Changes in Biomarkers of Exposure on Switching from a Conventional Cigarette to Tobacco Heating Products: A Randomised, Controlled Study in Healthy Japanese Subjects

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Introduction

Smoking is a leading cause of numerous human disorders including pulmonary disease, cardiovascular disease and cancer. Disease development is primarily caused by years of exposure to cigarette smoke constituents, many of which are known toxins. Switching smokers to modified risk tobacco products (MRTPs) has been suggested as a potential means to reduce the risks of tobacco use, by reducing such exposure. We recently reported a proof-of-concept study of the glo tobacco heating product (THP1.0),1,2 which electronically heats tobacco to a temperature of around 240°C,3 and both its yields of machine-measured toxics and environmental emissions are greatly reduced compared to those from conventional cigarettes.4,5

Aim

To determine whether reductions in machine yields translate into a lowering of toxicant exposure, by measuring biomarkers of exposure (BoE) in a clinical confinement study in Japanese subjects who either continued smoking, switched to the glo (THP1.0) or an in-market comparator tobacco heating product (IQOS/THS), or abstained completely from tobacco product use, for 5 days.

Methods

Study Design

The full study protocol has been published previously.6 In brief, this was a randomised, controlled, 6-arm, parallel group, open-label study conducted at two sites in Fukuoka, Japan (ISCTRIN1403190 / UMIN00024988), 180 healthy Japanese smokers smoked combustible cigarettes during a 2-day baseline period. After this period, they were randomised to either continue smoking, switch to using mentholated or non-mentholated variants of the glo THP, switch to using a non-mentholated variant of the IQOS THP, or quit any nicotine or tobacco product use completely, for 5 days (Figure 1). Both baseline and post-randomisation, 24-h urine samples were collected for BoE analysis. Carbon monoxide was also measured daily in exhaled breath (eCO). Data from the pharmacokinetic assessment, which took place on Day 8, is not reported here.

Subjects

- Aged 23-55 years
- Provided informed consent
- 3+ years’ consecutive smoking
- 10-30 cigarettes per day
- ISO tar band 6-8 mg/cig
- Deemed healthy at Screening by the Investigator
- Not planning to quit smoking in next 12 months*  

Sample Size

Based on the BoE requiring the most pairs to power and allowing for potential attrition, a sample size of 30 subjects per group was deemed sufficient to perform a paired t-test with 80% power for a decrease in BoE levels of ≥40%. This sample size was also determined to provide sufficient power for the secondary objective of between-group comparisons, based on a minimum of a 40% reduction in BoE.

Statistical Analysis

For biomarker data, the mean of the 2 values taken prior to first randomised product-use was used as the baseline value. Baseline and Day 7 values were used to investigate within-arm changes in biomarkers for each arm separately using a paired t-test. These values were also used to compare between arms using a mixed ANOVA.

Study Products

- 7mg/cig ISO tar non-menthol cigarette tobacco
- 7mg/cig ISO tar mentholised cigarette tobacco
- glo (THP1.0) THP with non-menthol Neostics
- glo (THP1.0) THP with menthol Neostics
- IQOS (THS) THP with non-menthol consumables

Results

Subject Demographics

<table>
<thead>
<tr>
<th>Non-menthol</th>
<th>glo THP</th>
<th>Menthol</th>
<th>glo THP</th>
<th>IQOS THP</th>
<th>Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>32 ± 8.2</td>
<td>34 ± 10.1</td>
<td>33 ± 8.6</td>
<td>31 ± 7.7</td>
<td>33 ± 9.5</td>
</tr>
<tr>
<td>Mean F/M</td>
<td>15:15</td>
<td>15:15</td>
<td>14:16</td>
<td>16:14</td>
<td>15:15</td>
</tr>
<tr>
<td>Mean CPD ± SD</td>
<td>17.5 ± 5.7</td>
<td>17 ± 4.6</td>
<td>15 ± 3.9</td>
<td>15 ± 4.3</td>
<td>15 ± 3.7</td>
</tr>
<tr>
<td>Mean FTCD score</td>
<td>5.2 ± 2.0</td>
<td>5.1 ± 1.6</td>
<td>5.1 ± 1.7</td>
<td>4.2 ± 2.2</td>
<td>4.1 ± 1.5</td>
</tr>
</tbody>
</table>

Safety

14 exposure period AEs [12 mild, 1 moderate, 1 severe] were reported by 10 of the 180 subjects (5.6%). The numbers are similar for all study arms. The severe AE, which was considered to be an SAE, was a pregnancy detected at discharge (negative at Screening and Admission). None of the 14 exposure period AEs were considered to be related to the study product.

