Clinical biomarkers of compliance for use in potentially reduced risk product switching studies

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<table>
<thead>
<tr>
<th>PHASE</th>
<th>STAGE (TYPE OF STUDY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Product design stability</td>
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<td></td>
<td>2. Chemical and physical characterisation</td>
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<td></td>
<td>3. In vitro Regulatory Toxicology</td>
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<td>4. Computational Toxicology</td>
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<td>5. In vitro models of disease</td>
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<td>6. Systems Science</td>
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<td>7. Exposure and pharmacokinetic studies</td>
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<td>8. Biomarker of effect study</td>
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<td>9. Consumer perception study</td>
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<td>10. Post-market surveillance</td>
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12-month Biomarker of Potential Harm Study

A randomised, controlled study to evaluate the effects of switching from cigarette smoking to using a Tobacco Heating Product on health effect indicators in healthy subjects.
## Study Design

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Visit</th>
<th>Intend-to-quit population</th>
<th>Conventional Cigarette</th>
<th>NGP Assisted Smoking Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Cigarette Use; n = 190</td>
<td>n = 50</td>
<td>n = 50</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Cigarette Use; n = up to 200</td>
<td>n = 50</td>
<td>n = 50</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Cigarette Use; n = up to 80</td>
<td>n = 50</td>
<td>n = 50</td>
</tr>
</tbody>
</table>

### Compliance is Key!

Ambulatory design | 506 enrolled subjects

Confidential – for discussion purposes only
Biomarkers of Compliance

- **Plasma Vitamin C and Carotenoids (Noad et al., 2016)**
  Dietary study on Polyphenol-rich diet on CVD risk

- **Serum non-cholesterol sterol concentrations (Mateo-Gallego et al., 2015)**: Familial Dyslipidemia study

- **DHA in plasma and isoflavones in urine (Harrison et al. 2004)**: Study on dietary effects on coronary disease

- Use of creatinine as a measure of completeness of 24 hour urine collection

- Urinary Phenylacetylglutamine (Mokhtarani et al., 2012)
  Study on sodium/glycerol phenylbutyrate
Requirements for Biomarkers of Compliance in a tobacco context

- **Specificity**
  - Must be specific for exposure to either the test or reference product emissions
  - Preferably not confounded by environmental or dietary sources

- **Sensitivity**
  - Can discriminate between levels of product use

- **Analytical Method**
  - Preferably rapid analytical methods – but not essential
  - Recommended - Biomarkers of compliance are not used as endpoints in the study
2-Cyanoethylvaline

Acrylonitrile converted to Glycidonitrile by epoxidation
- Can then attach to proteins or DNA as an adduct
- For Haemoglobin it attaches to the Valine terminal amino acid

2-Cyanoethylvaline (CEVal) Hb adduct
- Long-term Biomarker - Erythrocytes life-cycle 90 to 120 days
### Strategy for CEVal in the 1-Year BoPH study

#### Categorisation of subjects using CEVal levels
- Conservative estimate
- After the study, model will be reviewed with Cessation arm data

<table>
<thead>
<tr>
<th>Category</th>
<th>Day 90</th>
<th>Day 180</th>
<th>Day 360</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highly Likely Smoking</strong></td>
<td>&gt;164 pmol/g Hb</td>
<td>&gt;112 pmol/g Hb</td>
<td>&gt;78 pmol/g Hb</td>
</tr>
<tr>
<td><strong>Potential Dual Use</strong></td>
<td>78 - 164 pmol/g Hb</td>
<td>54 - 112 pmol/g Hb</td>
<td>35 - 78 pmol/g Hb</td>
</tr>
<tr>
<td><strong>Potential Solus Use</strong></td>
<td>&lt;78 pmol/g Hb</td>
<td>&lt;54 pmol/g Hb</td>
<td>&lt;35 pmol/g Hb</td>
</tr>
</tbody>
</table>
Provisional Day 90 data

**CEVal**
(Compliance marker)

- In glo arm 67% reduction in mean CEVal concentration at Day 90 compared to Day 1
- 79% reduction in “compliant” glo arm
- 83% reduction in “compliant” Cessation arm
- Red lines show categories at Day 90
Summary

- For large ambulatory Clinical studies ‘Compliance is key’
- Biomarkers of Compliance are a potential aid for monitoring compliance
- Specificity and Sensitivity are required
- CEVal has been employed in the BAT 1 year BoPH study
- Results at Day 90 show good compliance, but some non-compliance and Dual use
- Further work will be carried out after the study to refine the ‘rules’ for identifying compliant subjects using CEVal
THANK YOU

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