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.
Presentation Outline

1. Introduction
2. Eight Month ApoE^-/- Mouse Inhalation Study for Comparative Tobacco Product Testing
3. *In vitro* Systems Toxicology for Comparative Product Testing
4. Summary of ambulatory exposure clinical ZRHM-REXA-07-JP Study Results
5. Sbv IMPROVER
PMI R&D- Background

• Smoking causes serious diseases such as cardiovascular diseases, lung cancer and chronic obstructive pulmonary disease (U.S. Surgeon General, 2004)

• Smoking cessation remains the most effective approach to minimizing the risk for smoking-related diseases (Godtfredsen et al. 2008; Gepner et al., 2011)

• Providing reduced risk alternatives to adult smokers who would otherwise continue to smoke cigarettes represents the basis of the “Tobacco Harm Reduction” strategy (IOM, 2002)

• Philip Morris International (PMI) is developing novel products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes.

• To determine whether such potentially reduced-risk products (RRP) have the potential to reduce individual risk, we are conducting extensive and rigorous scientific studies comparing their biological impact with that of cigarettes.
Cigarette Smoke vs. Heat-not-Burn

Underlying Principles

- Approximately 8000 constituents identified in cigarette smoke
- Some of these constituents are categorized as harmful and potentially harmful (HPHCs)
- Many of the HPHCs are formed during combustion (burning) of the tobacco
- It is not known which HPHCs are responsible for tobacco-related diseases – selective reduction not an effective approach

Lower temperatures reduce constituents in the aerosol
Nicotine is transferred via distillation
THS2.2 – Operating Principles

Key Principles:

• Electrically heated tobacco system version 2.2 (THS2.2)
  – Tobacco plug which generates visible aerosol
  – Tobacco blends and flavor systems developed to suit lower operating temperature (< 350° C)

• Heating engine precisely controlled using built-in software
  – Heater maintains tobacco temperature in the distillation range
  – Heater also acts as a temperature sensor

*M.R. Smith et al. / Regulatory Toxicology and Pharmacology xxx (2016) 1–10*
• Compare switching to RRP with continued smoking and benchmark against smoking cessation.
• Assess how close switching to RRP is to smoking cessation.
Average reductions in formation of harmful or potentially harmful constituents for THS2.2 compared to levels measured in smoke from the 3R4F reference cigarette*:

- WHO (9 chemicals): > 95% reduction
- FDA (18 chemicals): > 90% reduction
- Health Canada (44 chemicals): ≈ 95% reduction
- PMI (58 chemicals): > 90% reduction
- Carcinogens (15 chemicals): > 95% reduction

*Aerosol collection with Intense Health Canada’s Smoking Regime (55 mL puff volume, 2 second puff duration, 30 second interval puff); Comparison on a per-stick basis. Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter. The PMI 58 list includes the FDA 18, and the 15 carcinogens of the IARC Groups 1.
Systems Toxicology

- Decoding the toxicological blueprint of active substances that interact with living systems
- Integrates classic toxicology approaches with network models and quantitative measurements of molecular and functional changes occurring across multiple levels of biological organization

Quantitative Mechanism-Based Systems Impact Assessment

1. **Experimental data production**
   - Identify perturbed biological networks
   - Compute systems response profiles

2. **Identify perturbed biological networks**
   - Compute network perturbation amplitudes
   - Experimental data production

3. **Compute network perturbation amplitudes**
   - Compute product biological impact

4. **Compute product biological impact**
   - Experimental data production

---

**Month**

- **Month 1**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**Differential Expression**

- **Month 2**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**Product Impact**

- **Month 3**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**Network Impact**

- **Month 4**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**BIF(c)**

- **Month 5**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**NPA**

- **Month 6**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

**For each ERK, evaluate**

- **Month 7**
  - Data from: Stress, pERK, Cdc20, Switch
  - Stress: Low, High
  - pERK: Low, High
  - Cdc20: Low, High
  - Switch: Low, High

