An Assessment of Nicotine Kinetics and Subjective Effects of Two Tobacco Heating Products in Comparison to Cigarettes and a Nicotine Replacement Therapy

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Introduction

Switching smokers to nicotine products which present less risk has been suggested as a potential means to reduce the risks of tobacco use.[1] The glo Tobacco Heating Product (THP; **Figure 2**) is one of a range of Potentially Reduced-Risk Products (PRRPs) developed by British American Tobacco, and has been shown to result in exposure to significantly lower levels of cigarette smoke toxicants.[2]

Nicotine is mainly responsible for the addictive properties of cigarette smoking.[3] Understanding nicotine pharmacokinetic (PK) profiles and smokers' subjective impressions of PRRPs relative to those of combustible cigarettes and other nicotine products is important, as this may help understand the likelihood of switching success and provide data on potential abuse liability.

Aim

The main aim of this study was to assess the profile of nicotine absorption into the blood of subjects when they smoke their usual-brand cigarette, use a THP (standard and higher nicotine), or use a nicotine replacement therapy (NRT; Nicorette Inhalator) for 5 minutes. Product liking, intent to use the study product again, urge to smoke a cigarette, and urge to use the study product was assessed.

Methods

Study Design

This study was an open-label, randomised, crossover, four-period study of nicotine-containing products carried out in 32 healthy adult smokers in Verona, Italy (EudraCT 2018-000701-23, ISRCTN13439529). Excluding their usual-brand cigarette, subjects were provided with each assigned product for familiarisation approximately 1 week prior to the PK assessment of that product (**Figure 1**).

PK assessments were performed following overnight clinical confinement to ensure a minimum of 12 hours' abstinence from nicotine use. During each assessment, subjects used their assigned product for a maximum of 5 minutes and blood samples were collected for 4 hours for nicotine analysis. Subjects also completed single-item questionnaires on 11-point Likert scales assessing product liking, urge to smoke a cigarette, urge to use the product (excluding during the cigarette assessment), and overall intent to use the product again, at various points before, during and after their PK assessment.

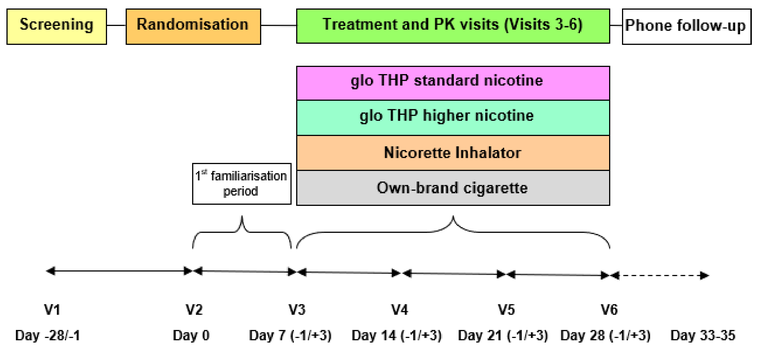

Figure 1: Schematic diagram of the study design

Sample Size

A sample size of 32 subjects was set for this study. This was determined based on the endpoints and assumptions made in the hypotheses. This sample size has been confirmed to be adequate to satisfy all the endpoints at 90% power.

Statistical Analysis

Plasma nicotine PK parameters were evaluated in the 4 sessions with the investigational products. Individual nicotine PK parameters were calculated using non-compartmental analysis and were summarized by means of descriptive statistics. The results from the questionnaires were summarised by means of descriptive statistics.

Study Products

- Subjects' usual-brand cigarette
- glo THP with standard (2.2 mg) nicotine tobacco sticks
- glo THP with higher (3.9 mg) nicotine tobacco sticks
- Nicorette Inhalator (15 mg)

Figure 2: The glo tobacco heating product.

Results

Table 1: Subject Demographics

	N = 32
Mean age ± SD	36 ± 9.7
Sex Males:Females	23:9
Mean Cigarettes per Day ± SD	17 ± 6.0
Mean Fagerström score ± SD	6 ± 1.5

Safety

8 Treatment-Emergent Adverse Events (TEAEs) [3 mild, 5 moderate] were reported by 6 of the 32 subjects (18.8%). There were no severe AEs. One of the 8 TEAEs was considered related to study product (mild cough, considered related to the subject's usual-brand cigarette).

