**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 (PPRPs), 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

Understanding nicotine pharmacokinetic (PK) profiles and smokers’ subjective impressions of PPRPs 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, ISRCTN13493629) 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).

**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). There were no severe AEs.

Nicotine PK profiles of the glo THPs were similar to that of the cigarettes – characterised by quick T<sub>max</sub> in plasma nicotine concentration, in comparison to Nicorette Inhalator (Figure 3). Systemic nicotine exposure, based on C<sub>max</sub> and AUC0-240min, was greater for the THPs than for the nicotine inhaler, but lower than the usual-brand cigarette. Median T<sub>max</sub> 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.
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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.

Key words: Nicotine, Abuse Liability Assessment, Tobacco Heating Products