---

PMI RESEARCH & DEVELOPMENT
Presentation Outline

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Case study 1: Eight Month ApoE⁻⁻ Mouse Inhalation Study for Comparative Tobacco Product Testing

This research was funded by Philip Morris International
Aim and scope of the presentation

- Assessment of the effects of conventional cigarette smoke and a potential Reduced-Risk Product (pRRP), using PMI’s Heat-not-Burn technology, in 2 animal models of COPD:
  - ApoE⁻/⁻ mouse (C57Bl6 background), typically used as model for cardiovascular disease
  - A/J mouse, used as model for lung cancer
- Both animal models are responsive to cigarette mainstream smoke and develop different pathologies, among which aspects of COPD such as lung inflammation, changed pulmonary function, emphysema*
- Other endpoints, such as general (chronic) toxicity, atherosclerosis, lung tumor development determined in these studies will not be reported here


Common disease mechanisms in different mouse models, relevance to human situation

- Possible interrelationships and roles for the identified common mechanisms in five mouse models of emphysema in a framework of classical human COPD mechanisms.
  - transcription factors ([black font](#))
  - inflammatory mediators ([orange font](#))
  - classical pathways of human COPD pathogenesis ([black arrows](#)) as depicted,

Methods – Conventional cigarette smoke and aerosol from a RRP

Assessment of smoke/aerosol – Health Canada Intense smoke protocol

Conventional cigarettes: **Smoke** from University of Kentucky Standard Reference Cigarette 3R4F

Potentially Reduced-Risk product: **Aerosol** from Heatsticks and Tobacco Heating System, THS2.2
ApoE−/− mouse switching study

Study design

• Comparative assessment of effects of THS2.2 and 3R4F
• Switching design upon initiation of disease:
  — to assess reversibility (switch to fresh air, i.e. cessation) and
  — To quantify how similar switching to THS2.2 is to cessation

Dissection time points: Month 1, 2, 3, 6 and 8
ApoE-/- mouse switching study

Methods - Exposure regime

- Animals were exposed 3 hours per day (3 x 1 hour interrupted exposure periods), 5 days per week
- Nicotine was measured during every exposure period (3 samples per chamber per day)
- Aerosol delivery (nicotine) was within +/- 10% of the targeted **29.9 µg/l** nicotine concentration

Nicotine concentration in exposure chamber (study average)

*29.9 µg/l nic corresponds to 6.5 mg/kg, daily dose- or the nicotine amount from approx. 32 cig/day for a 60 kg human, based on body surface comparison, Guidance document Heq dose, FDA*
ApoE−/− mouse switching study
Aerosol uptake (biomarkers of exposure)

Plasma Nicotine (month 8)

Means ± SEM

Groups

3R4F

Cessation

Switching

THS2.2

Sham / Air

HPMA (Acrolein metabolite)

CEMA (Acrylonitrile metabolite)

NNAL (NNK metabolite)

SPMA (Benzene metabolite)

Urinary Metabolites (months 3, 6, 8)
ApoE-/- mouse switching study
Result summary: Disease mechanisms – Lung inflammation

Free lung cells in Broncho-alveolar lavage fluid (BALF)

Total cells absolute

Differential counts

Groups
- 3R4F
- Cessation
- Switching
- THS2.2
- Sham / Air
### ApoE−/− mouse switching study

**Result summary: Disease mechanisms - Lung inflammation**

#### Multiple analyte profiling in Broncho-alveolar Lavage Fluid

<table>
<thead>
<tr>
<th>Fluid</th>
<th>3R4F</th>
<th>THS2.2</th>
<th>Cess.</th>
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</table>
ApoE-/- mouse switching study

Result summary: Disease endpoints - Lung function and lung volume

Lung function: Pressure Volume Loops (PVsP) (FlexiVent (Scireq))