Biomarker Results – Within group comparisons

All urinary and exhaled BoE assessed following the switch from a conventional cigarette to either menthol or non-menthol variants of the glo THP, the IQOS THP or to cessation were substantially and significantly decreased from baseline on Day 7 (p < 0.05) with the exception of total nicotine equivalents (TNeq) for the IQOS group (p = 0.09). Figure 3 shows the arithmetic mean of all subjects’ percentage change from baseline at Day 7, for each BoE assessed.

Figure 3: Mean percentage change from baseline at Day 7

BoE: Abbreviation [Smoke constituent, if different]: Exhaled carbon monoxide, eCO; Total nicotine equivalents [nicotine, cotinine, 3,4-`hydroxyctamine and their glucuronide conjugates], TNeq; 1-hydroxypropanone, 1-OHP; Glucuronides: 2-aminopyridine, 2-AN; 3-hydroxypropanomycinic acid, 3-HMPMA; Acrylamides, AAPP; acrylamido; 4-aminothiazole, 4-AT; 4-amino-3-carboxyarylthiobenzoylacetic acid, AAMTA [Acrylamide]; 2-cyano-3-oxo-N-ethylacrylamide, CENAA [Acrylamide]; N-acetyl-5-(2- hydroxy-2-carboxyethylsulfocyanate, GAMA [Acrylamide]; 2-hydroxy-3-methyl-1-propanomycinic acid, HMPMA [Crotalinidahyde]; monohydroxybutenyl-mercaptoacetic acid, MBHMA [1,3-butanediol]; S-nitrosodimethylnitrosamine, SDNM; B-nitrosomethylurea; 4,5-dihydro-1,2-benzofuro[3,4-b]pyridine-3-carboxylic acid, Total NNAL (4-methylthiorosamine-1-(5-oxopyridin-1)-butan-1-one) N-nitrosonicotine and its glucuronide conjugates, Total NNN = Tobuline, arN

Biomarker Results – Between group comparisons

For the majority of the BoE, the magnitude of the reductions from baseline in the glo THP groups were similar to those observed in the cessation group. Changes from baseline on Day 7 for 3-HMPMA, HMPMA, S-MHA, CEMA, 4-ABP, o-tol, 2-AN, Total NNAL, and glo THP groups were not significantly different compared to the cessation group (p > 0.05 in all cases). Similarly, changes from baseline for eCO in the non-menthol glo THP group, and Total NNAL and 1-OHP in the menthol glo THP group, were not significantly different compared to the cessation group. Finally, although statistically-significant decreases from baseline were observed on Day 7 in both glo THP variant groups TNEQ, AAMA, and GAMA, the changes from baseline were significantly smaller than those observed in the cessation group (p < 0.05 in each case).

Conclusion

This clinical study demonstrated that when smokers switched from smoking combustible cigarettes to using tobacco heating products (glo or IQOS), their exposure to smoke toxics was significantly decreased. In many cases, this was to the same extent as that seen when subjects quit smoking completely. These results suggest that tobacco heating products have the potential to be reduced exposure and/or reduced risk tobacco products when used by smokers whose cigarette consumption is displaced completely.

Disclosure

This work was funded in full by British American Tobacco (Investments) Ltd. All authors are or were current employees of British American Tobacco at the time of the study.

References


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* All subjects were informed that they were free to quit smoking and withdraw from the study at any time. Any subject who decided to quit smoking was directed to appropriate stop smoking services.