A randomized, single blinded, cross-over study to evaluate the pharmacokinetic profiles of e-cigarettes with nicotine salt formulations in UK adults who use e-cigarettes

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INTRODUCTION

When an organic acid combines with a freebase nicotine, it forms a nicotine salt. Recently e-liquids marketed as containing nicotine salts have become popular and it appears that nicotine in salts form can provide a sensorial experience that some adult consumers perceive as more enjoyable and satisfying versus freebase nicotine e-liquids. The presence of nicotine salts in e-liquids may influence nicotine uptake and intake compared to freebase nicotine according to the current scientific literature[1]. Here, we evaluated nicotine pharmacokinetic (PK) profiles and subjective effects following single and multiple *ad libitum* use of an e-cigarette with two e-liquid pods, one containing nicotine salts and one without nicotine salts.

MATERIALS AND METHODS

The study was a single-center, single-blinded, randomized, 2-period 2-sequence, cross-over study conducted in the UK, in 20 healthy adults who used e-cigarettes daily. Subjects used assigned product once in an *ad libitum* setting for 5 mins in the morning and used the assigned product as many times as they liked in a multiple use setting for 6 hours in the afternoon. Sequences were determined by randomization [ISRCTN : 97168882].

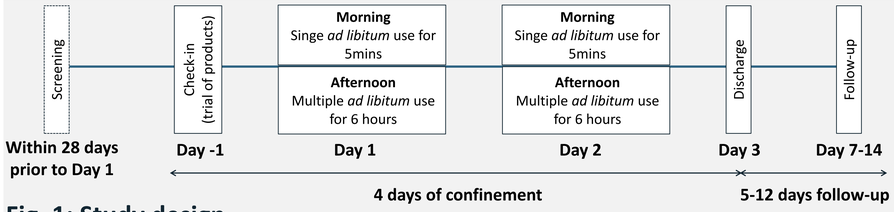

Fig. 1: Study design

Study products: eDNC3 (Logic Compact) with two variants of tobacco flavored e-liquid pods.

Product A: E-liquid with 18mg/ml nicotine

Product B: E-liquid with 18mg/ml nicotine, containing nicotine salts

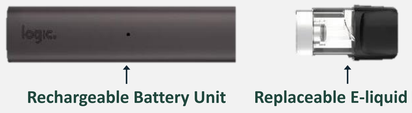

Fig. 2: Study product components

- **Plasma nicotine PK analysis:** Blood samples were obtained for plasma nicotine analysis at –5, 2.5, 5, 7.5, 10, 15, 30, 60, 120, and 240 min relative to the first puff of the product during single *ad libitum* use. During multiple *ad libitum* use, which began immediately after the last (240 min) blood draw for single *ad libitum* use, blood samples were taken at 360, 480 and 600 min.
- **Theological nicotine consumption:** Weight of product before/ after use, adjusted for nicotine content.
- **Subjective effects:** Modified Product evaluation Scale (mPES)[2] and Visual Analog Scale (VAS) for Intent to Use the Product Again.

RESULTS

A total of 37 subjects were consented for the study, 20 subjects were enrolled and completed the study.

Plasma Nicotine Pharmacokinetics and Theological Nicotine Consumption

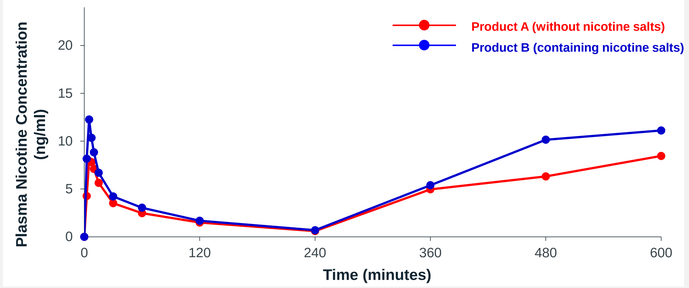

Fig. 3: Plasma nicotine concentration curve on Product A and B

Table 1: PK parameters and theological nicotine consumption

Parameters	Single *ad libitum* use				Multiple *ad libitum* use	
	Theological Nicotine Consumption* (mg) Mean (SD)	C_{max} (ng/mL) GLS mean** (95% CI)	AUC_{0-240} (ng/mL*min) GLS mean** (95% CI)	T_{max} (min) Median (min, max)	Theological Nicotine Consumption* (mg) Mean (SD)	C_{max} (ng/mL) GLS mean** (95% CI)
Product A (without nicotine salts)	**1.11** (0.653)	**7.11** (5.05, 10.0)	**410** (292, 576)	**7.5** (5.0, 30.0)	**7.32** (5.14)	**6.69** (4.84, 9.26)
Product B (containing nicotine salts)	**1.33** (0.664)	**10.9**† (7.69, 15.3)	**492** (350, 691)	**5.0** (5.0, 10.0)	**8.79** (4.64)	**10.6**† (7.65, 14.7)

**The theoretical nicotine consumption was estimated by subtraction of the post use product weight from the pre use product weight.*

***GLS (Geometric Least Square) means obtained using an ANOVA with fixed effects for sequence, study day and product and a random effect of subject nested within sequence.*

† Significantly different between Product A and Product B ; $p < 0.05$.

- The C_{max} of plasma nicotine was statistically greater following single *ad libitum* use and following multiple *ad libitum* use of Product B (containing nicotine salts) rather than Product A (without nicotine salts), while AUC was greater (not statistically) following single *ad libitum* use of eDNC3 with e-liquids containing organic acid rather than freebase nicotine.
- During both single and multiple *ad libitum* product use, the mean of theological nicotine consumption of Product B was approximately 20% higher than Product A.
- The differences in the PK parameters ($C_{max\text{-}single}$, AUC_{0-240} and $C_{max\text{-}multiple}$) between the Product A versus Product B were associated with an increase in the consumed amount of e-liquid corresponding to theological nicotine consumption.

Fig. 4: PK curves on Product A and B in single *ad libitum* use

(Modified from Liu J, et al. 2022)

Fig. 5: Available nicotine PK data on conventional cigarettes

- The mean nicotine C_{max} measured during single *ad libitum* use of Product A and Product B were both within the range reported in published literature for conventional cigarettes[3] .

Subjective Effects

- No major differences were observed between Product A and B for any of the subjective effects measured in this study (mPES/VAS).

Conclusion

- These results indicate that use of e-liquid with nicotine salt formulation, made by adding organic acid, leads to an increase in nicotine uptake compared to freebase nicotine e-liquid, and these differences may be explained by increased consumption of e-liquid.
- Plasma nicotine concentrations following use of the two e-liquid variants (containing nicotine salts or without nicotine salts) of eDNC3 did not exceed that of conventional cigarette, based on data available from the literature.

Reference

[1] O'Connell G, *et al.* A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers, *Internal and Emergency Medicine*, 2019;14(6):853-861

[2] Hatsukami DK, *et al*. Subjective responses to oral tobacco products: scale validation. *Nicotine Tob Res.* 2013;15(7):1259-64

[3] Liu J, *et al.* Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users*, Psychopharmacology,* 2022; 239, 2863-2873

* The present study was approved by the Wales Research Ethics Committee 1 (REC) in the UK and was conducted in accordance with the Declaration of Helsinki and in compliance with International Conference for Harmonization (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements in the UK.

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