- Month 2
- Month 3
- Month 6
- Month 8

Groups:
- 3R4F
- Cessation
- Switching
- THS2.2
- Sham / Air

Means ± SEM

PMI RESEARCH & DEVELOPMENT
ApoE−/− mouse switching study

Result summary: Histopathology of the lung – Pulmonary inflammation

Results, Lung Inflammation
unpigmented macrophages in the alveolar lumen

- Decrease in mean scores after switching to fresh air or THS2.2 (statistically significant from month 6)
- No statistically significant difference between Cessation group and THS2.2-Switch group at month 3

Groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean score ± SEM</th>
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<td>3R4F</td>
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<td>THS2.2</td>
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<td>Sham / Air</td>
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</table>

*: Statistically significant compared to sham
*: Statistically significant compared to 3R4F:CONT at month 2
Switching Study in an Animal Model of Disease

Result summary: Tissue changes - Histopathology

Histopathological Assessment emphysema

Groups:
- 3R4F
- Cessation
- Switching
- THS2.2
- Sham / Air

*: Statistically significant compared to sham
**: Statistically significant compared to 3R4F:CONT at month 2
ApoE^-/- mouse switching study

Result Summary: Lung tissue changes - Morphometry

- Bronchiolar attachments
  - Fewer Bronchiolar attachments in 3R4F-exposed group

- Mean chord length (MCL)
  - Mean linear intercept length
  - Increased MCL in 3R4F-exposed group

- Destructive index (DI)
  - Index of parenchymal destruction
  - Increased DI in 3R4F-exposed group

Groups
- 3R4F
- Cessation
- Switching
- THS2.2
- Sham / Air
ApoE−/− mouse switching study
Result Summary: Systems response profile: differential gene expression - Lung

3R4F
Cessation
Switch
THS2.2

3R4F Month 1  3R4F Month 2  3R4F Month 3  3R4F Month 4

Cessation Month 3  Cessation Month 6

Switch Month 3  Switch Month 6

THS2.2 Month 1  THS2.2 Month 2  THS2.2 Month 3  THS2.2 Month 4

log2 (fold change)  -log10 (p value)  Down regulated  Up regulated

q = 0.05
# ApoE⁻/⁻ mouse switching study

**Result Summary:** Disease mechanisms - Network perturbations - Lung

<table>
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<td><strong>THS2.2</strong></td>
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</table>

- **3R4F**
- **Cessation**
  - Cell proliferation
  - Tissue repair
  - Inflammation
- **Switch**
  - Senescence
  - DNA damage
  - Apoptosis
  - Cell stress

CH & DEVELOPMENT
Switching Study in an Animal Model of Disease
Summary and Conclusions

• The ApoE⁻/⁻ mouse model is suitable for studying smoke-related aspects of COPD
• Continuous exposure to smoke from 3R4F causes lung inflammation, lung function and emphysematous changes as of one month of treatment
• Continuous exposure to aerosol from THS2.2 for up to 8 months does not increase inflammation and emphysema in comparison to Sham group
• Switching from cigarette smoke exposure after 2 months to fresh air (Sham) exposure reverses the onset of disease as measured in apical, functional, and molecular endpoints
• Switching from cigarette smoke exposure to THS2.2 aerosol exposure reverses the onset of disease in a similar manner as cessation


Ongoing study: A/J Mouse Study Design (OECD TG 453 - Chronic toxicity & Carcinogenicity Study)

This research was funded by Philip Morris International
Study Objective

• Objective: To assess the impact of lifetime exposure to THS aerosol, compared with 3R4F cigarette smoke, on development of emphysema and on lung tumor incidence and multiplicity in a 18-month exposure study in A/J mice.

