Creating a New Category: Reduced Risk

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.
Tobacco Harm Reduction
The Objective Is 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*

\[
\text{Population} \quad \text{Harm} \quad \text{Reduction} \quad = \quad \text{Reduced-Risk} \quad \text{Products} \quad \times \quad \text{Product} \quad \text{Adoption} \quad \text{and} \quad \text{Usage}
\]

• Successful harm reduction requires that adult smokers who would otherwise continue to smoke be offered a range of satisfying, scientifically substantiated, reduced-risk products to which they can switch completely

* 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 switch to these products versus continued smoking.
May 2014, Public Health England:
“[…] Nicotine does not cause serious adverse health effects such as acute cardiac events, coronary heart disease or cerebrovascular disease, and is not carcinogenic. The doses of nicotine delivered by electronic cigarettes are therefore extremely unlikely to cause significant short or long-term adverse events.[…]”

July 2017, FDA Commissioner Dr. Scott Gottlieb:
“[…] nicotine in itself is not responsible for the cancer, the lung disease and heart disease that kill hundreds of thousands Americans every year. […] it is the other chemical compounds in tobacco and in the smoke created by setting the tobacco on fire that directly cause illness and death.”
A Growing Number of Countries Are Recognizing the Benefit of Better Alternatives

Governments recognize the potential benefits of smoke-free alternatives for public health

“…new product innovations could make a lot of sense and help people transfer off cigarettes”
- Scott Gottlieb, Commissioner Food & Drug Administration

“help people to quit smoking by permitting innovative technologies that minimise the risk of harm” / “maximise the availability of safer alternatives to smoking”

“The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes.”

“heat-not-burn, snus, moist snuff, dissolvables and inhaled nicotine may be significantly safer than cigarettes.”
- Nicky Wagner, Associate Health Minister
### PMI’s Reduced-Risk Product Portfolio

<table>
<thead>
<tr>
<th>Heated Tobacco Products</th>
<th>Products Without Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLATFORM 1</strong></td>
<td><strong>PLATFORM 2</strong></td>
</tr>
<tr>
<td>Electrically Heated Tobacco Product (EHTP) or Tobacco Heating System (THS)</td>
<td>Carbon-Heated Tobacco Product (CHTP)</td>
</tr>
<tr>
<td><strong>PLATFORM 3</strong></td>
<td><strong>PLATFORM 4</strong></td>
</tr>
<tr>
<td>Nicotine Delivery System</td>
<td>E-Vapor Products</td>
</tr>
</tbody>
</table>

Note: The RRP(s) depicted are subject to ongoing development; therefore, the descriptions are illustrative and do not necessarily represent the latest stages of product development.
Combustion
Elimination of Combustion Is Key

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


The Tobacco Heating System 2.2
How THS Works

- The Tobacco Heating System (THS, marketed as IQOS) is designed to heat tobacco without burning and smoke – the maximum temperature reaches approximately 350°C.
- In contrast, cigarettes can exceed 850°C during puffs.
- THS is designed as an alternative to cigarettes for current adult smokers who would otherwise continue to smoke.
THS Temperature Profile

Radial position of thermocouple relative to the surface of the heater

Heater turned off

Combustion T°

Programmed heater profile

Puffs

Distance from the Blade

0.1 mm*
0.2 mm
0.5 mm
1.7 mm
3.4 mm

Time (s)

Temperature (°C)

0 50 100 150 200 250 300 350 400

* Radial position of thermocouple relative to the surface of the heater
Smoke and aerosol were collected on a Cambridge filter pad using the Health Canada Intense smoking regime.

- Water and glycerin form 50% of smoke mass.
- HPHCs
- Contains carbon-based solid particles
- Water and glycerin form 90% of aerosol mass.
- HPHCs reduced by >90%
- No carbon-based solid particles

Smoke is different from tobacco vapor (aerosol).
Smoke Is Different from Tobacco Vapor (Aerosol)

Cigarette smoke
Carbon-based nanoparticles
Median diameter = 75 nm
Amount: $6 \times 10^{11}$ particles $\approx 0.7 \text{ mg}$

Blank (Air)

THS aerosol
No solid particles

* Under the Health Canada Intense smoking regime.


How We Assessed It
Assessing Risk Reduction

18 Non-Clinical and 10 Clinical Studies
PMI’s Scientific Assessment Approach

Assessment Framework

The descriptions in this chart are for illustrative purposes only.

Assessing Risk Reduction - Reduced Emissions

Toxic Cigarette Emissions → Exposure → Molecular Changes → Disruption of Biological Mechanisms → Cell/Tissue Changes → Disease → Population Harm

Reduced Emissions → Reduced Exposure → Reduced Risk

18 Non-Clinical and 10 Clinical Studies
Reductions of Toxicants by Disease Category

Note: Intense Health Canada’s Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine
Assessing Risk Reduction - Reduced Exposure

- Toxic Cigarette Emissions
- Exposure
- Molecular Changes
- Disruption of Biological Mechanisms
- Cell/Tissue Changes
- Disease
- Population Harm

18 Non-Clinical and 10 Clinical Studies

Reduced Emissions → Reduced Exposure → Reduced Risk
Changes in Exposure to HPHCs with THS Use

