



A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part A: Pharmacokinetics



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ABSTRACT

The pharmacokinetic (PK) profile of nicotine delivered by an Electronic Vapour Product (EVP) was characterised in a 2-part study in smokers. The study was designed as a randomised, controlled, four-way crossover trial. Part 1 compared an unflavoured e-liquid (UF2.0%) and a flavoured e-liquid (FL2.0%) to a conventional cigarette (CC; JPS Silver King Size, 0.6 mg) and a licensed nicotine inhalator (Nicorette[®]; 15 mg). Part 2 compared e-liquids with increasing nicotine concentrations (0%, 0.4%, 0.9%, 2.0%). Subjects used each different product for a daily use session. In Part 1, maximum plasma nicotine concentration (C_{max}) for UF2.0%, FL2.0%, Nicorette[®] and CC was 3.6, 2.5, 2.5 and 21.2 ng/mL, respectively. The time to maximum plasma nicotine concentration (T_{max}) was longer for the EVP (UF2.0%, 9.0 min; FL2.0%, 10.0 min) and the nicotine inhalator (13.0 min) compared to CC (3.0 min). In Part 2, EVP with 0%, 0.4%, 0.9% and 2.0% nicotine produced C_{max} values of 0.6, 1.0, 1.9 and 3.6 ng/mL, respectively. At the maximum nicotine concentration of 2% as prescribed by the European Tobacco Directive, the EVP achieved nicotine delivery that was comparable to the inhalator. EVPs thus offer a potential alternative to nicotine inhalator devices for those finding it difficult to quit smoking.

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1. Introduction

There has been rapid growth in the use of electronic cigarette (e-cigarettes) otherwise known as electronic vapour products (EVPs) among smokers worldwide (Adkison et al., 2013; Berg et al., 2014; Dockrell et al., 2013; King et al., 2013). Nicotine Replacement Therapy (NRT) has had modest success in helping smokers to quit (Beard et al., 2015) and studies have shown EVPs are often used as a means to stop smoking conventional cigarettes (CC) (Berg et al., 2014; Dockrell et al., 2013; Etter and Bullen, 2011).

EVPs comprise of three principal components: a battery for power supply; an e-liquid reservoir and a heating element, or atomiser. When a user draws on the device, the e-liquid in close proximity to the heater rapidly vaporises and condenses into an

aerosol. Typically e-liquids consist of propylene glycol, glycerol, water, flavouring and/or nicotine. EVPs exist in various designs, and may vary considerably in the amount of nicotine they deliver in the aerosol. The use of new-generation EVPs, (*i.e.* systems with large-capacity batteries and larger atomisers/“Mods”) has been shown to be more effective in increasing blood nicotine levels in users, compared with first generation devices (*i.e.* devices with low-capacity batteries, designed to look like CC) (Farsalinos et al., 2014b). The nicotine concentration in the e-liquid also appeared to correlate with nicotine uptake levels achieved by users (Etter, 2014). Furthermore, recent studies have shown that experienced users of EVPs were able to achieve higher levels of blood nicotine when compared to novice users and that blood nicotine levels are similar to those of CC smokers, (*i.e.* around 15 ng/mL), particularly if they use the product *ad-libitum* (Dawkins and Corcoran, 2013; IOM, 2011; Vansickel and Eissenberg, 2013). When experienced EVP users used their preferred EVP product, with nicotine concentrations in e-liquids ranging from 12 to 24 mg/mL (1.2–2.4% w/v), plasma nicotine rose to a mean of 19.2 ng/mL immediately after use

Abbreviations: CC, conventional cigarettes; CO, carbon monoxide; EVP, electronic vapour product; NRT, nicotine replacement therapy.

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(Spindle et al., 2015). This observation was suggested to be due to differences in puffing topography, with experienced users taking longer and larger puffs (up to 4 s and up to 101 mL) than novice EVP users and CC smokers (around 2 s, 51 mL) (Farsalinos et al., 2013b; Spindle et al., 2015).