• Rationale for the use of A/J mouse strain:

  The A/J mouse is highly susceptible to lung tumor induction. Several studies including ours showed aerosol concentration dependent increased lung tumors following exposure to mainstream cigarette smoke (MS) in A/J mice. (Coggins, 1998; Stinn, 2005; Stinn, 2010)

  Transcriptomics analysis demonstrated differences between lung tumors that developed from MS-exposed versus spontaneously arising tumors (Luettich, 2014)

  A/J mice also develop inflammatory and emphysematous changes following chronic exposure to MS (Stinn et al., 2012, 2013)
A/J Mouse Study Design (OECD TG 453 – Chronic toxicity & Carcinogenicity Study)

Equivalent to the 300 µg TPM/l concentration in the previous studies (Stinn et al., 2012, 2013)

26.8 µg/l nic (high dose) corresponds to 11.6 mg/kg, daily dose - or the nicotine amount from approx. 56 cig/day for a 60 kg human, based on body surface comparison, Guidance document Heq dose, FDA
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Case study 2: *In vitro* Systems Toxicology for Comparative Product Testing

This research was funded by Philip Morris International
Establishment of Reliable in vitro Systems Supports the Principles of 3Rs

Translation between species and experimental systems

- Human organotypic tissues based on primary cells cultured in three dimensions, with proper cell-cell contact, recapitulating biological functions (e.g. mucus secretion, muco-ciliary clearance,..) and allowing whole cigarette smoke exposure at the air-liquid interface.

“The Food, Drug, and Cosmetic Act directs the FDA to consult with the Institute of Medicine (IOM) on the design and conduct of studies for the assessment of MRTPs. In its 2011 report, Scientific Standards for Studies on Modified Risk Tobacco Products, the IOM identified, as a standard step in this assessment, in vitro tests for cytotoxicity, genotoxicity, proliferation, apoptosis, oxidative stress, inflammation, mucus production, and endothelial cell activation.”

PETA issued a letter in March 2014 (include reference at the bottom to the link) whereby PETA stated the in-vitro field has progressed significantly with many varied technological advances and the in vitro testing of tobacco products is no longer “limited to a small number of cytotoxicity and genotoxicity assays”

Belgium, Estonia, Germany, UK and Slovakia have banned animal testing for tobacco testing
Sampling the bronchial epithelium to identify potential biomarkers of exposure response and disease has yielded significant insights.

Many of the smoking-related changes in the bronchial epithelium are also present in the nasal and buccal epithelium.


Reduced Biological Impact of THS2.2 Aerosol Exposure was Observed in Human Nasal and Oral Cultures Compared with CS at Comparable Nicotine Concentrations

Reduced Biological Effects of THS2.2 Aerosol Exposure in Human Nasal Cultures as Compared to CS at comparable nicotine concentration

Concentrations of Representative Carbonyls (µg/mL)

FoxJ1-Marker of Ciliated Cells

Alterations in FoxJ1-proportions, ciliary frequency, secreted pro-inflammatory mediator level, and activity of CYP1A1/1B1 were markedly lower following THS2.2 aerosol than 3R4F smoke at comparable nicotine concentration (0.15 mg/L)
### A Series of Studies: Cigarette Smoke (CS) Exposure Assessment using Organotypic Three Dimensional (3D) Upper and Lower Airway Epithelial Tissue Cultures

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<td>4 cig/d (8 d)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrand 2015</td>
<td>Single exposure of whole CS</td>
<td>1 cig</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>Epithelial sodium channel activity</td>
</tr>
<tr>
<td>Azzopardi 2015</td>
<td>Single exposure of whole CS</td>
<td>30 min</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuehn 2015</td>
<td>Repeated exposure of whole CS</td>
<td>4 cigs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>CYP activity</td>
</tr>
<tr>
<td>Mathis 2015</td>
<td>Single exposure of whole CS</td>
<td>7-28 min</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>miRNA profile</td>
</tr>
<tr>
<td>Iskandar 2015</td>
<td>Single exposure of whole CS</td>
<td>28 min</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Histology, CYP activity</td>
</tr>
<tr>
<td>Schamber 2015</td>
<td>Single exposure of CSE</td>
<td>7-28 d</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Protein expression</td>
</tr>
<tr>
<td>Zanetti 2016</td>
<td>Single exposure of whole CS and RRP</td>
<td>28 min</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Histology, CYP activity, miRNA profile</td>
</tr>
<tr>
<td>Iskandar 2016</td>
<td>Single exposure of whole CS and RRP</td>
<td>28 min</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Histology, CYP activity, miRNA profile</td>
</tr>
</tbody>
</table>

