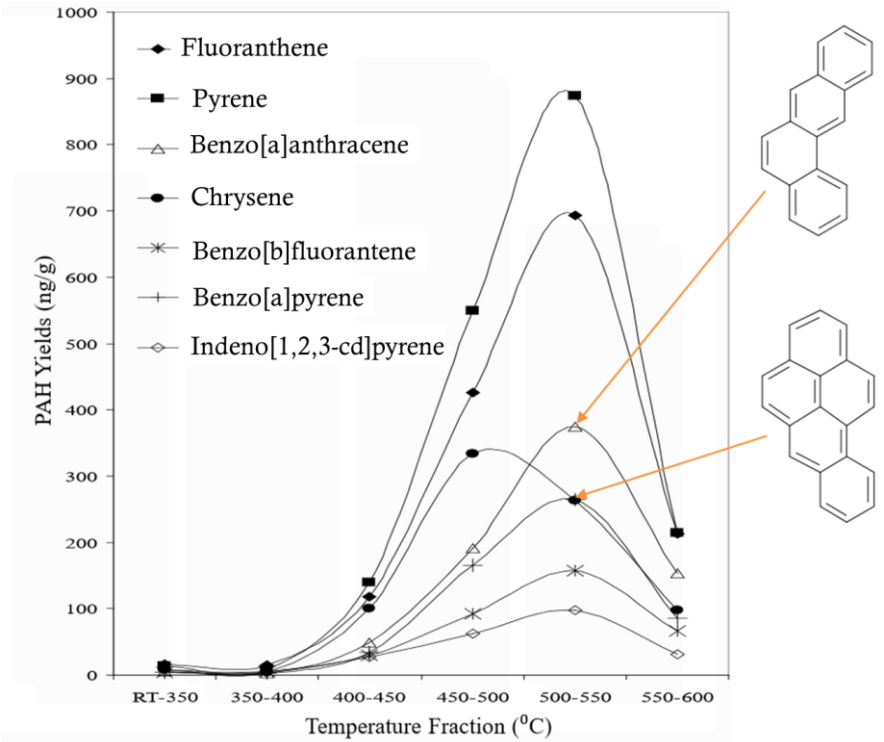
Elimination of Combustion Is Key

Scientific studies have shown that as the temperature of tobacco increases, the levels of harmful chemicals formed increases





Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.



Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

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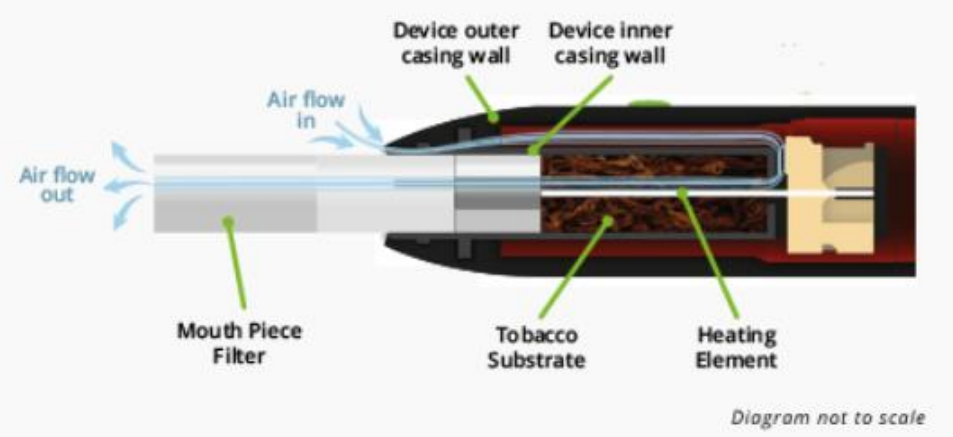
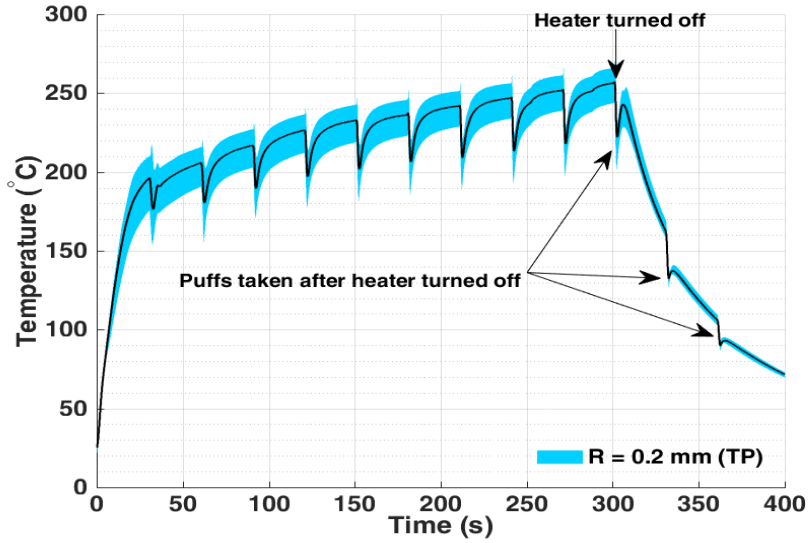
The Tobacco Heating System 2.2

Why Heat Tobacco Rather than Burn It?

The Tobacco Heating System (THS) is designed and has been demonstrated to:

- Heat tobacco without combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile, and ritual characteristics of cigarettes





