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

There is a recognized need to provide cigarette smokers with alternative nicotine-delivery devices that yield lower levels of chemical toxicants compared to conventional cigarette smoke.[1-3] British American Tobacco (Investments) Limited, a manufacturer of tobacco products is developing Potentially Reduced Risk Products (PRRPs), one of which is the glo Tobacco Heating Product (THP; **Figure 1**). Studies have shown that when smokers switch from smoking combustible cigarettes to using a glo THP, their exposure to smoke toxicants decreases, in many cases, to similar levels as cessation.[4]

Figure 1: The glo Tobacco Heating Product with Neostik

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, 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

The study, which was conducted in Verona, Italy (EudraCT 2018-000701-23, ISRCTN13439529) was an open-label, randomised, crossover, four-period study of nicotine-containing products carried out in one study cohort (non-menthol smokers) consisting of 32 healthy adult smoker subjects.

During a 5-min product use session, blood samples were collected for PK analysis. Subjects were also asked to complete a product liking questionnaire (PLQ), an Overall Intent to Use Again (OIUA) questionnaire, an Urge to Smoke (UTS) questionnaire and a Urge for Product (UFP; excluding during the cigarette assessment) at various points before, during and/or after their investigational product use session. There were four treatment and PK sessions in total, after which there was a follow-up by telephone (**Figure 2**).

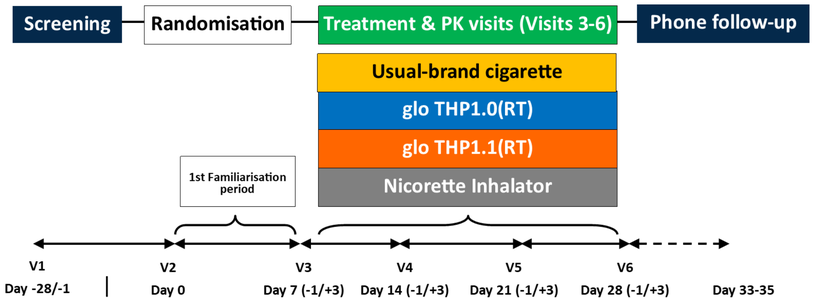

Figure 2: Schematic Diagram of the Study Design

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

PK parameters C_{max}, T_{max} and $AUC_{0\text{-}240min}$ 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 (**Table 2**). The results from the questionnaires were summarised by means of descriptive statistics (**Table 3**).

Study Products

1. Subjects usual-brand cigarette
2. glo THP 1.0(RT); 2.2 mg nicotine tobacco Neostik (Standard nicotine)
3. glo THP1.1(RT); 3.9 mg nicotine tobacco Neostik (High nicotine)
4. Nicorette Inhalator Inhalator; 15 mg

Results

Subject Demographics

Table 1: Mean age, sex, cigarette consumption and dependence of subjects

	N = 32
Mean age ± SD	35.8 ± 9.66
Sex; Male:Female	23:9
Mean CPD ± SD	16.8 ± 6.0
Mean FTCD score ±SD	5.59 ± 1.52

CPD– Cigarette per day; ***FTCD*** **-** Fagerstrom Test for Cigarette Dependence; **SD** – Standard Deviation

Safety

8 exposure period adverse events (AEs) [3 mild, 5 moderate] were reported by 6 of the 32 subjects (18.8%). One exposure period AE was related to cigarette use (cough with mild severity). The were no severe AEs.