CSE: cigarette smoke extract. Studies conducted at PMI.
Presentation Outline

1. Introduction

2. Eight Month ApoE\(-/-\) Mouse Inhalation Study for Comparative Tobacco Product Testing

3. *In vitro* Systems Toxicology for Comparative Product Testing

4. **Summary of ambulatory exposure clinical ZRHM-REXA-07-JP Study Results**

5. Sbv IMPROVER
Case study 3: Summary of ambulatory exposure clinical ZRHM-REXA-07-JP Study Results

This research was funded by Philip Morris International
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 Tobacco Heating System 2.2 Menthol (THS2.2 Menthol) 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.
Study Products and Interventions

= THSm2.2
(Tobacco Heating System 2.2 menthol)

= mCC
(Menthol conventional cigarettes)

= SA
(Smoking abstinence)
Primary Objective and Endpoints

• To demonstrate the reduction of biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) in smokers switching from menthol conventional cigarette (mCC) to THS2.2 Menthol (THSm2.2) compared to smokers continuing to smoke mCC

• MHBMA, 3-HPMA, S-PMA, COHb after 5 days (confinement)

• Total NNAL after 90 days (ambulatory)
Additional Objectives and Endpoints

• To determine the reduction of a list of BoExp and to determine the levels of nicotine over the entire exposure period
• To evaluate self-reported nicotine/tobacco product use and human smoking topography
• To describe product evaluation and subjective effects of smoking
• To monitor selected risk markers and the safety profiles
Study Design
Study Design

### Study Design Diagram

- **Screening**: within 1-4 weeks prior to admission
- **Admission**
- **Baseline**
  - THS 2.2 Menthol
  - Smoking Abstinence
  - mCC
- **Day 1 to Day 5**
  - THS 2.2 Menthol
  - mCC ad libitum
- **Day 6 to Day 90**
  - THS 2.2 Menthol and mCC ad libitum
- **Day 91 to Day 119**
  - 9 days in confinement
  - 85 days ambulatory
  - 28 days follow-up

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>THSm2.2 (N=78)</th>
<th>mCC (N=42)</th>
<th>SA (N=40)</th>
<th>Overall (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females – n(%)</td>
<td>33 (42.3)</td>
<td>17 (40.5)</td>
<td>18 (45.0)</td>
<td>68 (42.5)</td>
</tr>
<tr>
<td>Age (years) - Mean±SD</td>
<td>37 ± 11</td>
<td>37 ± 11</td>
<td>37 ± 10</td>
<td>37 ± 11</td>
</tr>
<tr>
<td>BMI Normal Weight– n(%)</td>
<td>60 (76.9)</td>
<td>32 (76.2)</td>
<td>32 (80.0)</td>
<td>124 (77.5)</td>
</tr>
<tr>
<td>Daily mCC Consumption– n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 cig/day</td>
<td>40 (51.3)</td>
<td>23 (54.8)</td>
<td>21 (52.5)</td>
<td>84 (52.5)</td>
</tr>
<tr>
<td>&gt; 19 cig/day</td>
<td>38 (48.7)</td>
<td>19 (45.2)</td>
<td>19 (47.5)</td>
<td>76 (47.5)</td>
</tr>
<tr>
<td>ISO Tar yields – n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 mg</td>
<td>46 (59.0)</td>
<td>22 (52.4)</td>
<td>23 (57.5)</td>
<td>91 (56.9)</td>
</tr>
<tr>
<td>6-8 mg</td>
<td>21 (26.9)</td>
<td>14 (33.3)</td>
<td>12 (30.0)</td>
<td>47 (29.4)</td>
</tr>
<tr>
<td>9-10 mg</td>
<td>7 (9.0)</td>
<td>4 (9.5)</td>
<td>2 (5.0)</td>
<td>13 (8.1)</td>
</tr>
<tr>
<td>&gt; 10 mg</td>
<td>4 (5.1)</td>
<td>2 (4.8)</td>
<td>3 (7.5)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>ISO Nicotine ≤ 0.6mg – n(%)</td>
<td>63 (80.8)</td>
<td>32 (76.2)</td>
<td>30 (75.0)</td>
<td>125 (78.1)</td>
</tr>
</tbody>
</table>

