A Clinical Study Investigating Changes in Exposure to Cigarette Smoke Chemicals in UK Smokers Who Switch to Using a Tobacco Heating Product Over a Five Day Period

Michael McEwan[1], Nathan Gale[1] , Alison Eldridge[1], Graham Errington[1], Donald Graff[2], James Murphy[1] , Christopher J. Proctor[1], Ian M. Fearon[2].

[1]British American Tobacco (Investments) Ltd, Southampton, SO15 8TL, UK

[2]Celerion Inc, Lincoln, Nebraska, 68502, USA.

Correspondence: mike_mcewan@bat.com

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Introduction

Smoking is a leading cause of numerous human disorders including lung cancer, chronic obstructive pulmonary disease, and atherosclerotic cardiovascular disease. Switching smokers to modified risk tobacco products (MRTPs) has been suggested as a potential means to reduce the risks of tobacco use, by reducing exposure to cigarette smoke toxicants.

Next Generation Products (NGPs) are nicotine delivering devices that can be broadly categorised as either electronic inhalable vapour products (e-cigarettes) or Tobacco Heating Products (THPs).

THPs are electronic devices that heat tobacco, rather than combust it. We recently reported a pre-clinical assessment 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 toxicants 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 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.

Materials and Methods

Study Design

In brief, this was a randomized, controlled, 5-arm, parallel group, open-label study conducted at a single site in Belfast, UK (ISRCTN80651909). 150 healthy smokers smoked combustible cigarettes during a 2-day baseline period. The subjects were then randomized to either continue smoking cigarettes, switch to using the glo THP, 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 e-cigarette exposure and the pharmacokinetic assessment, which took place on Day 8, is not reported here.

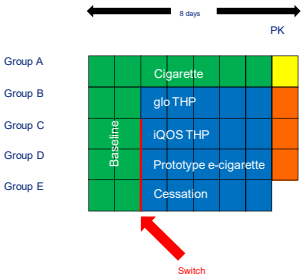


Figure 1. Diagram representing the study design.

Subjects

- Aged 21-55 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*

** 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.*

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.

Study Products

- 7mg/cig ISO tar **non-menthol cigarette**
- **glo** (THP1.0) **THP** with **non-menthol** Neostiks
- Prototype **e-cigarette** with Tobacco Flavoured e-liquid
- **iQOS** (THS) **THP** with non-menthol consumables

Figure 2. The glo tobacco heating product.

Results

Figure 3. Exhaled Carbon Monoxide

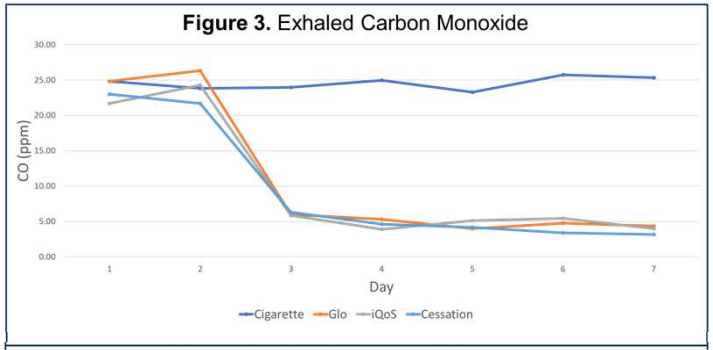
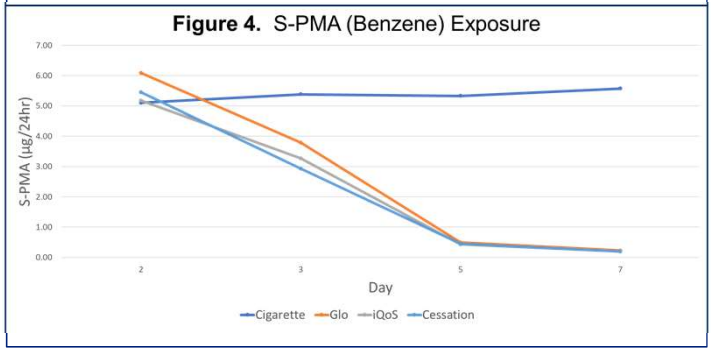


