A 12-month randomised, controlled trial evaluating the effects of switching from smoking to using a Tobacco Heating Product on health effect indicators: 90-Day Biomarkers of Exposure

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Introduction

Switching smokers to modified risk tobacco products (MRTPs) has been suggested as a potential means to reduce the risks of tobacco use. Pre-clinical assessment of the glo tobacco heating product (THP),[1] which electronically heats tobacco to a temperature of around 240°C,[2] has shown that both its yields of machine-measured toxicants and environmental emissions are greatly reduced compared to those from conventional cigarettes,[3,4] which in turn leads to reductions in biological effects *in vitro*.[5] In a confined, clinical study, biomarker measurements have demonstrated that smokers who switched to exclusive use of glo for 5 days experienced reduced exposure to cigarette smoke toxicants, to similar levels as those seen in subjects who ceased all tobacco use.[6]

Aim

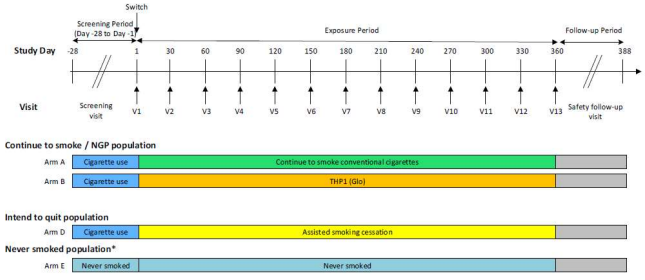
In addition to evaluating the impact of switching to glo on a range of health effect indicators, this 12-month study aims to extend the findings of the previous confinement study[6] and determine whether lowering of toxicant exposure when switching from smoking to using glo is maintained over a longer period of time in an ambulatory setting.

Methods

Study Design

The full study protocol has been published previously.[7] In brief, this was a randomised, controlled, 4-arm, ambulatory switching study conducted across 4 clinical sites in the UK (ISRCTN81075760). Following successful screening assessments, regular smokers were randomised to either continue to smoke their own brand cigarettes or switch to using the glo THP for one year. A further group of smokers intending to quit were provided with pharmacological and behavioural assistance to do so. The final group consisted of never-smokers. Baseline biomarker of exposure (BoE) assessments were performed on a 24-hour urine sample provided on day 1 by each subject, and carbon monoxide was measured in exhaled breath. These assessments were repeated by each subject at nominal days 30, 60 and 90 (day 90 only for never-smokers).

Figure 1. Diagram representing the full study design.



Statistical Analysis

A full statistical analysis plan has been published previously.[8] In summary, BoE levels were computed at each timepoint, and the levels at day 90 were compared between the glo arm (B) and the continued smoking arm (A) using specific contrast tests from statistical models adjusted for baseline measurements. Alpha level across timepoints was adjusted using the O'Brien-Fleming approach, with 0.0006 overall alpha available at day 90. Multiplicity adjustment for family-wise error was performed using Holm's method. A planned interim analysis was performed on those subjects who were enrolled on or before the day the 42nd subject was enrolled into the continue to smoke study arm, and who were still participating at day 90. This was chosen to ensure that 30 subjects in arm A were still enrolled on the study at day 90 to give sufficient power to detect a statistical difference between arms A and B for total NNAL, the primary BoE endpoint.

Results

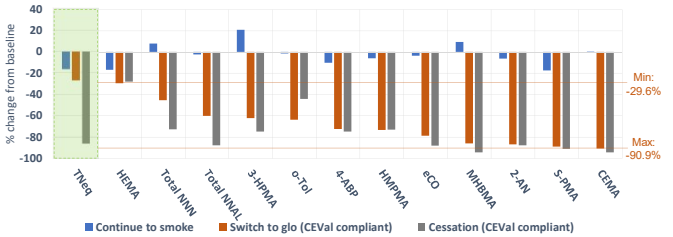
Table 1. Subject disposition and selected demographics for interim analysis PP population.

Study arm	Enrolled before interim cut-off date	Included in interim PP population	Sex M:F	Mean age ± SD	Mean CPD at Screening ± SD
A: Continue to smoke	42	32 (76.2%)	19:13	38 ± 9.3	18 ± 5.5
B: Switch to glo	105	75 (71.4%)	38:37	39 ± 8.8	18 ± 5.5
D: Cessation	190	136 (71.6%)	82:54	38 ± 9.0	18 ± 5.3
E: Never-smoker	40	37 (92.5%)	15:22	40 ± 9.9	N/A

Approximately 71% of subjects enrolled into the glo and cessation arms completed the study to day 90 with no major deviations, and were included in the interim per-protocol population (Table 1). The majority of those excluded either withdrew prior to day 90 or were withdrawn for self-reported non-compliance with smoking restrictions. Pre-specified thresholds for levels of *N*-(2-cyanoethyl)valine (CEVal), a haemoglobin adduct of acrylonitrile measured in each subject's blood at day 90, were used to further define compliance in the glo and cessation PP populations, resulting in the removal of 12 and 21 subjects, respectively.

Figure 2. Example time-series plots – Mean 24-hour excretion of NNAL and S-PMA.

Figure 3. Mean change in biomarkers of exposure at day 90 as % of mean baseline.



BoE, **Abbreviation** [Smoke constituent, if different]: Total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates), **TNeq**; 2-hydroxyethylmercapturic acid, **HEMA** [Ethylene oxide]; N-nitrosonornicotine and its glucuronide conjugates, **Total NNN**; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide conjugates, **Total NNAL** [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone]; 3-hydroxypropylmercapturic acid, **3-HPMA** [Acrolein]; o-Toluidine, **o-Tol**; 4-aminobiphenyl, **4-ABP**; 3-hydroxy-1-methylpropylmercapturic acid, **HMPMA** [Crotonaldehyde]; Exhaled carbon monoxide, **eCO**; monohydroxybutenyl-mercapturic acid, **MHBMA** [1,3-butadiene]; 2-aminonaphthalene, **2-AN**; S-phenylmercapturic acid, **S-PMA** [Benzene]; 2-cyanoethylmercapturic acid, **CEMA** [Acrylonitrile]

Figure 2 shows example time-series plots of mean 24-hour NNAL and S-PMA excretion in the CEVal compliant population. For each BoE assessed in the glo arm, reductions were observed between baseline and day 90, with some reaching levels approximating those seen in the cessation arm and close to levels observed in never-smokers. Mean changes from baseline in the glo arm ranged from -30 % (for HEMA) to -91 % (CEMA) of the baseline values for this arm, in line with cessation which ranged from -28 % (HEMA) to -95 % (MHBMA, CEMA) (Figure 3).

When compared to the differences between baseline and day 90 in the continued smoking arm, the reductions in the glo arm were statistically significant (99.94% CI; $p < 0.0001$) for NNAL, 3-HPMA, 4-ABP, HMPMA, eCO, MHBMA, 2-AN, S-PMA and CEMA. Despite the mean reductions from baseline being in line with cessation for HEMA and o-Tol, and NNN reducing over half as much as seen for cessation, statistical significance was not reached for these markers following multiple-comparison adjustment.

Conclusions

The findings demonstrate that when smokers switched from smoking combustible cigarettes to using glo, reductions in their exposure to smoke toxicants were sustained for the 90-day period. This shows that glo is a potentially reduced exposure tobacco product with potential to be a reduced risk tobacco product. The continuation of this study will examine changes in health effect indicators in subjects switching to glo for up to one year.

Disclosure

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