THSm2.2= THS 2.2 Menthol, mCC menthol Conventional Cigarettes, SA: smoking abstinence, SD: standard deviation.
Exposure to Harmful and Potentially Harmful Compounds
Biomarkers following 90 days of exposure (1/3)

% Reduction of acrolein exposure
Day 5: 49%
Day 90: 46%

% Reduction of 1,3 butadiene exposure
Day 5: 87%
Day 90: 82%
Biomarkers following 90 days of exposure (2/3)

% Reduction of benzene exposure
Day 5 : 89%
Day 90 : 87%

% Reduction of CO exposure
Day 5 : 55%
Day 90 : 48%
% Reduction of NNK exposure
Day 5: 56%
Day 90: 77%

% Reduction of NNN exposure
Day 5: 73%
Day 90: 71%
Product use
## Product Use – Average Daily Product Use

<table>
<thead>
<tr>
<th>Time point</th>
<th>THSm2.2 Mean±SD</th>
<th>mCC Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mCC</td>
<td>13.1±3.8</td>
<td>12.5±3.9</td>
</tr>
<tr>
<td>Day 5</td>
<td>13.9±4.3</td>
<td>13.6±4.7</td>
</tr>
<tr>
<td>Day 5-30</td>
<td>11.7±5.9</td>
<td>13.8±4.2</td>
</tr>
<tr>
<td>Day 30-60</td>
<td>12.7±6.2</td>
<td>14.9±5.7</td>
</tr>
<tr>
<td>Day 60-90</td>
<td>12.7±6.5</td>
<td>15.2±5.0</td>
</tr>
</tbody>
</table>

THSm2.2 = THS 2.2 Menthol, mCC menthol Conventional Cigarette, SD: standard deviation; n: subjects in the main analysis population (Per Protocol Set)
Nicotine Uptake

Exposure THSm2.2 vs. mCC

- Nicotine uptake profile is similar, marginally higher for THSm2.2
  - 80% of subjects smoke low-nicotine containing mCC.
  - A process of adaptation is observed throughout the 3-month period, resulting in a 4% difference on day 90.
  - Nicotine yield in mCC variable, and fixed in THSm2.2

Nicotine exposure:
Day 5: 16% higher in THSm2.2 vs mCC
Day 90: 4% higher in THSm2.2 vs mCC

![Graph of Nicotine Uptake over Visit Days]
### Selected Clinical Risk Endpoints
(Indicative results, not statistically significant)

<table>
<thead>
<tr>
<th>Disease Pathway</th>
<th>Marker</th>
<th>Expected SA Effect at 6m(*)</th>
<th>REXA-07 SA Effect at 3m</th>
<th>REXA-07 THS Effect at 3m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Metabolism</td>
<td>HDL-C</td>
<td>4.13 mg/dL</td>
<td>6.4 mg/dL</td>
<td>4.5 mg/dL</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
<td>-0.81 10^9/L</td>
<td>-0.41 10^9/L</td>
<td>-0.57 10^9/L</td>
</tr>
<tr>
<td>Airway Impairment</td>
<td>FEV₁</td>
<td>2.18 %pred</td>
<td>1.93 %pred</td>
<td>1.91 %pred</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>sICAM-1</td>
<td>20.0 %reduction</td>
<td>10.9 %reduction</td>
<td>8.7 %reduction</td>
</tr>
<tr>
<td>Oxidative Stress</td>
<td>8-epi-PGF$_{2α}$</td>
<td>32.0 %reduction</td>
<td>6.0 %reduction</td>
<td>12.7 %reduction</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B$_2$</td>
<td>22.0 %reduction</td>
<td>19.4 %reduction</td>
<td>9.0 %reduction</td>
</tr>
</tbody>
</table>

