CARDIOVASCULAR EFFECTS OF THE TOBACCO HEATING SYSTEM (THS) 2.2 COMPARED WITH CONTINUED SMOKING

Athens, Greece

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Philip Morris International
9 June 2018
Creating a New Category: Reduced-Risk Products

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 RRP in various stages of development, scientific assessment, and commercialization.

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


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.

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.
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
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)

<table>
<thead>
<tr>
<th>Age (a)</th>
<th>Lung Cancer</th>
<th>IHD</th>
<th>Stroke</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>-</td>
<td>-</td>
<td>4.78</td>
<td>13.32</td>
</tr>
<tr>
<td>to 49</td>
<td>6.98</td>
<td>1.47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50 to 59</td>
<td>10.39</td>
<td>5.22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>60 to 69</td>
<td>10.60</td>
<td>7.48</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70 to 79</td>
<td>12.99</td>
<td>13.77</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

[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)
Combustion
Elimination of Combustion Is Key

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


The Tobacco Heating System 2.2
PMI’s Reduced-Risk Product Portfolio

Heated Tobacco Products

1. Electrically Heated Tobacco Product (EHTP) or Tobacco Heating System (THS)

2. Carbon-Heated Tobacco Product (CHTP)

Products Without Tobacco

3. Nicotine Delivery System

4. E-Vapor Products

Note: The RRs depicted are subject to ongoing development; therefore, the descriptions are illustrative and do not necessarily represent the latest stages of product development.
Why Heat Tobacco Rather than Burn It?

The Tobacco Heating System (THS) (currently commercialized as IQOS in > 38 countries) 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
Scientific Assessment Approach
PMI’s Scientific Assessment Approach

Assessment Framework

From Epidemiology

Point of Intervention

Smoking

Switching to THS

Cessation

Disease Risk

Time

Post-Market Studies and Surveillance

Consumer Perception and Behavior Assessment

Clinical Trials

Systems Toxicology Assessment

Standard Toxicology Assessment

Aerosol Chemistry and Physics

Product Design and Control Principles

Assessment Framework: Informed by Epidemiology

High-Level Adverse Outcomes Pathway of Cigarette Smoking

**Toxic Emissions**
- Biomarkers of exposure
  - Proteomics
  - Transcriptomics
  - Genomics
  - Lipidomics
- Oxidative stress
- Inflammation
- Cell adhesion and migration

**Exposure**
- Disruption of Biological Mechanism
  - Cytology
  - Cell death
  - Cell proliferation
  - Cell count
  - Gross pathology
  - Histopathology

**Cell / Tissue Changes**
- Lipid profile
- Atherosclerotic plaque formation
- Lung function

**Disease**

**Population Harm**

**Analytical Chemistry**
- HPHCs*

*Harmful and potentially harmful constituents*
Exposure Reduction and Carbon-Based Nanoparticles
Reduced Formation of HPHCs by Disease Categories

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>% of Reference Cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogens in IARC Group 1</td>
<td>97%</td>
</tr>
<tr>
<td>Carcinogens (FDA)</td>
<td>93%</td>
</tr>
<tr>
<td>Cardiovascular toxicants (FDA)</td>
<td>92%</td>
</tr>
<tr>
<td>Respiratory Toxicants (FDA)</td>
<td>92%</td>
</tr>
<tr>
<td>Reproductive and Developmental Toxicants (FDA)</td>
<td>94%</td>
</tr>
</tbody>
</table>

**Note:** Intense Health Canada’s Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

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

<table>
<thead>
<tr>
<th>No. of toxicants</th>
<th>12</th>
<th>29</th>
<th>8</th>
<th>18</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Category</td>
<td>Carcinogens in IARC Group 1</td>
<td>Carcinogens (FDA)</td>
<td>Cardiovascular toxicants (FDA)</td>
<td>Respiratory Toxicants (FDA)</td>
<td>Reproductive and Developmental Toxicants (FDA)</td>
</tr>
</tbody>
</table>
Changes in Exposure to HPHCs
Reduced Exposure in Healthy Human Subjects

Levels of HPHCs are Drastically Reduced in THS Aerosol

Exposure is Significantly Reduced After Switching to THS

<table>
<thead>
<tr>
<th>Carbon monoxide (mg/stick)</th>
<th>Leads to</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.3</td>
<td>- 98.6%*</td>
</tr>
<tr>
<td>282</td>
<td>- 98.0%*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNK (ng/stick)</th>
<th>Leads to</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.3</td>
<td>- 98.6%*</td>
</tr>
<tr>
<td>282</td>
<td>- 98.0%*</td>
</tr>
</tbody>
</table>

* On equivalent nicotine basis
Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects

Switching to THS achieves almost 95% of the reduction achieved by smoking abstinence
Reduced Formation of HPHCs by Disease Categories


Cigarette smoke
Carbon-based nanoparticles
Median diameter = 75 nm
Amount: 6x10^{11} particles &asymp; 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.