Despite a number of pharmacokinetic (PK) studies performed, being able to draw any firm conclusions on the capacity of EVPs to deliver nicotine has proven to be challenging. This is in part due to the lack of standardised methodologies for the comparative testing of EVPs (Orr, 2014). In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has strongly encouraged manufacturers to register EVPs as medicinal products (MHRA, 2013). According to the Agency, such regulation would ensure that products comply with quality standards. The Royal College of Physicians was supportive of such regulation, and also requested that 'clear, simple and easily achievable standards of dose kinetics and purity are established to encourage new innovation in nicotine products and new entrance into the nicotine market'. At the European level, under the revised Directive on Tobacco Product a maximum concentration of 20 mg/mL (2% w/v) as a limit for nicotine will be set for e-liquids placed on the market after May 2016. After that time no products can be placed on the market above that limit, except for those regulated as medicinal products (EU, 2014).

Here, we report the results of a human PK study, consisting of two parts. The aim of Part 1 was to compare the plasma nicotine PK profile of an unflavoured (UF) and a flavoured (FL) e-liquid containing 2.0% nicotine delivered via the EVP closed-system prototype device to the plasma PK profile obtained after use of an NRT product and a commercially available CC. Part 2 investigated the plasma nicotine PK profile following use of the EVP with unflavoured e-liquids containing increasing levels of nicotine (0%, 0.4%, 0.9% and 2.0%). Safety parameters, smoking urges and withdrawal symptoms were investigated in both study parts, and are published elsewhere (Walele et al., 2015).

2. Materials and methods

2.1. Study design

This study was performed at a single clinical site (Simbec Research Ltd, Wales) in a confinement setting. A total of 24 healthy male subjects, recruited in the UK, participated in the study: 12 assigned to Part 1 and 12 to Part 2. Both study parts were designed as a randomised, controlled, four-way crossover trial. Part 1 was performed open-label and Part 2 was blinded. Following overnight abstinence from smoking or using EVPs, subjects used each different product for one daily use session.

The study was approved by the South East Wales Research Ethics Committees on 31 October 2013, and is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02032212. All procedures were performed in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP). The MHRA-UK has granted Clinical Trials Authorisation (CTA) for the use of the NRT product in this study.

All subjects signed an informed consent form prior to any study procedures being performed.

2.2. Study population

In order to be eligible, subjects had to be 21–65 years old, have a body mass index (BMI) in the range of 18–35 kg/m² and a self-reported cigarette consumption of 5–30 cigarettes per day for at least one year. Subjects had to test positive for urinary cotinine (NicAlert strip with a score of 3 and above was considered positive)

and for exhaled carbon monoxide (CO; measured with a portable Bedfont Micro + Smokerlyser device, where a readout of over six ppm was considered positive).

Exclusion criteria included: taking or receiving any form of NRT, snuff or chewing tobacco, or any intention to use it during the study; willingness to stop smoking or considering to stop smoking; use of any kind of medication within 14 days of the screening visit; clinically significant illness such as bronchitis or a history of any clinically significant disorders likely to affect study results; history of drug or alcohol abuse or lung function test results considered unsuitable.

2.3. Products used in this study

The EVP consisted of a rechargeable battery, an atomiser and capsules that contained different e-liquids (Fig. 1). The capsules were replaceable and the battery and atomiser were reusable. The base components of the e-liquids used are propylene glycol (70–75% w/w), glycerol (18–20% w/w) and water (5% w/w). Two e-liquids were used in Part 1 of the study, which differed solely in their flavour content: an unflavoured base e-liquid with 2.0% nicotine (UF2.0%; 2.7 mg/capsule) and a flavoured (menthol) e-liquid with 2.0% nicotine (FL2.0%; 2.7 mg/capsule). In Part 2, four unflavoured e-liquids were used, which differed in their nicotine content: 0% nicotine (UF0%), 0.4% nicotine (UF0.4%; 0.4%; 0.54 mg/capsule), 0.9% nicotine (UF0.9%; 1.22 mg/capsule) and UF2.0%. The EVP with UF2.0%, FL2.0% and UF0.4% delivers mean amounts of 0.013, 0.007 and 0.002 mg nicotine per puff, respectively (internal data, generated under Health Canada Intense smoking regime). Nicotine delivery with UF0.9% was not measured.