Source: PMI Research and Development

R = Radial distance from heater

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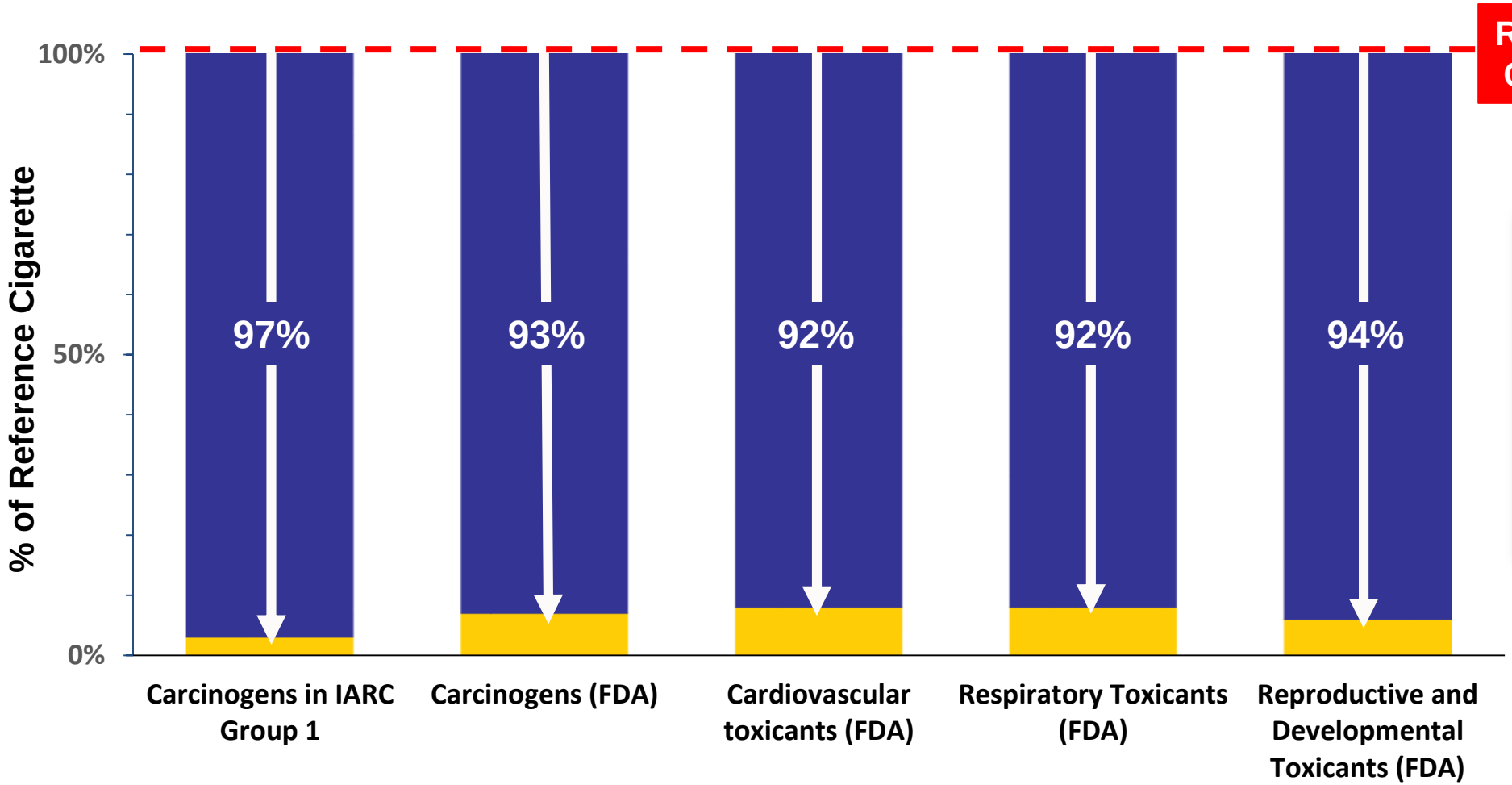
Exposure Reduction and Carbon-Based Nanoparticles

Reduced Formation of HPHCs by Disease Categories



No. of toxicants	12	29	8	18	7

THS 2.2 produces an aerosol that contains **on average 90-95% lower levels of harmful and potentially harmful chemicals than a reference cigarette**

Notes:
THS stands for Tobacco Heating System version 2.2
Intense Health Canada's Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

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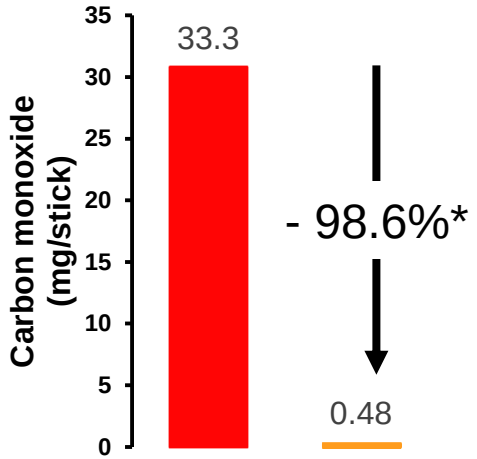
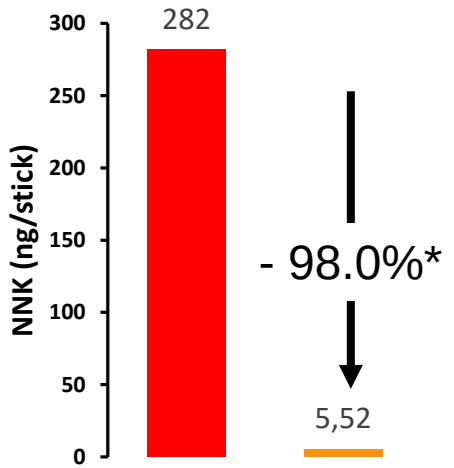
Changes in Exposure to HPHCs