(*) Expected SA effect from literature data
Safety

- No serious or severe adverse events (AEs).
- During the run-in (product test), 22 AEs observed in 16 (9%) of 175 enrolled.
- Following randomization, 49 AEs in 32 (41%) subjects in THS, 22 AEs in 14 subjects for both mCC (33%) and SA (35%) arms. One mild not expected AE related to product in THS arm (Diarrhea). Most frequent AEs were decreased hemoglobin and decreased neutrophils.
- No clinically relevant abnormality in vital signs, ECGs, or physical examination.
Common conclusion

- All studies demonstrated that switching from mCC smoking to THSm2.2 aerosol resulted in substantial reductions in exposure to selected HPHCs.
- Reduction following switching to THSm2.2 achieved HPHC levels close to those observed following smoking abstinence (SA).
- Initial exploratory clinical data on monitored risk markers indicate favorable shifts in the direction of SA. While in ApoE-/- mice, switching from cigarette smoke exposure to THS2.2 aerosol exposure reverses the onset of disease in a similar manner as cessation.
Presentation Outline

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3. \textit{In vitro} Systems Toxicology for Comparative Product Testing

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5. Sbv IMPROVER
sbv IMPROVER Leverages the Crowd to Complement the Classical Peer Review System

- **Crowd-sourcing**: A natural evolution of web technologies led to the development of distributed problem-solving. Challenges are broadcasted to potential interested stakeholders (solvers). The winning participants are rewarded either with monetary awards, prizes, certificates, or with recognition.

- **Collaboration by Competition**: The scientific community sought to understand the limitations and comparative advantages of their methods by challenging model developers to make blind predictions on previously unseen data in a competitive framework.

- The community appreciates the successful methods which grow in credibility. Therefore, consideration of the scientific community is one of the forces that shape what is currently considered as the way to do the science right.

sbv IMPROVER Leverages the Crowd to Complement the Classical Peer Review System

Marriott Waterfront Hotel
Baltimore, MD, USA
7th November 2016

Systems Toxicology Symposium
Description of the scientific assessment program

Poster session™ - ACT 2016

1. Intro Presentation 7:30
2. Poster Review 8:00
3. SciPi™ Survey 8:00
4. Results & Discussion 9:00
5. Networking 9:30

Question 1?
- Answer a
- Answer b
- Answer c

Question 2?
- Answer d
- Answer e
- Answer f

SciPinion

Non-clinical and early clinical assessment of THS2.2, a heated tobacco product

PMI RESEARCH & DEVELOPMENT
Thank You For Your Attention!

Peitsch, M; Hoeng J; Vanscheeuwijck, P; Luettich, K, Ee Tsin
(Study Design)

Tissue Processing
Trivedi, K
Benyagoub, A

Transcriptomics
Guedj, E
Baumer, K
Dulize, R
Peric, D
Bonard, D

Seow, E (Bioanalytics, dissection and histoprocessing)
Bundularatne,E & Ng,G
(Veterinarian)
Ansari, S (Biobanking)

Computational Analysis
Martin, F
Xiang, Y
Titz, B
Talikka M

PMI high performance computing
PMO team, Betch P,
Lebrun S, Schilli L,
Ertan A

Statistical Analysis
Leroy, P
Gregory, V

Genomics
Sierro, N
Ouadi, S
Thomas, J
Batty, J

Proteomics
Elamin, A
Nury, C
Schneider, T
Dijon, S
Titz B

Ivanov N
Research Technologies

PMI cellular labs
Frentzel, S, Iskandar A,
Majeed S, Zanetti F et all.

The Singapore Team
Thank you for your attention