A clinical study in Japanese smokers investigating changes in exposure to cigarette smoke chemicals in participants who switch to using a tobacco heating product for a five day period

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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)
Biomarkers of Exposure

- **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</td>
<td>Nicotine</td>
</tr>
<tr>
<td>(Nic + 5)</td>
<td></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>
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<tr>
<td>MHBMA</td>
<td>1,3-Butadiene</td>
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</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>
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</tbody>
</table>

- **Additional endpoints**
  - Biomarkers of effect - Urinary 8-epi-PGF2α (Type III) and Blood white blood cell count
  - Nicotine pharmacokinetics ($C_{max}$, $T_{max}$ and AUC)
Study Design

• A multi-centre, randomised, open label, 6 arm, confinement study 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 = 180 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
  - Menthol smokers were assigned to menthol products

- All urine voided by each subject collected over each 24-hour period (Days 1 to 7)
  - Urine tested for biomarkers of exposure

- Carbon monoxide in exhaled breath measured on all 7 days

- A ‘spot’ sample of blood also collected on Days 2, 5 and 7
  - Blood sample analysed for white blood cell count

- Nicotine pharmacokinetic assessment on Day 8 (excluding cessation group)
  - 12 hour nicotine abstinence
  - 5 minutes use of assigned product
Biomarkers of Exposure

- We have assessed the main biomarker of exposure data
  - Determined mean baseline excretion and mean excretion on each day, by group
  - N=30 for each group, unless stated otherwise

- In the subsequent line graphs, for clarity:
  - Data has been normalised (group mean baseline values set at 100)
  - Values above 100 indicate an increase in exposure
  - Values below 100 indicate a decrease in exposure
  - No variability estimates are shown

- We are yet to assess the biological effect markers and PK data
Biomarker of Exposure
To benzene

Mean urinary excretion of S-PMA (Biomarker of exposure to benzene)

- Non-menthol cigarette
- Non-menthol glo™ THP
- Menthol cigarette
- Menthol glo™ THP
- Cessation
Biomarkers of Exposure
To other vapour phase toxicants

Mean urinary excretion of HMPMA (Biomarker of exposure to crotonaldehyde)

Mean urinary excretion of 3-HPMA (Biomarker of exposure to acrolein)

- Non-menthol cigarette
- Non-menthol glo™ THP
- Menthol cigarette
- Menthol glo™ THP
- Cessation
Biomarker of Exposure
To NNK

Mean urinary excretion of Total NNAL (Biomarker of exposure to NNK)

- Non-menthol cigarette
- Non-menthol glo™ THP
- Menthol cigarette
- Menthol glo™ THP
- Cessation
Biomarkers of Exposure

Summary

Mean excretion on Day 7 vs. mean excretion at Baseline

- Non-menthol cigarette
- Non-menthol glo™ THP
- Menthol cigarette
- Menthol glo™ THP
- Cessation
Summary

- First clinical study on the glo™ THP

- When smokers switched from smoking conventional cigarettes to glo™ THP, their exposure to cigarette smoke toxicants was significantly reduced
  - Variable reductions; many reaching levels similar to cessation

- These data may suggest the potential of the glo™ THP as a 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
Acknowledgements

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