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

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.
From Risk Assessment Framework to *In Vitro* Study Design

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

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**INDIRECT**
- Soluble mediators from MM6 cells
- Stable CS components

**DIRECT**
- Stable CS components
- Stable CS components

**FRESH DIRECT**
- Unstable CS components
- Stable CS components

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Figure 1: Effects of THS2.2 abPBS and 3R4F abPBS 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%).

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.
From Risk Assessment Framework to *In Vitro* Study Design

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

**Conclusions:**

- 3R4F aqueous cigarette smoke extract promoted adhesion of MM6 cells to HCAEC in indirect and fresh direct exposure conditions.

- At the same concentrations, no significant adhesion of MM6 cells to HCAECs.

- The concentrations of THS 2.2 required to be increased by ~10 and 20 times to observe similar effects at functional and molecular levels to the ones observed with 3R4F.

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.
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**

**Group**
- Cigarette
- Cessation
- Switching
- Candidate MRTP

**Exposure**
- 3R4F
- Cessation
- THS
- THS
- Air

**Reference: Air**

**Notes:**
- The descriptions in the chart are for illustrative purposes only

Phillips et al. (2015) An 8-Month Systems Toxicology Inhalation/Cessation Study in Apo e-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared with Conventional Cigarettes. Toxicological Sciences, in press
Reduced Effects on Disease Mechanisms

Cell Stress

Cell Fate & Apoptosis

Cell Proliferation

Tissue Repair & Angiogenesis
8-month Apoe-/- mouse switching study

*Interaction between monocytes and endothelial cells*

- Network Perturbation Amplitude of:
  - Inflammation/Endothelial cell activation ↓
  - Inflammation/Neutrophil Signaling ↓

Vascular Inflammation/
Endothelial cell – monocyte interaction

- **Cigarette**
- **THS**
- **Cessation**
- **THS Switch**
Heart (left ventricle) Transcriptomics

- Muscle structure and function
- Inflammatory response
- Cardiovascular disease

From Risk Assessment Framework to in vivo Study Design

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

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

- Plaque surface area (mm²)
- Aorta mean occlusion (%)
- Plaque volume (mm³)

Exposure Response Study
Clinical Assessment - Results to Date

High-Level Adverse Outcomes Pathway of Cigarette Smoking

Exposure → Molecular Changes → Disruption of Biological Mechanism → Cell / Tissue Changes → Disease → Population Harm

Analytical Chemistry

Toxic Emissions

Biological Networks
Toxicology, Systems Biology, and Clinical Studies

Models and Clinical

Public Health

Reduced Emissions

Reduced Exposure → Reduced Adverse Health Effects

PK / PD Studies
4 single-use studies

Nicotine absorption similar to CC

Reduced Exposure
4 up to 3-month studies

Exposure Response Study
6 + 6-month study

• Statistically significant changes in CREs linked to smoking-related disease
• All co-primary CREs shifting in the same direction as they would upon smoking cessation

• 15 biomarkers of exposure significantly reduced vs. CC
• Directional shift of CREs shift towards cessation

*Harmful and potentially harmful constituents
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.

**Primary Objective and Co-Primary Endpoints**

**Epidemiologic link to smoking-related disease?**
- Affected by smoking status
- Reversible upon smoking cessation

**Co-Primary Endpoints Representative of Patho-Mechanisms**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Co-primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL - C</td>
</tr>
<tr>
<td>Clotting</td>
<td>11 – DTXB - 2</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>S – ICAM - 1</td>
</tr>
<tr>
<td>CO acute effect</td>
<td>COHb</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>PGF2 - a</td>
</tr>
<tr>
<td>Lung Function</td>
<td>FEV1</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Total NNAL</td>
</tr>
</tbody>
</table>

Based on Smoking Cessation, the changes can be observed across these endpoints.
Study Population - Main Eligibility Criteria

**Inclusion Criteria**

- Healthy subjects. Minimum 30 year of age.
- 10 years of smoking history with at least 10 CC/day for the last year
- Subjects did not intend to quit smoking

**Exclusion Criteria**

- Clinically relevant disorders that would jeopardize the participants safety
- Female, not pregnant or breast feeding
- Subjects did use medication with an impact on co-primary endpoints
Study Design and Disposition - Exposure Response Study

ZRHR-ERS-09-US (Clinical trials.gov: NCT02396381)
- n = 496 Cigarettes
- n = 488 THS 2.2

ZRHR-ERS-09-EXT (Clinical trials.gov: NCT02649556)
- n = 363 (86%) Cigarettes
- n = 309 (81%) THS 2.2

15 sites in U.S.