Reduced Exposure in Healthy Human Subjects

Levels of HPHCs are Drastically Reduced in THS Aerosol





Leads to

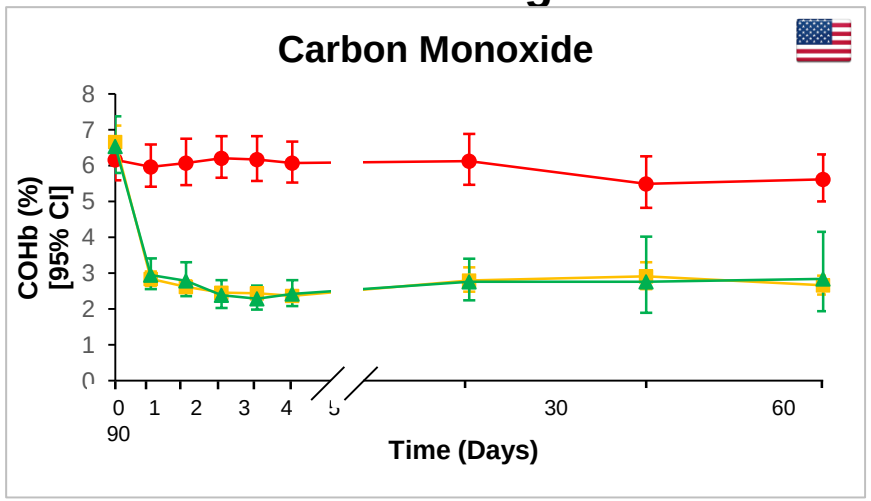
Leads to

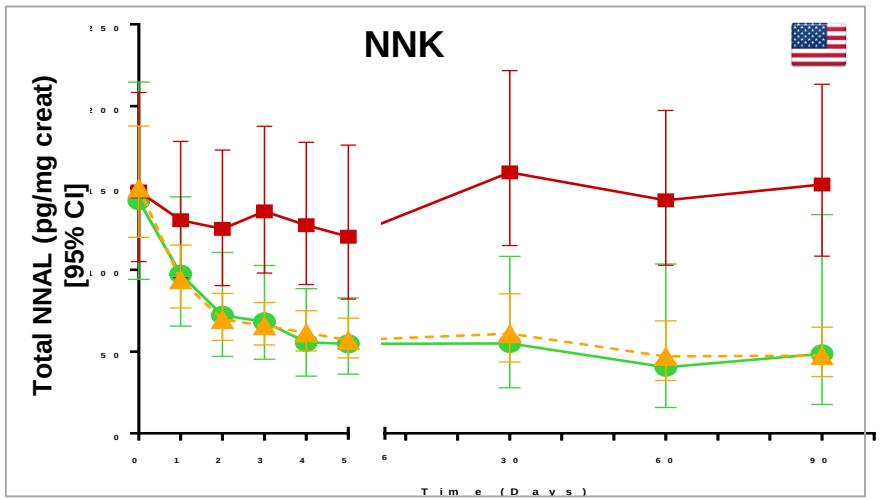
Cigarette

THS

Smoking Abstinence

Exposure is Significantly Reduced After Switching to THS



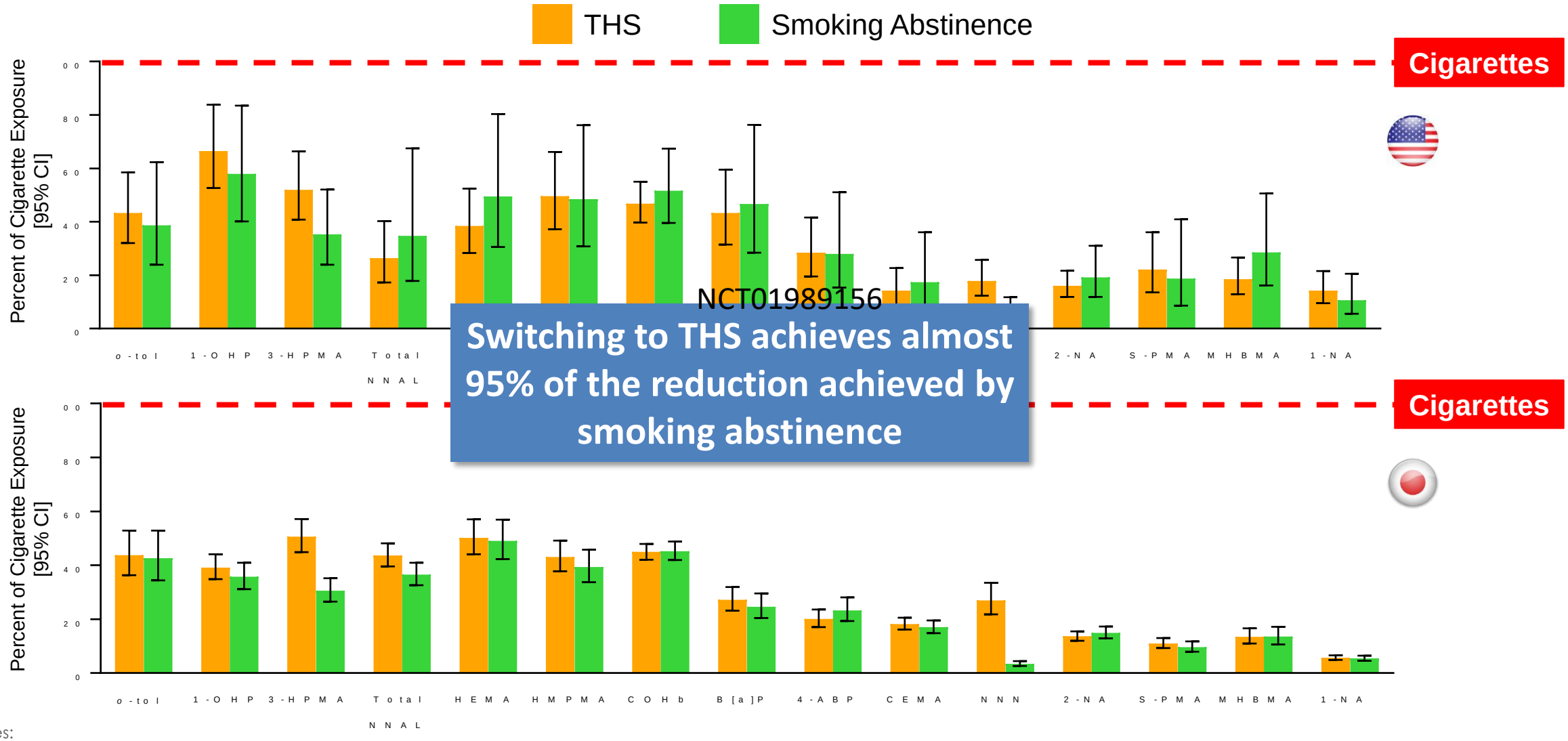


Notes:
* On equivalent nicotine basis. THS stands for Tobacco Heating System Version 2.2
Source: PMI Research and Development;

Registered on clinicaltrials.gov: NCT01989156

Reduced Exposure Similar to Smoking Abstinence

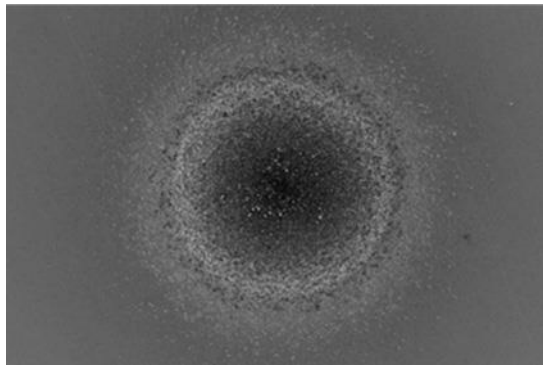
Reduced Exposure in Healthy Human Subjects



Notes:
THS stands for Tobacco Heating System version 2.2
Source: PMI Research and Development

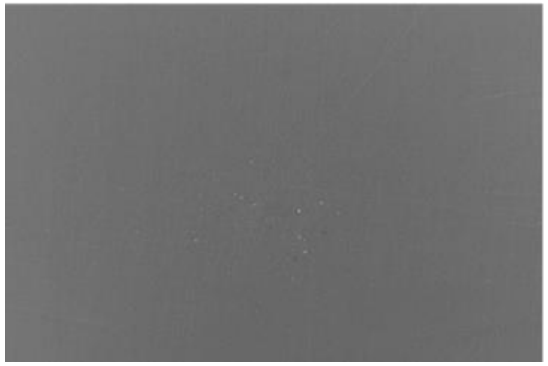
Registered on clinicaltrials.gov: NCT01989156 and NCT01970995

Reduced Formation of HPHCs by Disease Categories

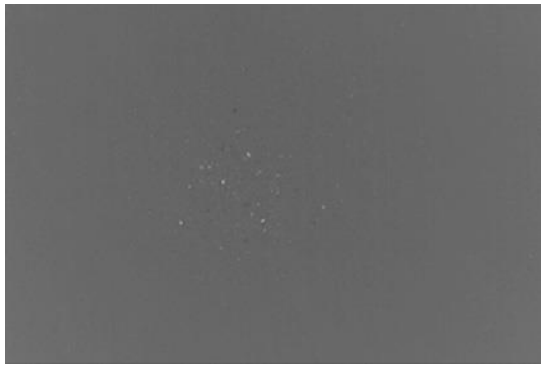


Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm
Amount: $6x10^{11}$ particles ~= 0.7 mg*



Blank (Air)



THS aerosol

No solid particles

Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300º C to remove the volatile portion / collected material characterized by Electron Diffusive X-ray.

* Under the Health Canada's Intense Smoking Regime.

Pratte et al. Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. *Hum. Exp. Toxicol*, 2017; 36:1115-1120

Cohen et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; 1907-1918.