In Part 1 of the study, the NRT Nicorette Inhalator (15 mg nicotine, manufacturer Johnson & Johnson; coded NIC15) was used as a comparator product and the JPS Silver King Size CC (0.6 mg nicotine; manufacturer Imperial Tobacco Group) was used as a control.

2.4. Study interventions and schedule

Subjects visited the study site for a screening visit within 21 days of baseline (Day -2), where they were checked for eligibility and were asked to sign a written informed consent form. Demographic data and smoking history were recorded using internal questionnaires and the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). At this stage, subjects were assigned to Part 1 or Part 2 of the study, depending on their availability. Once enrolled, the subjects were admitted to the study site on the morning of Day -2 (baseline) for re-confirmation of eligibility, and were given training on how to use the EVP or NIC15.



Fig. 1. Schematic of the external appearance and parts of the tested EVP. From left to right, pieces are: the housing, which contains the battery and has a LED indicator on the side, the atomiser, the capsule containing the e-liquid and the mouthpiece.

From the time of admission, subjects were not permitted to use any EVP, NRT or CC other than that assigned as part of the study design and were not allowed to consume alcohol. On Day -1, the twelve subjects in each study part were randomly assigned to one of four pre-defined sequences of product use, in a 3:3:3:3 ratio (randomisation was performed using PROC PLAN procedures of SAS[®] version 9.4). Subjects remained in the clinic until the end of the study period, on the morning of Day 5.

On study Days 1, 2, 3, and 4, after overnight smoking abstinence, subjects used the allocated product for four product administrations at one-hour intervals (0 h, 1 h, 2 h and 3 h). Each administration consisted of 10 inhalations at 30 s intervals. Each inhalation was monitored, and subjects were instructed to take 4-s puffs for the EVP and NIC15, and 2-s puffs for the CC (an electronic tablet was used instructing subjects when to inhale and exhale). This regimen was chosen based on published data indicating that experienced EVP users take longer puffs than CC smokers (Farsalinos et al., 2013b). PK blood samples (4.5 mL, from forearm vein, in lithium heparin) for plasma nicotine were taken 1 min before (–1 min) and 1 min after (+1 min) the first, second and third product administrations, and 1 min before and at +1, 2, 3, 4, 5, 6, 7, 8, 10, 13, 15, 30, 45 and 60 min and at +2, 4, 6, 8, 12 and 21 h after the fourth product administration.

On Day 5, subjects were provided full verbal smoking cessation advice by the investigator and were discharged from the clinic after all study assessments were performed.

2.5. Study outcome measures

For both study parts, the primary outcomes were C_{\max} (maximum plasma concentration) and AUC_t (area under the curve from 0 to 21 h) after the 4th hourly administration, and the secondary outcomes were $t_{1/2}$ (terminal half-life) and t_{\max} (time to C_{\max}) after 4th hourly administration.

2.6. Bioanalytical methods

Each human plasma sample (stored at –20 °C) was thawed and extracted with a solution of acetonitrile, ethanol, water, propane-2-ol, ammonium acetate and formic acid containing the internal standard nicotine-d4 (0.1 ng/mL) using a solid phase extraction method (Waters Oasis HLB, 30 mg, 96 Well μ elution plate). Quantitative analysis of nicotine concentrations was performed using liquid chromatography with tandem mass spectrometry detection (Applied Biosystems MDS Sciex API 4000 triple quadrupole atmospheric pressure ionisation) using the instrument in turbo ionspray, positive ion Multiple Reaction Monitoring (MRM) mode. Chromatography was performed on a Betasil silica-100 column. The instrument was calibrated for nicotine concentrations ranging from 0.5 ng/mL to 50 ng/mL. The method was fully validated internally to the standards required for submission of resulting data to regulatory authorities worldwide. The lower limit of quantification (LLOQ) was 0.5 ng/mL. Carboxyhaemoglobin (COHb) in whole blood samples was assessed with the Roche Cobas B221 Blood Gas Analyser System using a spectrophotometric method (Roche, 2009).