Reduced Exposure in Healthy Human Subjects

HPHCs Are Drastically Reduced in THS Aerosol

<table>
<thead>
<tr>
<th>Carbon monoxide (mg/stick)</th>
<th>Acrolein (µg/stick)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.3</td>
<td>161</td>
</tr>
<tr>
<td>- 98.6%*</td>
<td>- 94.2%*</td>
</tr>
</tbody>
</table>

Leads to

Carbon Monoxide

- 98.6%*

Acrolein

- 94.2%*

Leads to

Cigarette

THS

Smoking Abstinence

Exposure Is Significantly Reduced After Switching to THS
Changes in Exposure to HPHCs with THS Use
Reduced Exposure in Healthy Human Subjects

HPHCs Are Drastically Reduced in THS Aerosol

<table>
<thead>
<tr>
<th>HPHC</th>
<th>NNN (ng/stick)</th>
<th>NNK (ng/stick)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette</td>
<td>274</td>
<td>282</td>
</tr>
<tr>
<td>THS</td>
<td>7.74</td>
<td>5.52</td>
</tr>
</tbody>
</table>

- **NNN**: -97.2%*  
- **NNK**: -98.0%*

* On equivalent nicotine basis

Exposure Is Significantly Reduced After Switching to THS

**NNN**

Leads to Smoking Abstinence

**NNK**

Leads to

www.pmiscience.com
Reduced Exposure Compared with Cigarettes

Reduced Exposure in Healthy Human Subjects

Percent of Cigarette Exposure [95% CI]

THS

Cigarettes

Percent of Cigarette Exposure [95% CI]
Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects

![Bar chart showing percent of cigarette exposure with error bars for THS and Smoking Abstinence across different compounds and percentages.]

Cigarettes

Percent of Cigarette Exposure [95% CI]

THS  Smoking Abstinence

Cigarettes

Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects

![Bar chart showing percent of cigarette exposure with error bars for THS and Smoking Abstinence across different compounds and percentages.]

Cigarettes
Switching to THS achieves almost 95% of the reduction achieved by smoking abstinence.

Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects
Assessing Risk Reduction - Reduced Adverse Health Effects

Reduction of Toxic Cigarette Emissions leads to:
- Reduced Emissions
- Reduced Exposure
- Reduced Risk

Resulting from:
18 Non-Clinical and 10 Clinical Studies
### Improvements in Clinical Risk Endpoints After Six Months

<table>
<thead>
<tr>
<th>Pathomechanisms</th>
<th>Co-Primary Endpoints</th>
<th>Type of Change</th>
<th>Observed Change*</th>
<th>Halperin-Rüger Adjusted CI</th>
<th>1-Sided p-Value (0.0156)</th>
<th>THS Directional Change vs. SA (Literature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<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>Inflammation</td>
<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>Endothelial Function</td>
<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>Clotting</td>
<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>Oxidative Stress</td>
<td>8-epi-PGF$_{2\alpha}$</td>
<td>% Reduction</td>
<td>6.80 %</td>
<td>−0.216, 13.3</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Acute Effects</td>
<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>Lung Function</td>
<td>FEV$_1$ %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>Genotoxicity</td>
<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>

**Notes:**

- All CREs shifted in the same direction as the smoking cessation effect observed in the literature.
- 5 out of 8 CREs were statistically significant compared with continued smoking.

* Observed change presented as LS Mean Difference / Relative Reduction
** Denotes significant p-value at the 1.5625% level, following test multiplicity adjustment using the Halperin-Rüger approach

These data alone do not represent a claim of reduced risk.

THS stands for Tobacco Heating System version 2.2.

Registered on clinicaltrials.gov: NCT02396381
# Increasing Number of Third-Party Studies

## Aerosol Chemistry
- Committee on Toxicology (COT)
- Public Health England (PHE)
- British American Tobacco
- National Tobacco Quality Supervision and Test Center
- Federal Institute for Risk Assessment (BfR)
- University of Bern
- National Institute of Public Health
- Food & Drug Administration
- Onassis Cardiac Surgery Center
- National Institute for Public Health and the Environment (RIVM)

## Indoor Air Quality
- Fondazione IRCCS Istituto Tumori
- Sapienza University
- Medved Research Center of Preventing Toxicology, Food and Chemical Safety

## Pre-Clinical
- British American Tobacco
- UCSF

## Clinical
- Kazan Federal University
- British American Tobacco
- National Scientific Centre "M.D. Strazhesco Institute of Cardiology"
Scientific Substantiation Results to Date

The totality of the scientific evidence on THS 2.2 demonstrates that it presents less risk of harm to individual adult smokers. MRTP and PMTA applications filed with the U.S. FDA.

**Totality of Scientific Evidence Supporting Reduced Risk Potential**
- No combustion
- Reduced toxicant formation
- Reduced toxicity
- Reduced exposure
- Reversal of clinical risk endpoints
- Pre-market perception & behavior assessment
- Validated Population Health Impact Model

**Reduced Impact on Users and Those Around Them**
- Less smell
- No ash
- No risk of burning
- No negative impact on indoor air quality

**Improved Oral Hygiene**
- Better breath
- Less unpleasant after taste
- Reduced tooth staining
THANK YOU!