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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Annual Meeting of the Japanese Society of Toxicology
July 1, 2016
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 RRPs 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.
The U.S. Institute of Medicine ("IOM"), called the "gold standard" for the assessment of an RRP, providing "an aspirational goal for risk and exposure."

To date, there is a gap of epidemiological evidence concerning the impact of our RRPsm with regard to the health risks of conventional cigarette (CC) smokers who choose switching to RRPsm compared to CC smoking and smoking cessation.
PMI’s Reduced Risk Product Portfolio

Heated Tobacco Products

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

P1 - THS

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

P2

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

P3

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

P4

Commercialized

Product development ongoing

Commercialized

The RRPs 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

1. Pharmacokinetics/Pharmacodynamics
   - 4 Studies completed
   - Full results Q1 2015

2. Reduced Exposure 1-week confinement
   - 2 Studies completed
   - Full results Q2 2015

3. Reduced Exposure 3-month ambulatory
   - 2 Studies completed
   - Full results Q3 2015

4. Exposure Response
   - 1 Study on going
   - Results expected Q2 2017

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Post-Market Studies & Surveillance
Consumer Perception and Behavior Assessment
Clinical Trials
Systems Toxicology Assessment
Standard Toxicology Assessment
Aerosol Chemistry and Physics
Product Design and Control Principles
Heat-not-Burn

THS-Specific Science and Results to Date
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

ClinicalTrials.gov ID: NCT01970995

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.
Reduced Exposure

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)

Note: These data alone do not represent a claim of reduced risk.
Source: PMI Research and Development
Registered on clinicaltrials.gov: NCT01970995
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Satisfaction index is on a seven-point scale where 7 = “Extremely Satisfying” and 1 = “Not at All Satisfying”

Source: PMI Research & Development
Biomarkers Related to Cardiovascular Disease

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

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

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

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

Source: PMI R&D; Clinicaltrials.gov: NCT 01970995

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.
Acknowledgements to the PMI ZRHM-REXA-07-JP Study Team:

Christelle Haziza
Nicola Lama
Andrea Donelli
Gizelle Baker
Jacek Ancerewicz

Muriel Benzimra
Mikael Franzon
Masahiro Endo
Patrick Picavet