2.7. Statistical methods

2.7.1. Sample size

The sample size was selected based on similar PK studies for similar products (Bullen et al., 2010; Dawkins and Corcoran, 2013; Farsalinos et al., 2014b) and on guidance given by competent authorities (EMA, 2010; HC, 2012). Twelve subjects per study part were considered sufficient in the crossover design as it is ensured that all subjects used each of the four different products.

2.7.2. PK parameters

For each study part, the plasma PK parameters for nicotine were derived using non-compartmental methods from the individual concentration-time data analysed with WinNonlin Phoenix 6.4. In Part 1, CC and UF2.0% were used as reference products. AUC_t and C_{\max} values were logarithmically transformed (natural logarithm) and then subjected to an analysis of variance (ANOVA) including fixed effects for sequence, day and product and a random effect for subject. The least square means of the product differences and 90% confidence intervals (CIs) to the reference product were transformed to the original scale in order to obtain the test/reference geometric mean ratios (GMR). The statistical analysis was performed only on the primary outcome measures C_{\max} and AUC_t in order to avoid an effect of multiple comparisons. In Part 2, dose proportionality was assessed (excluding UF0%) by performing a regression analysis of the log-transformed C_{\max} and AUC_t values versus the log-transformed dose with a fixed effect for dose and a random effect for subject. Slope estimates and associated 95% CIs were calculated. All analyses were performed using SAS[®] version 9.1.3.

3. Results

3.1. Subjects' characteristics

Subjects were screened from January 2014 to March 2014. All 24 subjects enrolled for both study parts completed the study according to the protocol. There were no withdrawals.

3.1.1. Part 1

The mean age of subjects was 31.1 years and the mean BMI was 25.0 kg/m². The mean FTND score was 4.3, indicating moderate nicotine dependence according to the FTND scale. Subjects smoked between 5 and 30 cigarettes per day (self-reported), for 6–20 years. At baseline (Day -2), urine cotinine levels were positive for all subjects, with NicAlert scores ranging from 4 to 6. Blood COHb levels ranged from 4.9 to 10.7% saturated haemoglobin and mean exhaled CO levels were at 22.9 (\pm 9.3) ppm. Subjects were thus confirmed smokers.

3.1.2. Part 2

The mean age of subjects was 37.4 years and the mean BMI was 26.1 kg/m². The mean FTND score was 3.6, which indicated moderate nicotine dependence according to that scale. Subjects smoked between 5 and 30 cigarettes per day (self-reported). The majority of subjects had smoked for 6–20 years; one subject had smoked for less than 6 years and five for over 20 years. Urine cotinine levels at baseline were positive for smoking for all subjects, with NicAlert scores ranging from 4 to 6. Blood COHb levels ranged from 4.1 to 10.5% saturated haemoglobin and mean exhaled CO levels were at 20.1 (\pm 12.4) ppm. Subjects were thus confirmed smokers.

3.2. Pharmacokinetics

3.2.1. Part 1

Fig. 2 shows the mean plasma concentration-time curves for nicotine starting one minute prior to the first product administration (–181 min time-point) and up to 240 min after the 4th administration (the 0 time point represents the 4th administration).

Fig. 3 shows a close-up view of the curves for both EVPs and NIC15, from the zero time point up to 45 min.