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In Vitro Models of Disease

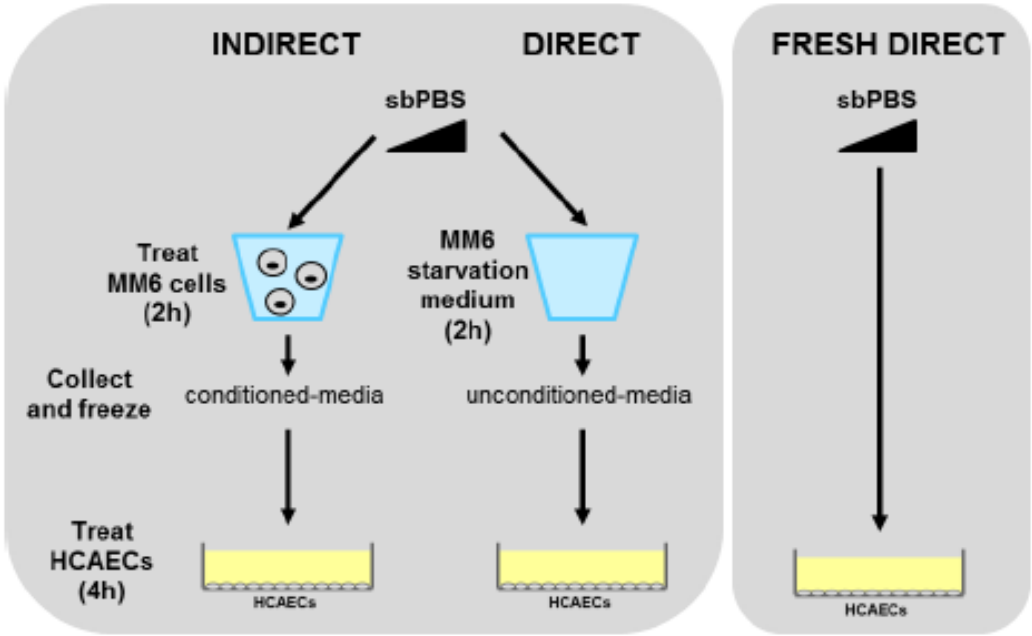
From Risk Assessment Framework to *In Vitro* Study Design

In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells

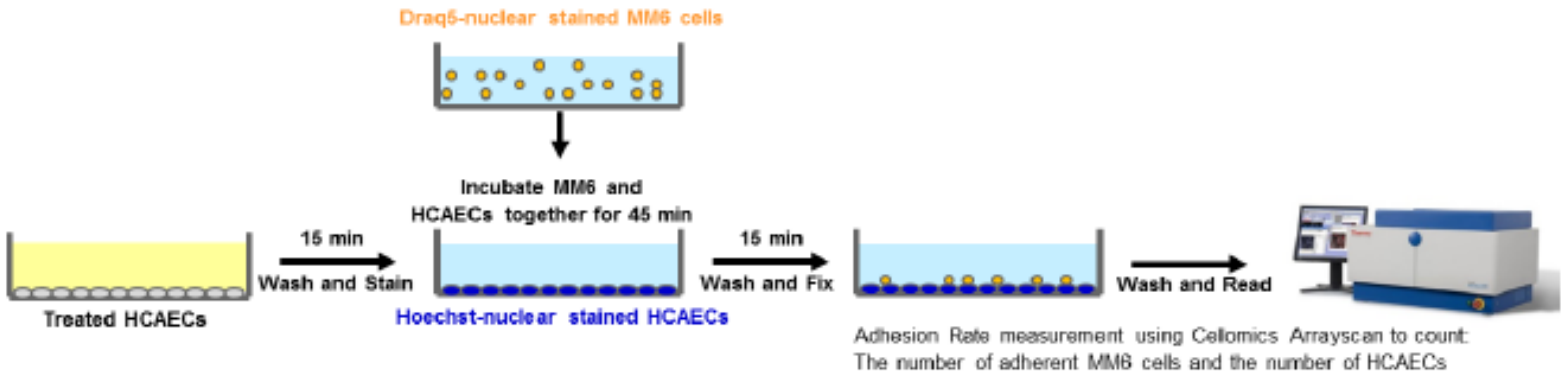
1. **Cell exposure to 3R4F or THS 2.2 (aqueous smoke / aerosol extract)**

2. **Treatment of human coronary arterial endothelial cells (HCAEC)**

3. **Adhesion Assay**
   - Untreated MM6 cells and 4h-treated HCAECs were nuclear-stained for 15 min. and then incubated together for 45 min
   - After cell fixing and washing, remaining adherent MM6 cells and HCAECs were counted
   - The adhesion rate was calculated



- **Adhesion assay (functional endpoint)**
- **Transcriptomics (molecular endpoints)**



Note: THS stands for Tobacco Heating System version 2.2

Source: Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. Toxicology 2016; 73–86.

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From Risk Assessment Framework to *In Vitro* Study Design

In vitro model: Adhesion of monocytic cells to human coronary arterial endothelial cells