Nicotine PK and Subjective Effects

Figure 3 shows mean plasma nicotine concentrations over the first 60 minutes of the PK assessment period. Nicotine PK parameters and selected questionnaire data are presented in **Table 2**.

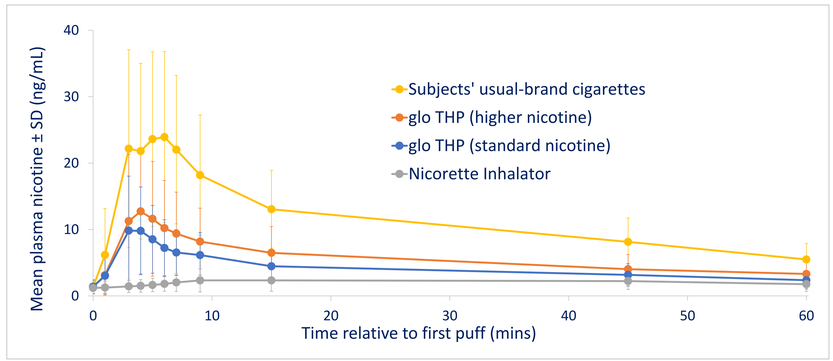

Figure 3: Mean plasma nicotine concentrations (0-60 mins)

Table 2: Nicotine PK Parameters and Questionnaire Data

	Subjects' usual-brand cigarettes	glo THP (standard nicotine)	glo THP (higher nicotine)	Nicorette Inhalator
C_{max} (ng/mL)				
Geometric LS mean	23.3	8.7	10.9	2.2
(90% CI)	(18.46, 29.33)	(6.93, 10.95)	(8.63, 13.70)	(1.78, 2.82)
$AUC_{0\text{-}240min}$ (min*ng/mL)				
Geometric LS mean	1374	527	695	341
(90% CI)	(1142.4, 1653.1)	(438.7, 633.3)	(577.6, 835.6)	(283.8, 410.6)
T_{max} (min)				
Median	6.0	4.1	4.1	15.0
Range	3.0 – 9.1	1.1 – 45.0	1.2 – 15.4	1.0 – 91.7
Product Liking ($AUC_{3\text{-}240min}$)				
Mean ± SD	2107 ± 403	720 ± 733	820 ± 724	356 ± 474
Median	2281	640	675	124
Urge to Smoke a Cigarette (at 5 min post 1st puff)				
Mean ± SD	2.6 ± 3.50	5.0 ± 3.33	4.8 ± 3.27	5.8 ± 3.11
Median	1.0	5.0	5.0	6.0
Urge for Product (mean at 15 & 120 min post 1st puff)				
Mean ± SD	-	2.3 ± 2.28	2.8 ± 2.37	1.5 ± 1.89
Median	-	2.5	2.5	0.8
Overall Intent to Use Again (at 240 min post 1st puff)				
Mean ± SD	9.1 ± 1.37	2.5 ± 2.67	3.1 ± 2.84	1.0 ± 1.77
Median	10.0	2.0	2.0	0.0

The nicotine PK profiles of the glo THPs were visually similar to that of the cigarettes – characterised by a fast peak in plasma nicotine concentration, unlike the profile for the Nicorette Inhalator. Systemic nicotine exposure, based on C_{max} and $AUC_{0\text{-}240min}$, was greater for the THPs than for the Nicorette Inhalator, but lower than the usual-brand cigarette. Median T_{max} for the THPs was closer to that observed for the cigarette than for the Nicorette Inhalator. Product liking and overall intent to use again was greater for the THPs than for the Nicorette Inhalator, but lower than for cigarettes. Urge to smoke at the end of the 5min product use period was reduced to the greatest extent when smoking a cigarette, and to the least extent when using the Nicorette Inhalator.

Conclusions

This clinical study demonstrated that the nicotine PK profiles of the glo THPs assessed were more representative of that of the subjects' usual-brand cigarettes than the Nicorette Inhalator, and that subjective impressions of glo were more positive than those of the Nicorette Inhalator.

Disclosure

This work was funded in full by British American Tobacco (Investments) Ltd. All authors are current employees of British American Tobacco.

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