The plasma PK parameters (means or medians) C_{\max} , AUC_t , t_{\max} and $t_{1/2}$ obtained for nicotine after the 4th hourly administration are summarised for each product in Table 1, and a summary of the

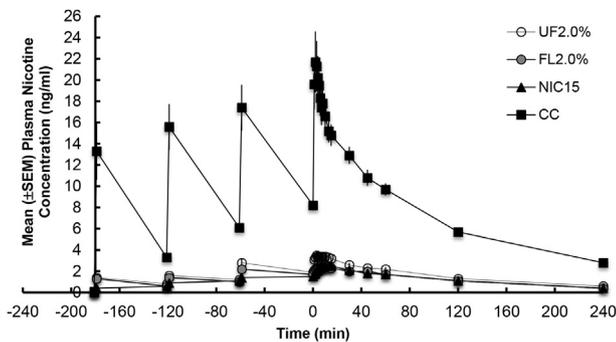


Fig. 2. Mean (\pm SEM) plasma nicotine concentration-time curves, shown for up to 240 min after the 4th product administration. Twelve subjects received each product in a crossover design. UF2.0%, unflavoured base e-liquid at 2.0% nicotine; FL2.0%, flavoured base e-liquid at 2.0% nicotine; NIC15, Nicorette Inhalator 15 mg nicotine; and CC, JPS 0.6 mg conventional cigarette; SEM, standard error of the mean.

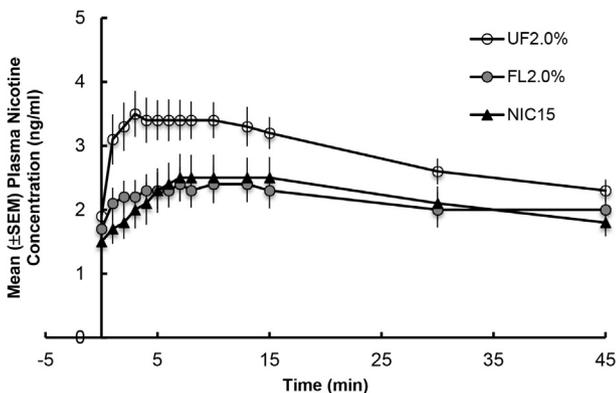


Fig. 3. Mean (\pm SEM) plasma nicotine concentration-time curves, shown for EVP products and NIC15 from zero up to 45 min after the 4th product administration. Twelve subjects received each product in a crossover design. UF2.0%, unflavoured base e-liquid at 2.0% nicotine; FL2.0%, flavoured base e-liquid at 2.0% nicotine; NIC15, Nicorette Inhalator 15 mg nicotine; SEM, standard error of the mean.

statistical analyses performed is presented in Table 2.

Mean C_{max} and AUC_t were statistically significantly higher for CC than for all other products. C_{max} and AUC_t for CC were 21.2 ng/mL and 2247.0 min*ng/mL, respectively. Mean C_{max} and AUC_t for UF2.0% were statistically significantly higher than C_{max} and AUC_t for FL2.0% (Table 2). Mean C_{max} and AUC_t for UF2% were 3.6 ng/mL and

425.3 min*ng/mL, respectively and for FL2.0%, 2.50 ng/mL and 277.2 min*ng/mL. For NIC15, the C_{max} and AUC_t was 2.50 ng/mL and 320.56 min*ng/mL, however there was no statistically significant difference for AUC_t between NIC15 and UF2.0%.

The shortest median t_{max} was observed for the CC (3.0 min), indicating that the rate of nicotine absorption was fastest for the CC. The median t_{max} values were similar for UF2.0% (9.0 min), FL2.0% (10.0 min) and NIC15 (13 min). The median $t_{1/2}$ values were similar for the CC (125.6 min), UF2.0% (122.8 min), FL2.0% (111.4 min) and NIC15 (124.2 min), suggesting that the elimination rate of nicotine was comparable for the four product types.

3.2.2. Part 2

Fig. 4 shows the mean plasma concentration-time curves for nicotine, starting one minute prior to the first product administration and up to 240 min after the 4th administration. The plasma nicotine PK parameters C_{max} , AUC_t , t_{max} and $t_{1/2}$ following the 4th administration are summarised in Table 1 for each product.