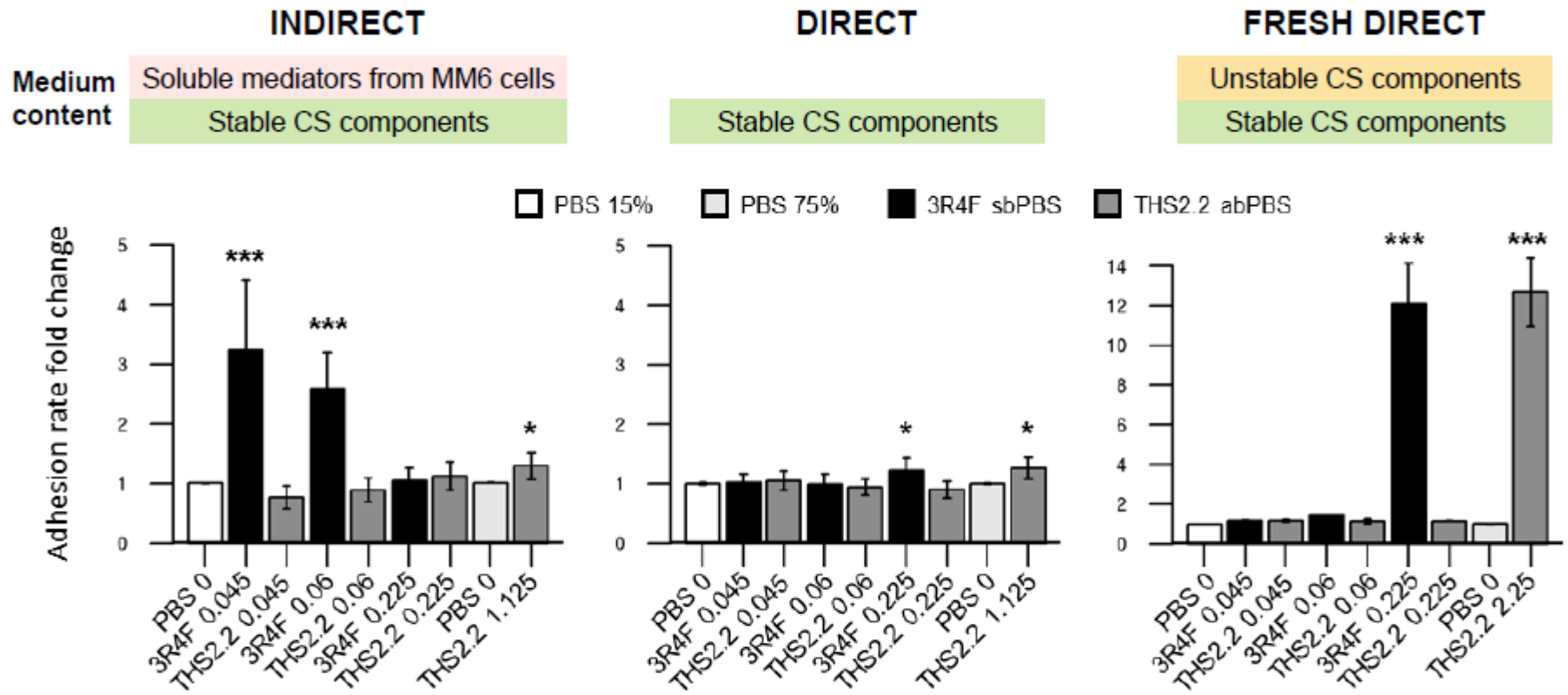

*Figure 1: Effects of THS2.2 abPBS and 3R4F sbPBS on the adhesion of MM6 cells to HCAECs following indirect, direct, and fresh direct treatments of HCAECs. Bar charts represent fold changes of the adhesion rate relative to respective vehicle controls. The adhesion rate reflects the number of adherent MM6 cells relative to the total number of HCAECs counted in the same well multiplied by 100. Data are presented as the mean ± SEM; N=2–3 independent experiments (n=3–6 replicates). *p≤0.05, ***p≤0.001 vs. 0 puffs/ml (PBS 15% or 75%).*

Note: THS stands for Tobacco Heating System version 2.2

Source: Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. Toxicology 2016; 73–86.

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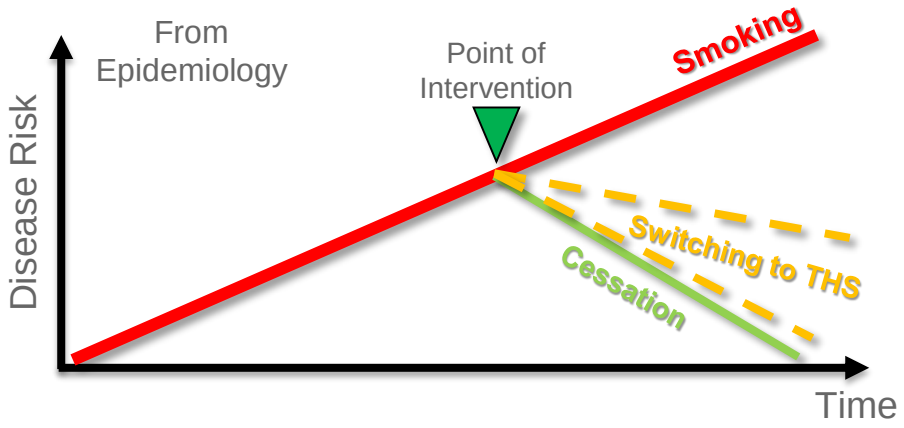
Animal Models of Disease

From Risk Assessment Framework to in vivo Study Design

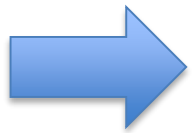
Animal Model: ApoE -/- mouse – Concomitant analysis of CVD and COPD endpoints

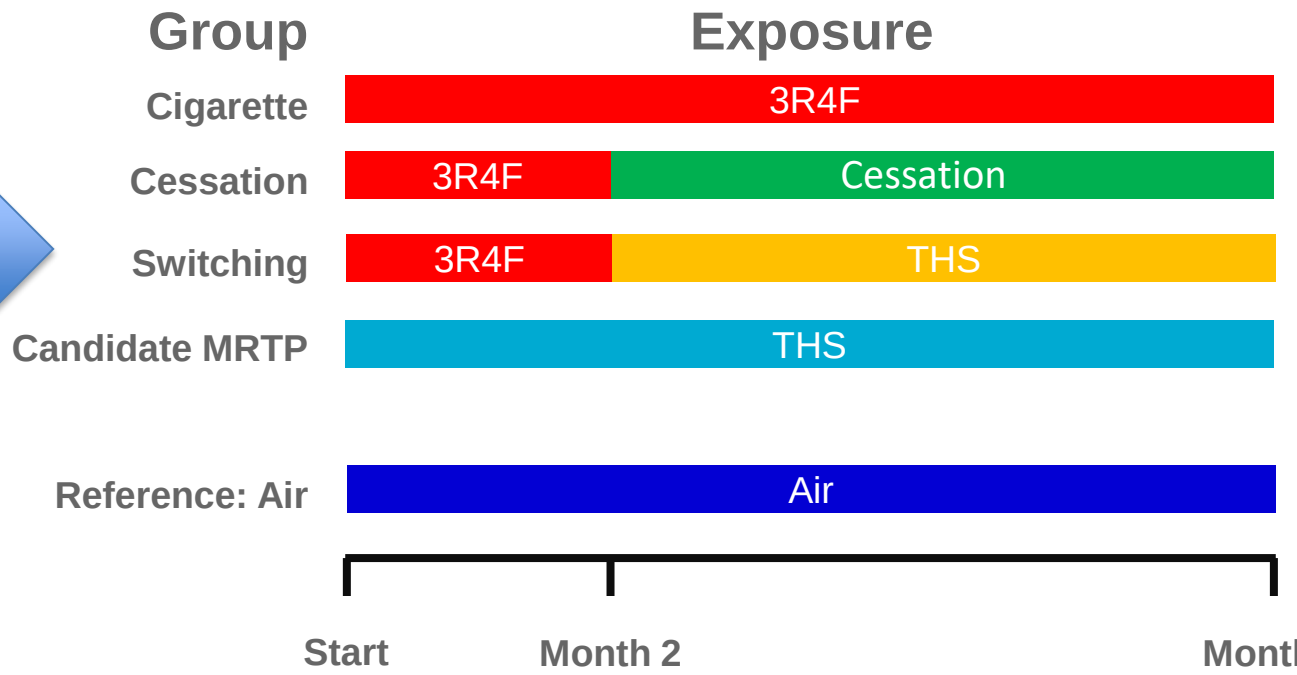
- 8 months duration (approximately 40% of lifetime)
- Concomitant analysis of CVD and COPD endpoints
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison

Assessment Framework



Note: The descriptions in the chart are for illustrative purposes only





Notes: THS stands for Tobacco Heating System version 2.2

Source: Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences 149(2): 411-432.

Use of animal model reviewed in: Lo Sasso et al. The Apoe−/− mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. J. Transl. Med., 2016; 14:146.