Figure 4. S-PMA (Benzene) Exposure



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Biomarker Results

Preliminary results for exhaled Carbon Monoxide (eCO) and urinary S-Phenylmercapturic Acid (S-PMA) a BoE to benzene are shown in figures 3 and 4 respectively. These both show that following the switch from a conventional cigarette to either the glo THP, the iQOS THP or to cessation show a substantial decrease in levels from baseline to Day 7.

Compared to baseline values the levels of eCO show a mean reduction of 80% for the glo THP, for subjects who switched to this product. Urinary S-PMA levels were reduced by 93% in subjects switching to glo.

Conclusions

This was the first clinical BoE study conducted in Western Europe on the glo THP product.

These initial results demonstrate that when smokers switched from smoking combustible cigarettes to using tobacco heating products (glo or iQOS), their exposure to some smoke toxicants was decreased. For levels of eCO and urinary S-PMA these reductions in exposure were similar in extent to that seen when subjects quit smoking completely. These preliminary 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.

Further studies are required to assess where these NGPs lie on the continuum of risk for nicotine containing products[6] and would be necessary to:

- demonstrate that these reductions continue or are sustained over a longer period of time,
- quantify any translation to reductions in smoking-related health risks

References

Disclosure

This work was funded in full by British American Tobacco (Investments) Ltd. All authors except D. Graff are or were current employees of British American Tobacco at the time of the study. D. Graff is an employee of Celerion Inc. who were contracted to perform the clinical and selected bioanalytical services for this study.

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[2]Celerion Inc., Lincoln, Nebraska, 68502, USA.

Correspondence: mike_mcewan@bat.com

Abstract

Tobacco Heating Products (THP) are electronic devices that heat tobacco, rather than combust it. Due to this lack of combustion, significantly fewer chemical toxicants are formed but nicotine is still released into the inhaled aerosol. Clinical studies measuring biomarkers of exposure (BoE) are an important method to determine if this translates into a reduction in exposure to cigarette smoke toxicants when smokers switch to using a THP.

A clinical study with 150 subjects was conducted to investigate changes in exposure to selected smoke toxicants when smokers switched to using a THP. This study, conducted in Belfast, UK (ISRCTN80651909), was approved by a local Research Ethics Committee and run in accordance with ICH-GCP.

The study comprised of a 2-day baseline phase and a five day exposure phase, followed by a pharmacokinetic (PK) phase on the last day to investigate nicotine uptake. During the baseline phase all subjects smoked combustible cigarettes. This was followed by the exposure phase with the subjects randomised into groups where they either continued to smoke the combustible cigarettes, switched to using a THP, or abstained from any tobacco or nicotine product use, for five days. In these phases of the study 24-hour urine samples were collected for analyses of a range of BoE, and exhaled Carbon monoxide (eCO) was also measured daily. Finally, a PK phase was conducted with all subjects excluding the abstinence group. This comprised of a single use of the subjects' assigned product, with blood samples taken before, during and after product use for nicotine analysis.

Levels of urinary BoE and eCO showed reductions of 25.5 to 93.1% in subjects who switched to a THP for 5 days, and reductions of 69.3 to 95.5% in the levels in subjects who abstained from any tobacco or nicotine use for 5 days.

These data show that UK smokers experience reductions in levels of exposure to the selected smoke toxicants when switched to a THP. Longer term BoE and Biomarker of Biological Effect studies will be required demonstrate if these reductions in exposure are sustained, and if this translates into reductions in smoking-related health risks in subjects who switch to THP.

Key Words

Biomonitoring, Biomarkers, Nicotine, Tobacco/Tobacco Heating Products

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