The highest C_{max} and AUC_t values were observed for UF2.0% (3.6 ng/mL and 451.4 min*ng/mL), followed by UF0.9% (1.9 ng/mL and 240.3 min*ng/mL), UF0.4% (1.0 ng/mL and 57.7 min*ng/mL) and UF0% (0.6 ng/mL and 83.9 min*ng/mL). C_{max} and AUC_t values for UF0% were not zero since one subject, who was a heavy smoker (21–30 cigarettes per day) and had residual nicotine levels in blood during the study. Nicotine levels in blood were observed to increase with successively higher nicotine concentrations in the EVP e-liquids, even though the increase in C_{max} and AUC_t did not show full dose proportionality (for C_{max} , the slope estimate was 0.800 with a 95% CI of 0.710–0.889; for AUC_t , the slope estimate was 1.281 with a 95% CI of 1.005–1.557).

The median t_{max} was similar for UF0.4% (5.0 min), UF0.9% (7.0 min) and UF2.0% (7.0 min). Although a t_{max} of 60.0 min for UF0% was observed, this value was based on only one subject, who had residual nicotine levels in blood. The median $t_{1/2}$ for UF2.0%, UF0.9% and UF0.4% were calculated at 125.1 min, 169.7 min and 57.6 min, respectively.

4. Discussion

This study was conducted as part of the evaluation of an EVP prototype.

In Part 1 of our study, the nicotine level in plasma samples increased after each hourly administration of all products. The maximum mean plasma nicotine level in subjects using EVPs was 3.6 ng/mL, which was reached in nine minutes. NIC15 produced a maximum mean plasma nicotine level of 2.5 ng/mL, 13 min after

Table 1
Summary of nicotine PK parameters for each product for Part 1 and Part 2.

Product	C_{max} (ng/mL)	AUC_t (min*ng/mL)	t_{max} (min)	$t_{1/2}$ (min)
	Geometric mean (CV%)	Geometric mean (CV%)	Median (range)	Median (range)
Part 1				
UF2.0%	3.6 ^c (33.9)	425.3 ^c (34.3)	9.0 (1.0–15.0)	122.8 (76.2–183.2)
FL2.0%	2.5 ^{b,c} (41.6)	277.2 ^{b,c} (48.2)	10.0 (3.0–45.0)	111.4 (54.3–203.4)
NIC15	2.5 ^{b,c} (45.2)	320.6 ^c (47.6)	13.0 (5.0–15.0)	124.2 (64.1–291.0)
CC	21.2 ^b (43.1)	2247.0 ^b (28.6)	3.0 (1.0–6.0)	125.6 (87.1–301.3)
Part 2				
UF0%	0.6 (346.4)	83.9 (n/a) ^a	60 (n/a) ^a	NC
UF0.4%	1.0 (41)	57.7 (86.3)	5.0 (1.0–60.0)	57.6 (16.5–389.7)
UF0.9%	1.9 (32.8)	240.3 (82.8)	7.0 (1.0–15.0)	169.4 (70.1–372.5)
UF2.0%	3.6 (20.9)	451.4 (58.4)	7.0 (3.0–30.0)	125.1 (55.0–242.5)

Abbreviations: C_{max} , maximum plasma concentration; AUC_t , area under the curve from 0 to 21 h after the 4th product administration; t_{max} , time to C_{max} ; $t_{1/2}$, terminal half-life; n/a, not applicable; CV, coefficient of variation; NC, not possible to calculate.

^a Value based on n = 1. All other values based on n = 9–12.

^b Statistically significantly different from UF2.0% based on 90% CIs (Table 2).

^c Statistically significantly different from CC based on 90% CIs (Table 2).

Table 2
Statistical analysis for the nicotine PK parameters C_{\max} and AUC_t , for Part 1 of the study.

