A study to examine changes in exposure to cigarette smoke chemicals when a smoker switches to using a tobacco heating product.

Part I: Study Design.

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Content

Part I
• Background
• The glo™ tobacco heating product
• Biomarker of exposure study design

Part II
• Data
• Discussion
Tobacco Harm Reduction and the Risk Spectrum of Products

High

Conventional Cigarettes

Tobacco Heating Products (THPs)

Low-toxicant Smokeless Tobacco

Vapour Products (E-Cigarettes)

Licensed Medicinal Products

Level of Toxicants

Low

Tobacco products that involve no combustion

Nicotine products that contain no tobacco and involve no combustion
Substantiating the Risk Reduction Potential of Novel Products

- Population risk reduction
  - 10) Post-market surveillance
  - 9) Consumer perception study
- Individual risk reduction
  - 8) Biomarker of effect study
  - 7) Systems Science
- Toxicant exposure reduction
  - 6) *In vitro* models of disease
  - 5) Exposure and pharmacokinetic studies
  - 4) Computational toxicology
- Stewardship science
  - 3) *In vitro* regulatory toxicology
  - 2) Chemical and physical characterisation
  - 1) Product design stability
The glo™ Tobacco Heating Product

Battery-operated and recharged by microUSB

Heats a tobacco ‘Neostik’ to ~240°C

Neostiks are single-use and disposable

Emissions show much-reduced toxicant levels compared to cigarettes
Demonstrating Reduced Exposure – A BoE Study

• “A randomised, controlled, multi-centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional combustible cigarette to the glo™ tobacco heating product”

• ISRCTN14301360, UMIN000024988; IRB-approved

• Clinical conduct run at two clinics in Fukuoka, Japan
Objectives

Primary Objective

• To quantitatively assess within-arm changes in BoE and BoBE following a forced switch from a conventional cigarette to a NGP or cessation

Secondary Objectives

• To assess differences between arms in BoE and BoBE following a forced switch from a conventional cigarette to a NGP or cessation
• To determine nicotine PK parameters for the study products
• To assess subjects’ satisfaction with the study products
• To monitor the safety profile of subjects using THP products and conventional cigarettes, and subjects undergoing smoking cessation
Study Population

- Healthy male or female smokers, of Japanese origin, aged 23 – 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

- 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)
### Which Toxicants?

- **Biomarkers of Exposure (BoE) to a range of particulate and vapour phase smoke constituents:**
  - Carbon monoxide in exhaled breath
  - Urinary biomarkers:

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Smoke Constituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Nicotine equivalents (Nic + 5)</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Smoke Constituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEMA</td>
<td>Acrylonitrile</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>
<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>
</tbody>
</table>
Additional Endpoints

• **Biomarkers of Biological Effect (BoBE) / Biomarkers of Potential Harm (BoPH):**
  • In blood: white blood cell count – indication of general inflammation
  • In urine: 8-epi-PGF$_{2\alpha}$ (Type III) – indication of oxidative stress

• **Nicotine pharmacokinetics (PK)**
  • Determination of:
    • $C_{\text{max}}$ (Maximum concentration of nicotine in the blood plasma)
    • $T_{\text{max}}$ (Time from 1st puff to maximum plasma nicotine concentration)
    • AUC (Total amount of nicotine absorbed)
Study Design

- Research subjects resident in the clinic for 7 or 8 consecutive days
- 30 subjects in each of the study groups = 180 subjects
Study Design
Baseline period

- All subjects smoked cigarettes for two consecutive 24-hour periods
  - *Ad libitum* use (max. 120% of self-reported CPD)
  - Menthol smokers smoked menthol variant of cigarette

- All urine voided by each subject collected over each 24-hour period
  - Urine tested for biomarkers of exposure

- Carbon monoxide in exhaled breath measured on both days

- A ‘spot’ sample of blood also collected on Day 2
  - Blood sample analysed for white blood cell count
**Study Design**

**Exposure period**

- At end of baseline period, subjects randomised to one of six arms:

<table>
<thead>
<tr>
<th>Subject Type</th>
<th>Study Arm</th>
<th>Baseline Period</th>
<th>Exposure Period</th>
<th>PK Assessment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-menthol smokers</td>
<td>A</td>
<td>Conventional cigarette ( N = 120 )</td>
<td>Conventional cigarette ( N = 30 )</td>
<td>Conventional cigarette ( N = 30 )</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Conventional mentholated cigarette ( N = 60 )</td>
<td>glo™ THP with Neostik ( N = 30 )</td>
<td>glo™ THP with Neostik ( N = 30 )</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>iQOS THP with HeatStick ( N = 30 )</td>
<td>iQOS THP with HeatStick ( N = 30 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Cessation ( N = 30 )</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Menthol smokers</td>
<td>C</td>
<td>Conventional mentholated cigarette ( N = 60 )</td>
<td>Conventional mentholated cigarette ( N = 30 )</td>
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<td></td>
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<td>glo™ THP with mentholated Neostik ( N = 30 )</td>
<td>glo™ THP with mentholated Neostik ( N = 30 )</td>
<td></td>
</tr>
</tbody>
</table>
Study Design

Exposure period

- All urine voided by each subject collected over each 24-hour period
- Urine tested for biomarkers of exposure
- Exhaled breath measured on each day for carbon monoxide
- A ‘spot’ sample of blood also collected on Days 5 and 7
  - Blood sample analysed for white blood cell count
Study Design

PK assessment period

• All subjects, excluding those in the smoking cessation group

• No nicotine used from the end of Day 7 (min. 12-hours)

• Each subject had a single use of their assigned product
  • Puff count recorded

• Blood samples collected from -5min before, during, and to 240min after product use

• Samples individually processed and analysed for nicotine
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An overview of our research activities

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