Individual exposure levels in subjects switching to a Tobacco Heating Product for 5 days

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ENDS UK | London, United Kingdom | 6th June 2019
Disclosures

I declare that this work was fully funded by British American Tobacco (BAT) and I am a full-time employee of British American Tobacco (Investments) Ltd. BAT develops, manufactures and sells tobacco and nicotine products around the world.
Agenda

▪ Investigational product/Risk Assessment Framework
▪ Study Objectives
▪ Study Design
▪ Biomarkers of Exposure (BoE)
▪ Results
▪ Summary
glo THP

- Tobacco Neostik, single use and disposable
- Heats to ~240°C sufficient to release nicotine & flavours without combustion
- Battery-operated and recharged by micro USB

Emissions show much-reduced toxicant levels compared to cigarettes*

**TOXICANTS OF INTEREST glo vs cigarette**

<table>
<thead>
<tr>
<th>Toxicants</th>
<th>glo</th>
<th>Cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (9 PRIORITY TOXICANTS)</td>
<td>3%</td>
<td>100%</td>
</tr>
<tr>
<td>FDA (18 PRIORITY TOXICANTS)</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>HEALTH CANADA (MAIN 44 TOXICANTS)</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>FDA (93 HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS)</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products

Our Framework to Establish Reduced Risk Potential

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Type of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population risk reduction</td>
<td>Post-market surveillance</td>
</tr>
<tr>
<td></td>
<td>Consumer perception study</td>
</tr>
<tr>
<td>Individual risk reduction</td>
<td>Systems science</td>
</tr>
<tr>
<td></td>
<td>Biomarker of effect study</td>
</tr>
<tr>
<td>Toxicant exposure reduction</td>
<td><em>In vitro</em> models of disease</td>
</tr>
<tr>
<td></td>
<td>Exposure &amp; pharmacokinetic studies</td>
</tr>
<tr>
<td></td>
<td>Computational toxicology</td>
</tr>
<tr>
<td>Stewardship science</td>
<td><em>In vitro</em> regulatory toxicology</td>
</tr>
<tr>
<td></td>
<td>Chemical &amp; physical characterisation</td>
</tr>
<tr>
<td></td>
<td>Product design stability</td>
</tr>
</tbody>
</table>

**Study Title**

A Randomised Controlled Single-Centre Open-Label Study in Healthy Subjects to Evaluate the Effect on Biomarkers of Exposure (BoE) of Switching from a Combustible Cigarette to a Potentially Reduced Risk Product

**Study Objectives**

To quantitatively assess within-arm changes in Biomarkers of Exposure (BoE) and Biomarkers of Biological Effect (BoBE) when smokers switch to glo THP or cessation
Ethical & Regulatory Considerations

ORECNI
Office for Research Ethics Committees Northern Ireland
(ORECNI; ref.: 17/NI/0065)

ISRCTN registry
Registry number: ISRCTN80651909

Study Location: Belfast, United Kingdom
Study Population

**Age & Gender**
Healthy male or female smokers, aged 21 – 55 years
- Smoking status verified by urinary cotinine and eCO at Screening and Admission
- Healthy status verified by vital signs, clinical laboratory evaluations, physical examination, ECG and lung function tests

**Smoking History**
Typically smoke 10 – 30 FMCs per day, within 6 – 8 mg ISO tar bands
- Min. 6 month use of current brand and 3 years smoking history, prior to Screening

**Main Exclusion Criteria**
Planning to quit smoking in next 12 months
- Regular use of nicotine or tobacco products other than FMCs
- Non-inhalers (self-reported or observed at Admission)
Biomarkers of Exposure (BoE)

**Exhaled breath**
- Carbon monoxide (eCO)

**Urine**
- Urinary biomarkers

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<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Smoke Constituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Nicotine equivalents</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Total NNAL</td>
<td>NNK</td>
</tr>
<tr>
<td>Total NNN</td>
<td>NNN</td>
</tr>
<tr>
<td>3-HPMA</td>
<td>Acrolein</td>
</tr>
<tr>
<td>HMPMA</td>
<td>Crotonaldehyde</td>
</tr>
<tr>
<td>S-PMA</td>
<td>Benzene</td>
</tr>
<tr>
<td>MHBMA</td>
<td>1,3-Butadiene</td>
</tr>
<tr>
<td>CEMA</td>
<td>Acrylonitrile</td>
</tr>
<tr>
<td>HEMA</td>
<td>Ethylene oxide</td>
</tr>
<tr>
<td>AAMA</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>GAMA</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>4-ABP</td>
<td>4-Aminobiphenyl</td>
</tr>
<tr>
<td>o-Tol</td>
<td>o-Toluidine</td>
</tr>
<tr>
<td>2-AN</td>
<td>2-Aminonaphthalene</td>
</tr>
<tr>
<td>1-OHP</td>
<td>Pyrene</td>
</tr>
</tbody>
</table>

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**Nicotine + 5 metabolites**

**Tobacco Specific Nitrosamines (TSNAs)**

**Mercapturic Acids**

**Aromatic Amines**

**Polycyclic Aromatic Hydrocarbons (PAH)**
Study Design

- A single-centre, randomised, open label, 5-arm, 5-day *ad libitum* Exposure study during 8-day confinement

- Nicotine PK at end of confined switching period, during defined single-use session

- 30 subjects in each of the study groups = 150 subjects
## Study Design

- *Ad libitum* use of all products in study (max. 120% of self-reported CPD) excluding cessation group from days 3 to 7

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine sample</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Exhaled CO (eCO)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood sample</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Pharmacokinetics (PK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Results

Significant reductions in eCO and SPMA following switch*

*eCO

SPMA

Mean eCO (ppm)

Mean SPMA (ng/24-hrs)

Baseline Day 2 to 3 Day 3 to 4 Day 4 to 5 Day 5 to 6 Day 5 to 7

Baseline Day 2 to 3 Day 4 to 5 Day 6 to 7

Lucky Strike glo Nicotine Cessation

*These qualities do not necessarily mean this product produces less adverse health effects than tobacco products
Results

- Significant reductions in NNAL following switch
- Total Nicotine remained high, but flat following switch to glo THP*

![Graph showing NNAL and Tneq levels over time for Lucky Strike, glo, and Nicotine Cessation.]

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Results

Generally, levels of BoE significantly reduced following switch*

Mean excretion on Day 6 to 7 vs excretion at Baseline

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**O-Tol sensitivity analysis with one subject value removed from cessation group. With this value included cessation shows an increase of 274.7%**

**FF GAMA showed significant reductions in the glo group when Holm’s adjustment for multiplicity was applied**
Summary

- Data shows significant reduction in all BoEs (with o-Tol sensitivity test) and in a number of cases these are similar reductions to nicotine cessation

- These data may suggest the potential of glo THP as a potential reduced-risk product

- Further clinical studies would be necessary to:
  - demonstrate that these reductions continue or are sustained
  - quantify any translation to reductions in smoking-related health risks i.e. Biomarkers of Potential Harm (BoPH)
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THANK YOU

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