	UF2.0% (N = 12)	FL2.0% (N = 12)	NIC15 (N = 12)	CC (N = 12)
C_{\max} (ng/mL)				
Geometric LSMean	3.64	2.5	2.5	21.16
Geometric LSMean ratio (product/UF2.0%) (90% CI)	n/a	0.69 (0.52–0.91)	0.69 (0.52–0.91)	5.81 (4.38–7.71)
Geometric LSMean ratio (product/CC) (90% CI)	0.17 (0.13–0.23)	0.12 (0.09–0.16)	0.12 (0.09–0.16)	n/a
AUC_t (min*ng/mL)				
Geometric LSMean	425.33	277.16	320.56	2246.96
Geometric LSMean ratio (product/UF2.0%) (90% CI)	n/a	0.65 (0.47–0.90)	0.75 (0.55–1.04)	5.28 (3.84–7.26)
Geometric LSMean ratio (product/CC) (90% CI)	0.19 (0.14–0.26)	0.12 (0.09–0.17)	0.14 (0.10–0.20)	n/a

Twelve subjects received each product in a crossover design. The statistical parameters were obtained using a mixed effects ANOVA with fixed effects of study period, sequence and treatment and a random effect of subject (nested in sequence).

Abbreviations: C_{\max} , maximum plasma concentration; AUC_t , area under the curve from 0 to 21 h after the 4th product administration. n/a, not applicable.

the fourth administration. These findings indicate that the resulting nicotine plasma PK profile obtained with the tested EVPs is very similar to that obtained following the use of NIC15 (i.e. that the EVP prototype is as effective as NIC15 in raising systemic nicotine levels). Our results are in agreement with findings from other studies conducted with CC smokers who used an EVP for the first time and whose blood nicotine levels stayed below 5 ng/mL (Bullen et al., 2010; Hajek et al., 2014; Vansickel et al., 2010). In absolute terms, nicotine exposures were substantially (8-fold) lower for the EVP, regardless of the presence of flavouring, than for the CC. All four products had a similar $t_{1/2}$, indicating that the type of product used for nicotine administration does not influence the rate of nicotine elimination.

As seen on Fig. 3, nicotine C_{\max} was higher for UF2.0% compared with FL2.0%. Even if it was statistically significant, that difference is of a small magnitude when put in perspective with the C_{\max} value obtained with CC. The effect of menthol on nicotine PK has also been studied in smokers of CCs. The available evidence indicates that in most smokers, menthol has no effect on nicotine absorption (Benowitz et al., 2004; Wang et al., 2010; Werley et al., 2007). Use of the flavoured EVP resulted in t_{\max} and $t_{1/2}$ values similar to the unflavoured product, indicating that the added flavours had a limited effect, if any, on nicotine absorption and elimination rates. As EVP consumers report that having a choice of flavours is important in order to reduce or quit CC smoking (Farsalinos et al., 2013a), any regulation limiting the use of flavours could be counter-productive and should be thoroughly evaluated on a case-by-case basis. The comparability of the nicotine plasma PK profile of

EVPs tested in our study and NIC15 may suggest that they share at least part of the nicotine absorption mechanisms, e.g. from the oral mucosa and the pharynx. It has been reported (Spindle et al., 2015) that experienced EVP users obtained nicotine exposures similar to CC smokers immediately after use when using third-generation products. This may be suggestive of the presence of pulmonary absorption routes for nicotine following delivery by third-generation devices, and investigations of the respective sites of nicotine absorption for different generation EVPs and different subjects therefore warrants further research.

In Part 2 of our study, the PK parameters found for UF2.0% were very similar to those found in Part 1, even though in general, a higher inter-subjects variability was observed in Part 2. This is an indication that our results were reproducible, and that despite the observed variability, the number of subjects was appropriate. Part 2 showed that increasing nicotine concentrations in the e-liquids resulted in higher plasma nicotine levels, even though the increase did not show direct dose proportionality (the mean C_{\max} was 1.0 ng/mL with UF0.4%, 1.9 ng/mL with UF0.9% and 3.6 ng/mL with UF2.0%). In another study, a C_{\max} of 4.6 ng/mL was reached with an EVP containing 2.4% nicotine in its e-liquid (Hajek et al., 2014). It has also recently been shown that the yield of nicotine from an EVP correlates with the nicotine content in the e-liquids used with the device (Talih et al., 2015). Taken together, these results indicate that there is a dose-relationship between plasma nicotine levels and the nicotine concentration in e-liquids, even though strict dose proportionality was not demonstrated in our study.