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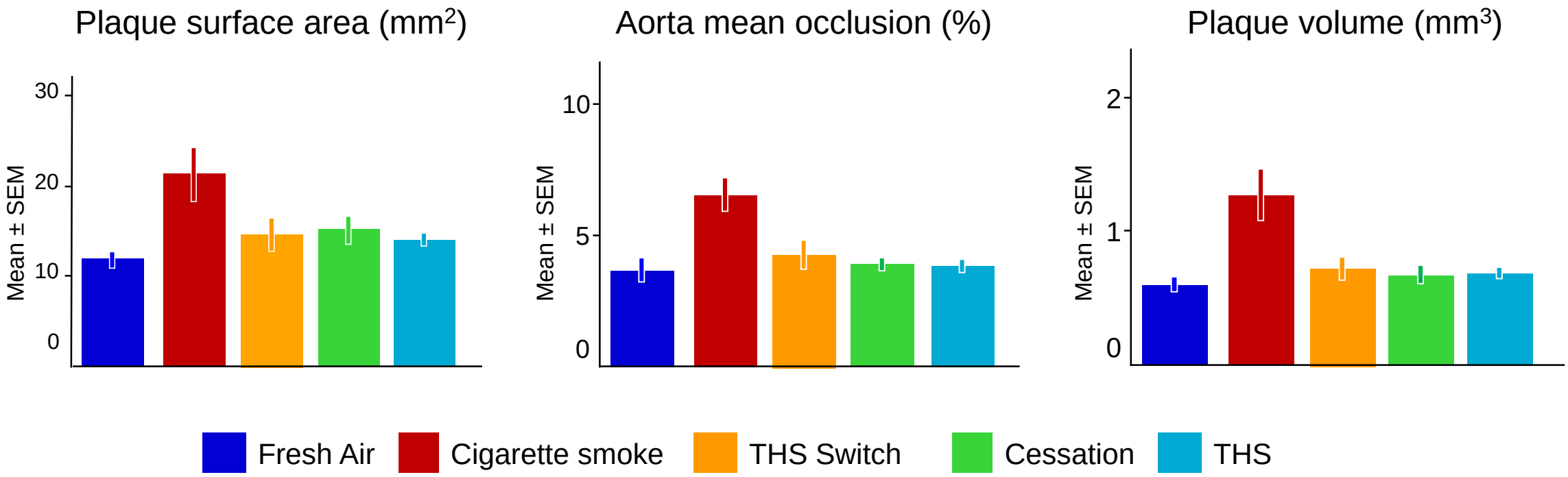
Atherosclerotic Plaque in the Aortic Arch
Data from µCT at month 7

Disease Endpoint for CVD

Atherosclerotic Plaque in the Aortic Arch

Data from µCT at month 7



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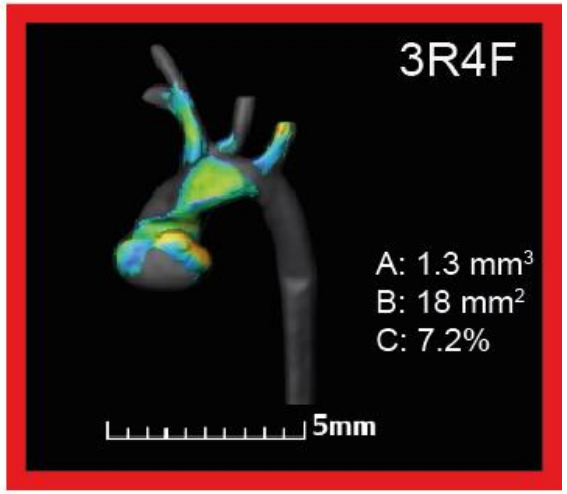