Run-in period
- Adult healthy smokers not willing to quit

Randomization
- Baseline visit
- 3-month visit
- 6-month visit

Disposition
- 12-month visit
**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 $\alpha=0.05$
    - Test-wise $\alpha=0.031$
  - 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 $\alpha$ level for multiple testing (1.5625%).
Analysis Populations
Reduced Exposure Studies vs Exposure Response Study

3 months Reduced Exposure Study
- Use of no more than 2 CC in a single day during the 30 days preceding the visit
- Average product use within a 3-month period of not more than 0.5 CC/day

6 months Exposure Response Study
- Analysis population: THS 2.2 as it is actually used
- ≥70% THS use over the 6-month analysis period
- ≥70% THS use on >50% of days in the 6-month analysis period

Primary Analysis Population

Primary Assessment Objective

Analysis of the effect of THS after full switching

Analysis of the effect of THS as actually used (up to 30% use of cigarettes)
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
## Product Use

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Product</th>
<th>THS Use Mean / Day (Min, Max)</th>
<th>CC Use Mean / Day (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Cigarettes</td>
<td>18.5 (10.0, 65.0)</td>
<td>19.5 (10.0, 90.0)</td>
</tr>
<tr>
<td></td>
<td>THS</td>
<td>16.5 (3.2, 63.0)</td>
<td>&lt; 0.01 (0.0, 0.44)</td>
</tr>
<tr>
<td>Post-randomization</td>
<td>Cigarettes</td>
<td>1.95 (0.0, 14.0)</td>
<td>16.8 (3.0, 43.7)</td>
</tr>
<tr>
<td></td>
<td>Overall tobacco</td>
<td>18.5 (3.2, 63.5)</td>
<td>16.9 (3.1, 43.7)</td>
</tr>
</tbody>
</table>
Reduction in Exposure and Exposure to Nicotine

- COHb: -32.2%
- Total NNAL: -43.5%
- Total 1-OHP: -16.2%
- 3-HMPMA: -28.4%
- 3-OH-B[a]P: -27.3%
- CEMA: -48.6%
- Total NNN: -40.8%
- 3-HPMA: -25.0%
- MHBMA: -42.9%

NEQ (mg/g creat) ± 95% CI

<table>
<thead>
<tr>
<th>THS-use</th>
<th>CC-use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.2</td>
</tr>
<tr>
<td>Month 3</td>
<td>8.85</td>
</tr>
<tr>
<td>Month 6</td>
<td>8.63</td>
</tr>
</tbody>
</table>
Clinical Changes After 90 Days
Reduced Exposure in Healthy Human Subjects

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to THS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>0.0 mg/dL [-5.77; 5.84]</td>
<td>1.4 mg/dL [-2.3;5.0]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.94 10^9/L [-2.00; 0.13]</td>
<td>0.17 10^9/L [-0.47; 0.81]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>2.0 % pred [-3.37; 7.36]</td>
<td>0.53 % pred [-2.79; 3.85]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-9.9 % [-19.7;1.1]</td>
<td>-10.6 % [-16.7; -4.0]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-8.5 % [-25.13; 11.8]</td>
<td>-13.5 % [-23.6; -1.95]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
<td>-7.2 % [-37.7; 38.3]</td>
<td>-3.6 % [-24.6; 23.3]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Endpoint</th>
<th>Abstinence Effect at 3m [95% CI]</th>
<th>Switching to THS Effect at 3m [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>6.4 mg/dL [2.5; 10.3]</td>
<td>4.5 mg/dL [1.17, 7.88]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.41 10^9/L [-0.95; 0.14]</td>
<td>-0.57 10^9/L [-1.04, -0.10]</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV1</td>
<td>1.94 % pred [-0.44; 4.31]</td>
<td>1.91 % pred [-0.14, 3.97]</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>-10.9 % [-17.8; -3.4]</td>
<td>-8.7 % [-14.94; -2.05]</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF2α</td>
<td>-5.9 % [-17.1; 6.8]</td>
<td>-12.7 % [-21.81; -2.55]</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
<td>-19.4 % [-30.1; -7.0]</td>
<td>-8.98 % [-19.52, 2.94]</td>
</tr>
</tbody>
</table>
# Changes in Clinical Risk Endpoints

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

* denotes significant p value at the 1.5625% level, following test multiplicity adjustment using the Halperin-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
Changes in Clinical Risk Endpoints When Adjusted for CEMA Exposure Levels

Note: The predominant THS Use category group was stratified by CEMA quartiles 1 (bottom) to 4 (top).
Note: Higher CEMA levels are indicative of higher levels of cigarette smoking. The panel for sICAM-1 shows the THS vs. continued smoking LS means ratios. The panel for leukocytes (WBC) shows the THS minus cigarette smoking LS means differences.
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
Thank you for your attention