Under the revised European Tobacco Products Directive, (Directive 2014/40/EU – effective May 2016), Article 20 prohibits manufacturers from placing on the market e-liquids whose nicotine concentration exceeds 20 mg/mL (2% w/v). If manufacturers wish to exceed this level, they must have obtained a medical product license from the Member States competent authority (2014). The UK MHRA have placed guidance on its website on the licensing procedure for EVPs as medical products (MHRA, 2015). The guidance states that given the intended route of administration, an inhaled nicotine product such as the Nicorette[®] Inhalator has been advised as being a suitable reference product. It further states, in order for conclusions regarding the safety and efficacy of a product to be reached, it is necessary to show where the product ‘sits’ in relation to other nicotine containing products (NCPs) and cigarettes, in terms of its nicotine PK profile. In addition to nicotine, excipients and flavouring compounds, a number of toxicants such as carbonyls have also been reported in EVP aerosols (Farsalinos et al., 2014a; Goniewicz et al., 2013; Hutzler et al., 2014; Kosmider et al., 2014). The levels of these toxicants delivered to the user depend upon the volume of aerosol inhaled, and the design of the EVP. Product design characteristics such as power output, along with user

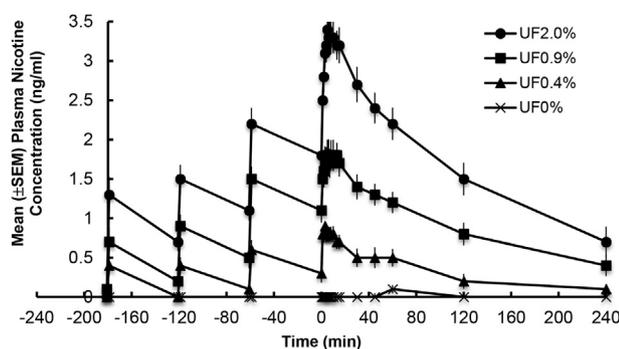


Fig. 4. Mean (\pm SEM) plasma nicotine concentration-time curves, shown for up to 240 min after the 4th product administration. Twelve subjects received each product in a crossover design. UF2.0%, unflavoured base liquid at 2.0% nicotine; UF0.9%, unflavoured base liquid at 0.9% nicotine; UF0.4%, unflavoured base liquid at 0.4% nicotine and UF0%, unflavoured base liquid at 0% nicotine; SEM, standard error of the mean.

behaviours have been shown to influence aerosol composition, and therefore user exposures (Kosmider et al., 2014; Talih et al., 2015). A framework that takes into account all these parameters for defining nicotine deliveries of EVPs need to be considered in the development of future regulation.

The EVP prototype tested in this study, when used on a short-term basis, resulted in comparable plasma nicotine PK profiles to an MHRA approved NRT product. The present study demonstrates that at the maximum e-liquid nicotine concentration of 2% as prescribed by the EU Tobacco Product Directive, the EVP device offered nicotine delivery that was comparable to the Nicorette® inhalator, with the advantage of replicating certain ritualistic elements of smoking a CC. The EVP studied here thus offers an alternative to NRT products, providing it complies with the safety, quality and efficacy standards set by a medicinal regulator, e.g. the UK MHRA.

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Declaration of interests

Tanvir Walele is an employee of Fontem Ventures B.V. and Josie Williams is an employee of Imperial Tobacco Group. Girish Sharma, Rebecca Savioz and Claire Martin received personal fees from Fontem Ventures B.V.

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Transparency document

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