

Original investigation

Evaluation of a Novel Nicotine Inhaler Device: Part 1—Arterial and Venous Pharmacokinetics

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Abstract

Introduction: In the United Kingdom, licensed nicotine-containing products can be recommended to reduce the harm associated with smoking. Many smokers find currently available nicotine replacement products unsatisfactory. The arterial and venous pharmacokinetics (PK) of nicotine delivered via a novel inhaler device were determined.

Methods: Results are reported for Parts A ($N = 18$) and C ($N = 18$) of a 4-part (A–D) Phase I study. Participants (18–55 years, ≥ 10 cigarettes/day, smoking within 1 hr of waking, expired carbon monoxide >10 ppm on screening) orally inhaled 2 single doses of nicotine (2 of 3 dose levels [0.22, 0.45, and 0.67 mg]) (Part A) and repeated hourly doses of 0.67 mg nicotine for 12 hr (Part C), via the novel device. Arterial and venous PK and tolerability were assessed.

Results: In Part A, mean arterial plasma nicotine concentrations at 2 min after the start of inhalation were 1.10, 2.06, and 2.59 ng/mL for the 0.22, 0.45, and 0.67 mg doses, respectively. Mean maximum arterial plasma nicotine concentrations (C_{\max}) were 2.11, 3.73, and 4.38 ng/mL and mean times to C_{\max} were 10.2, 7.3, and 6.5 min after the start of inhalation for the 0.22, 0.45, and 0.67 mg doses, respectively. In Part C, the mean pre- and postdose venous plasma nicotine concentration increased steadily and fluctuated in the range 8–10 mg/mL after 9 hr. The novel device was well tolerated; most adverse events were mild.

Conclusion: The novel inhaler device delivers nicotine rapidly into the systemic circulation and offers a viable alternative to cigarettes for those finding it difficult to quit the behavioral and sensory aspects of smoking.

Introduction

Tobacco smoking is the leading cause of premature mortality worldwide and is responsible for almost one in five adult deaths over 35 years of age in England alone.^{1,2} Until recently, measures to reduce the morbidity and mortality caused by smoking in the United Kingdom have focused on preventing the uptake of smoking and helping smokers to quit.³

Although smoking cessation services have had an increasing impact in helping smokers wanting to stop,⁴ the prevalence of smoking in England remains at around 20%.¹ Experience of the use of nicotine replacement therapy (NRT) products for smoking cessation

has indicated that their effectiveness may be modest; the proportion of smokers who successfully quit for 52 weeks without any behavioral support using NRT products in primary and secondary care is estimated at just 7%–10%.⁵

Existing NRT does not deliver nicotine in the same way as smoking and, moreover, the pharmacokinetic profile of the nicotine delivered may vary according to the NRT product used. Smoking leads to a rapid absorption of nicotine from the large surface area of the lungs and consequently to a sharp increase in arterial plasma nicotine levels.⁶ Comparison of a cigarette to various NRT delivery systems indicates that peak venous nicotine concentrations are

reached more rapidly with a cigarette or nasal spray than with an inhaler.⁷ Research suggests that currently available NRT formulations may also fail to help many smokers quit because they also do not replace the unique sensory cues or rituals associated with smoking.^{8,9}

A recognition that these approaches are ineffective for many smokers has triggered a major change in tobacco control policy to embrace the implementation of a harm reduction approach to smoking.¹⁰ The use of a tobacco harm reduction approach to smoking may include the use of licensed nicotine-containing products on a temporary or long-term basis.^{10,11}

The need for more effective and appealing products to provide satisfactory alternatives to smoking^{8,12} has led to the development of a new nicotine inhaler device. The inhaler enables the user to obtain nicotine in a similar way to using a cigarette and to replicate many aspects of their smoking-related behavior. By relieving or preventing nicotine cravings or withdrawal symptoms associated with stopping smoking, the recently licensed inhaler device could be used to cut down or stop smoking as part of a tobacco harm reduction approach.¹⁰ The novel nicotine inhaler contains no tobacco and, unlike electronic cigarettes, contains no battery or heating element to vaporize the nicotine, thus avoiding the associated production of other potentially toxic compounds¹³ and also removing a potential source of variability in device performance.^{14–18}

We performed a four-part study to evaluate nicotine delivery from this novel nicotine inhaler device. The two parts reported here aimed to determine the pharmacokinetics (PK) and tolerability of orally inhaled nicotine via the novel inhaler device. The results of the remaining two study parts, which compared the novel nicotine inhaler with the Nicorette® Inhalator (10 mg), are presented elsewhere.¹⁹

Methods

Study Design

This Phase I study comprised four parts: A, B, C, and D.

Part A: A randomized, single-blind, multidose level study to determine the tolerability and arterial PK of orally inhaled nicotine via the novel nicotine inhaler device at three nicotine dose levels: 0.22, 0.45, and 0.67 mg.

Part B: A randomized, open-label, single-blind, three-way crossover study to determine the venous PK of orally inhaled nicotine at two dose levels (0.45 and 0.67 mg) delivered via the novel nicotine inhaler device compared with the Nicorette® Inhalator (10 mg).

Part C: An open-label study to determine the tolerability and venous PK of repeat doses of orally inhaled nicotine delivered via the novel nicotine inhaler device at one dose level (0.67 mg).

Part D: A randomized, open-label, two-way crossover study to determine the venous PK of orally inhaled nicotine at one dose level (0.45 mg) delivered via the novel nicotine inhaler device compared with the Nicorette® Inhalator (10 mg).