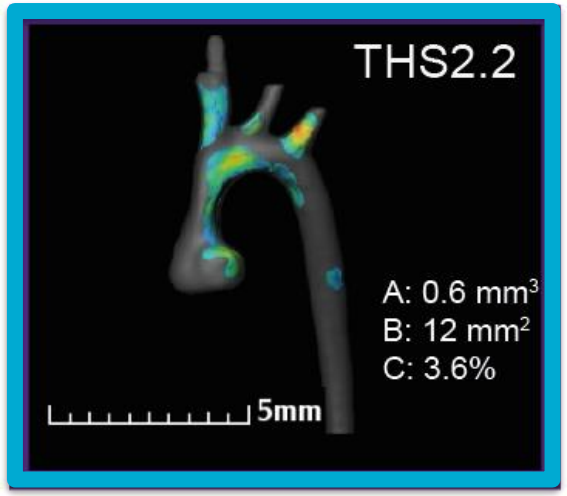

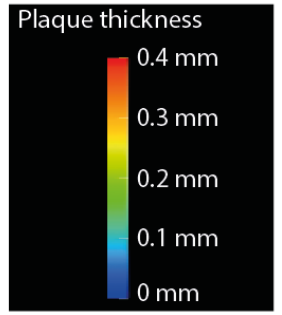

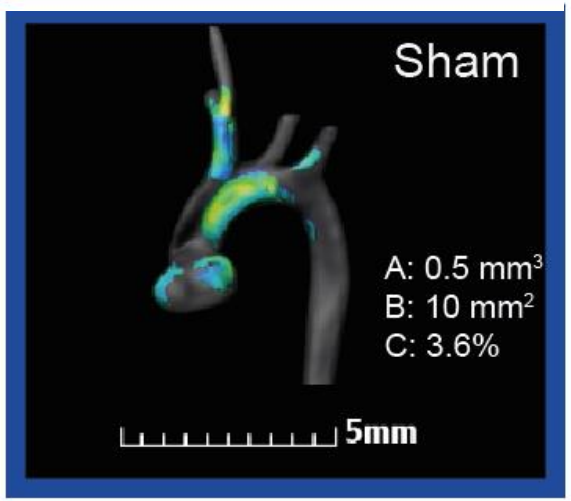

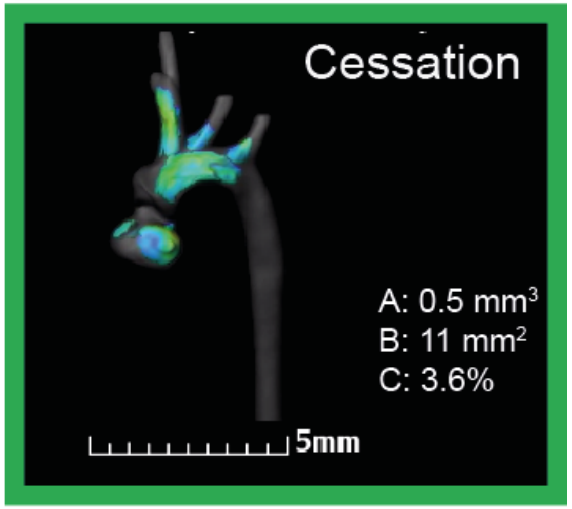

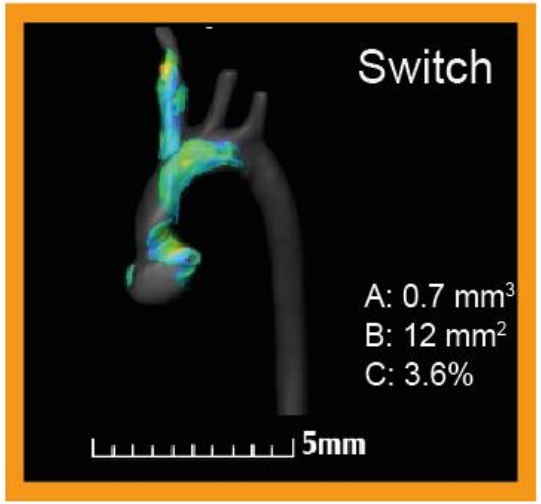

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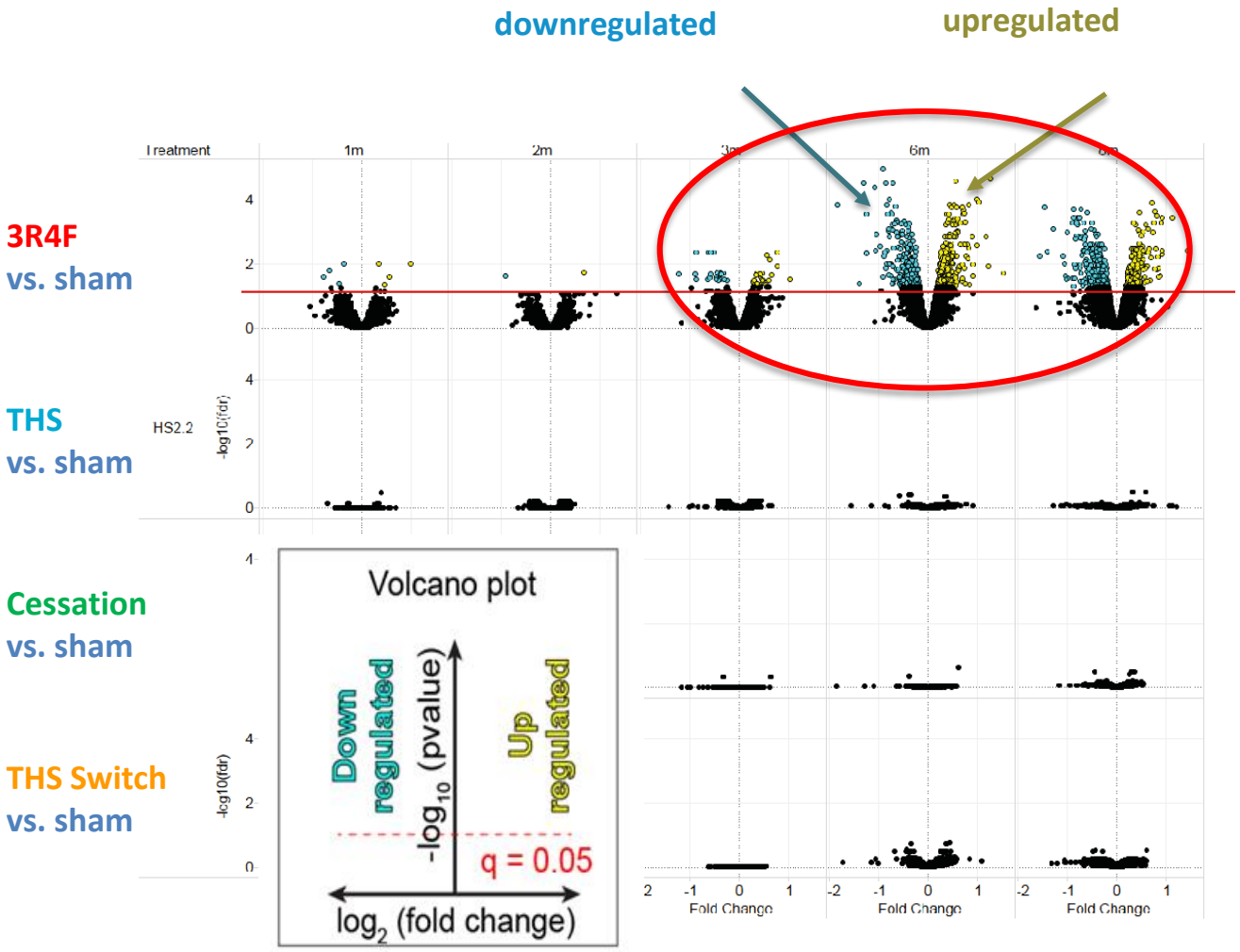
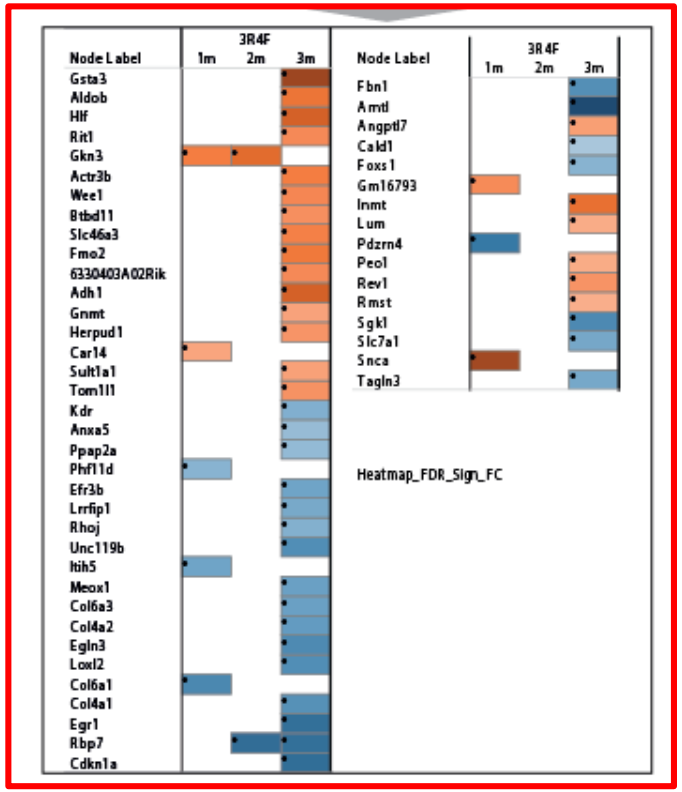
Heart (left ventricle) Transcriptomics





- Muscle structure and function
- Inflammatory response
- Cardiovascular disease

Notes: THS stands for Tobacco Heating System version 2.2
Soruce: Szostak, J., et al. (2017). "Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke." Food and Chemical Toxicology 101: 157-167.

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Exposure Response Study

Primary Objective and Co-Primary Endpoints

Smoking Cessation

Epidemiologic link to smoking-related disease?

Affected by smoking status

Reversible upon smoking cessation

Co-Primary Endpoints Representative of Patho-Mechanims	
Lipid Metabolism	HDL - C
Clotting	11 – DTBX - 2
Endothelial function	S – ICAM - 1
CO acute effect	COHb
Inflammation	WBC
Oxidative stress	PGF2 - a
Lung Function	FEV1
Genotoxicity	Total NNAL

Assess the changes across a set of the "8 co-primary clinical risk endpoints" in smokers who switch from smoking cigarettes to using THS as compared to those continuing to smoke cigarettes for 6 months