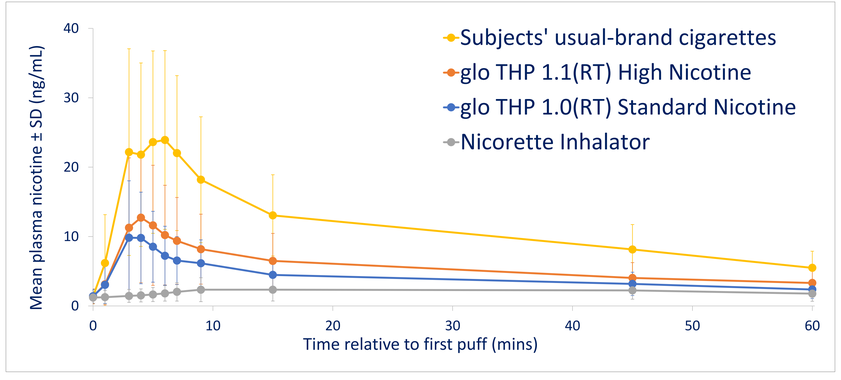

Figure 3: Mean ± SD Plasma Nicotine concentration (0-60 min)

Table 2: Plasma nicotine PK Parameters

	Subjects' usual-brand cigarettes	glo THP 1.0(RT) Standard nicotine	glo THP 1.1(RT) High 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

Table 3: Questionnaire Data

	Subjects' usual-brand cigarettes	glo THP 1.0(RT) Standard nicotine	glo THP 1.1(RT) High nicotine	Nicorette Inhalator
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

Nicotine PK profiles of the glo THPs were similar to that of the cigarettes – characterised by quick T_{max} in plasma nicotine concentration, in comparison to Nicorette Inhalator (**Figure 3**). Systemic nicotine exposure, based on C_{max} and $AUC_{0\text{-}240min}$, was greater for the THPs than for the nicotine inhaler, but lower than the usual-brand cigarette. Median T_{max} for the THPs was closer to that observed for the cigarette than for the nicotine inhaler (**Table 2**). Product liking and overall intent to use again was greater for the THPs than for the nicotine inhaler, but lower than for cigarettes. Urge to smoke at the end of the 5 min product use period was reduced to the greatest extent when smoking a cigarette, and to the least extent when using the nicotine inhaler (**Table 3**).

Conclusions

These findings demonstrate the glo THPs assessed had a closer nicotine PK profile to subjects' usual-brand cigarettes than the nicotine inhaler, and that subjective effects of glo THPs were more positive than those for the Nicorette inhalator

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.

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Abstract

Studies have shown that when smokers switch from smoking combustible cigarettes to using a tobacco heating product (THP), their exposure to smoke toxicants decreases, in many cases, to similar levels as cessation. Nicotine pharmacokinetics (PK) and subjective effects of potentially reduced risk products (PRRPs) relative to combustible cigarettes and other nicotine products, such as nicotine replacement therapy (NRT; e.g. nicotine inhaler), may determine the likelihood of switching success and provide data on potential abuse liability. This study aimed to test the hypotheses that glo THP with consumables of two different nicotine yields (THP1.0 and THP1.1) have a closer nicotine PK profile to combustible cigarettes compared to NRT, and subjective effects are more positive compared to NRT.

To test these hypotheses, 32 healthy smokers were recruited in a clinical study conducted in Verona, Italy (ISRCTN13439529), run in accordance with ICH-GCP following a research protocol approved by the local Research Ethics Committee. In accordance with pre-defined randomization sequences, subjects were assigned a different product for assessment during each of four PK periods, following overnight (minimum 12-hours) in-clinic nicotine abstinence. Subjective effects (product liking, urge to smoke a usual-brand cigarette, urge to use the study product, overall intent to use the product again) were also assessed at various timepoints during each PK period via single-item questionnaires.

Systemic nicotine exposure, based on Cmax and AUC0-240min, was greater for the THPs than for the nicotine inhaler, but lower than the usual-brand cigarette. Median Tmax for the THPs (4 min) was closer to that observed for the cigarette (6 min) than for the nicotine inhaler (15 min). Product liking and overall intent-to-use again was greater for the THPs than for the nicotine inhaler, but lower than for cigarettes. Urge to smoke was reduced to the greatest extent when smoking a cigarette, and to the least extent when using the nicotine inhaler.

These findings demonstrate the glo THPs assessed had a closer nicotine PK profile to subjects' usual-brand cigarettes than the nicotine inhaler, and that subjective effects of glo THPs were more positive than those for the nicotine inhaler.

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