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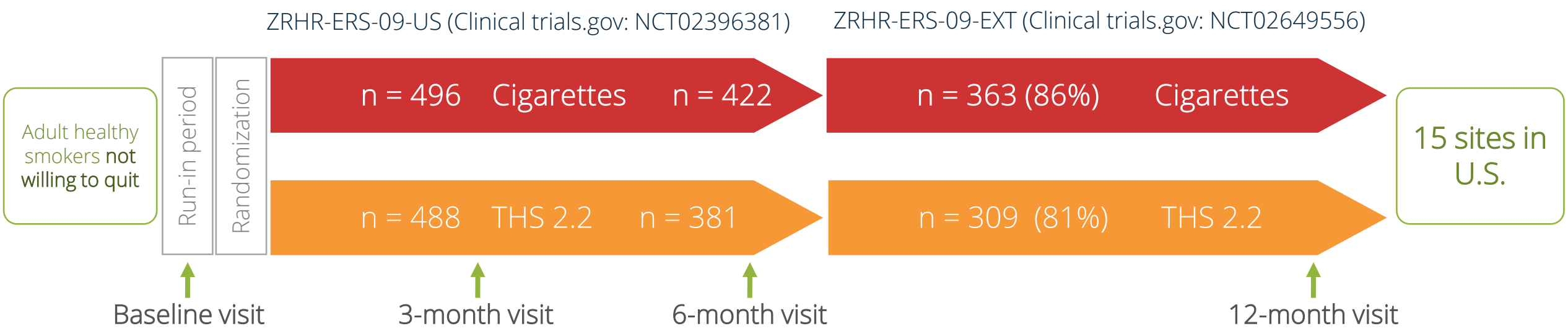
Note: THS stands for Tobacco Heating System version 2.2;
Registered on clinicaltrials.gov: NCT026396381; Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS

Study Design and Disposition - Exposure Response Study



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Statistical Analysis

Success Criteria:

To establish that the risk profile of THS is modified compared to cigarettes

1. All co-primary endpoints shift in the direction of cessation
2. ≥ 5 out of 8 clinical risk endpoints are statistically significant (Hailperin-Rüger Approach)
3. Majority of the smoking cessation effect is preserved

Primary Analysis: Predominant users of THS > 70%

Establish Modification of Risk

Smokers' Health Profile
Study-wise α=0.05
Test-wise α=0.031

If Modification of Risk is Established

≥ 5/8 significant clinical risk endpoints*

Results of the study can be verified with the effects measured for smoking cessation

*By using a 1-sided test with the Hailperin-Rüger adjusted α level for multiple testing (1.5625%).

Note: THS stands for Tobacco Heating System version 2.2;
Registered on clinicaltrials.gov: NCT026396381; Results submitted to the U.S. FDA on June 8, 2018, as an amendment to PMI's MRTP Application for THS

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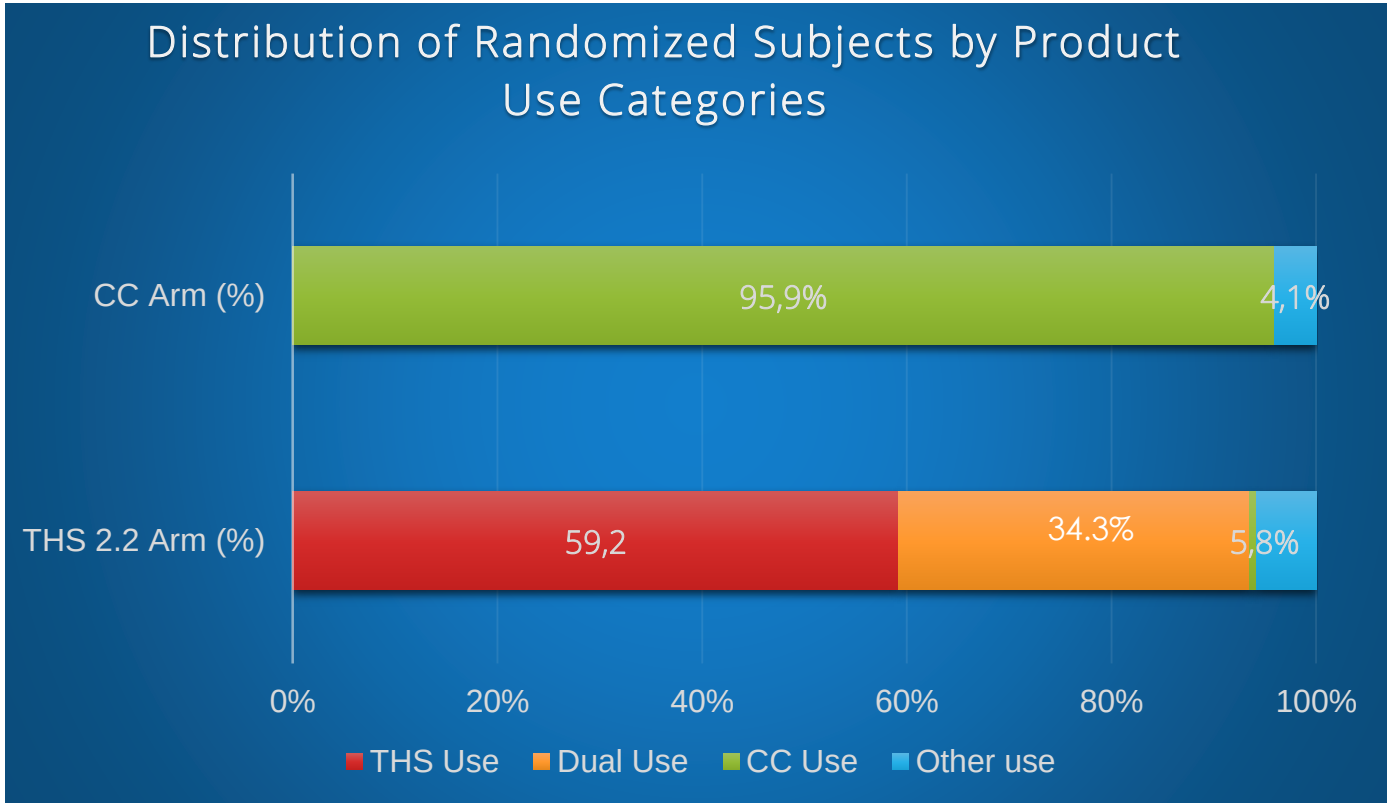
Main Analysis Population

THS-Use

- Randomized Product Use
- ≥ 70% THS use*

CC-Use

- Randomized Product Use
- ≤ 1% THS use*



* Calculated over the study and on at least 50% of the Study Days

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Changes in Clinical Risk Endpoints

Endpoint	Change From CC-use	Observed Change LS Mean Difference / Relative Reduction	Halparin Ruger Adjusted CI	1-sided p-value (0.0156)	THS directional change vs SA (literature)
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	<0.001*	✓ significant
WBC Count	Difference	-0.420 GI/L	-0.717, -0.123	0.001*	✓ significant
sICAM-1	% Reduction	2.86 %	-0.426, 6.04	0.030	✓
11-DTX-B2	% Reduction	4.74 %	-7.50, 15.6	0.193	✓
8-epi-PGF2α	% Reduction	6.80 %	-0.216, 13.3	0.018	✓
COHb	% Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV1 %pred	Difference	1.28 %pred	0.145, 2.42	0.008*	✓significant
Total NNAL	% Reduction	43.5 %	33.7, 51.9	<0.001*	✓significant

* denotes significant p value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

- All CRE shifted in the same direction as smoking cessation effect observed in the literature
- 5 out of 8 clinical risk endpoints were statistically significant compared to continued smoking

Note: THS stands for Tobacco Heating System version 2.2;
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Conclusion of the Exposure Response Study

- All clinical risk endpoints shifted in the same direction as the smoking cessation effect described in the literature
- 5 out of 8 endpoints showed statistically significant and favorable changes after switching to THS….
- ….despite the fact that up to 30% CC use was allowed in the primary analysis population
- Full switching is the best option for current adult smokers continuing to use tobacco products

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Thank you for your attention