Three nicotine formulations were developed for assessment in this clinical study. The concentrations chosen were designed to encompass the doses likely to be acceptable to users. Given the delivered mass of formulation from the device (approximately 0.8 g), the

mid-strength formulation (0.056% wt/wt nicotine) would deliver 0.45 mg, which is close to the dose delivered by the nicotine nasal spray²⁰; concentrations above and below this would bracket this dose and explore tolerability and effect on craving. This study therefore assessed the novel nicotine inhaler device at three dose levels: 0.22, 0.45, and 0.67 mg nicotine.

The study (Australian New Zealand Clinical Trials Registry Number 343206) was approved by the Queensland Clinical Trials Network Inc. (Human Research Ethics Committee Number 2011003) and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines. The study was performed at a single centre in Perth, Australia between January 9, 2012 and July 6, 2012 and all participants provided written informed consent prior to study start.

Participants

Healthy volunteers (male or female) aged 18–55 years were eligible for the study if they had smoked ≥ 10 manufactured cigarettes per day for the last year and smoked their first cigarette within 1 hr of waking. Women of child-bearing potential were eligible only if they tested negative for pregnancy prior to study start and were using an accepted method of contraception. All subjects had an expired carbon monoxide level of >10 ppm at screening and were required to abstain from smoking for 12 hr prior to their scheduled dosing time.

Participants were excluded if they had a known or suspected history of hypersensitivity to nicotine or any other component of the inhaler. Participants were also excluded if they had a history of confirmed chronic and/or serious pulmonary disease, including asthma, or chronic obstructive pulmonary disease, a history of myocardial infarction or cerebrovascular accident, other clinically significant cardiac or renal conditions, or any comorbidity that could place them at risk or interfere with the interpretation of the study data. Women who were breastfeeding were excluded from the study.

Study Treatment

The novel nicotine inhaler device is the size and shape of a conventional cigarette and comprises a small, breath-operated valve that allows a user to self-titrate the inhalation. The rate at which nicotine is delivered from one charge of the inhaler device is therefore dependent on the number of “puffs” over which one charge (or “dose”) is inhaled and this, in turn, depends on an individual’s depth of inhalation. For most users, the device provides a comparable number of puffs to that of a conventional tobacco cigarette. The device can be refilled approximately 20 times via a pressurized canister that contains a formulation of pharmaceutical grade (free-base) nicotine formulated with propylene glycol, ethanol, saccharin, menthol, and HFA134a (CFC free) propellant. The canister forms an integral part of the storage container, which is similar in size to a pack of 20 cigarettes ([Supplementary Figure S1](#)). Participants were familiarized with the novel inhaler device using a placebo formulation on the day prior to receiving active treatment. The placebo formulation was identical to the active formulation with the exception of nicotine. Participants inhaled the entire contents of one charge of the new inhaler in a similar way to a cigarette. All participants were instructed to inhale at the same rate of one inhalation every 15 s over approximately 2 min (i.e., approximately eight inhalations in total). The nicotine dose contained in 0.8 g of formulation (a single dose/refill of the novel device) is estimated to be 0.22, 0.45, and 0.67 mg for the 0.028%,

0.056%, and 0.084% wt/wt nicotine concentrations, respectively. The time when the participant took the first inhalation was recorded as the dose time ($t = 0$). Study participants were blinded to the dose of nicotine administered in each part of the study.

In Part A of the study, each participant was randomly assigned to one of three groups. Participants in each group ($n = 6$) received two single doses of nicotine via the novel inhaler device on a single study day. Participants received doses at two of the three dose levels available via the novel inhaler device. The first group received a 0.22 mg dose followed by a 0.45 mg dose; the second group received a 0.22 mg dose followed by a 0.67 mg dose; and the third group received a 0.45 mg dose followed by a 0.67 mg dose. The first and second doses were separated by a washout period of at least 5.5 hr (330 min), but not more than 6.5 hr (390 min) on the study day. This ensured that the plasma nicotine from the first dose had reached baseline concentrations through excretion before the second dose was inhaled.

In Part C, all participants received repeat doses of 0.67 mg nicotine delivered via the novel inhaler device on the study day, with one complete refill of the device being inhaled every hour for 12 hr.

Study Assessments

Pharmacokinetic Analysis

Plasma nicotine pharmacokinetic assessment was the primary outcome measure for this study. Approximately 4 mL of whole blood was collected at each specified time point from an arterial line for Part A and a venous line for Part C. Plasma was separated by centrifugation within 30 min of collection, aliquoted, and stored at $\leq -70^{\circ}\text{C}$. Plasma nicotine concentrations in the range 1–50 ng/mL were measured by liquid chromatography with tandem mass spectrometry, using a method validated for linearity, precision, and accuracy. Quality control samples at concentrations of 3.0, 7.5, and 37.5 ng/mL, as well as 37.5 ng/mL used as a dilute quality control for samples of low volume (diluted 1 in 2), were used to determine inter- and intra-precision and inter- and intra-accuracy. The mean inter-run accuracy was within 1% and precision was within 5%.

For Part A, arterial plasma concentrations of nicotine were measured over time and derived pharmacokinetic parameters were summarized separately by dose level. The pharmacokinetic parameters determined were the mean maximum plasma nicotine concentration (C_{max}), the median time to maximum plasma nicotine concentration (T_{max}), and the mean area under the plasma concentration–time curve, from time zero to the end of the sample collection period (AUC_{all}) and from time zero to the time of the last quantifiable concentration (AUC_{last}), following administration using the novel inhaler device. Radial arterial blood sampling was performed 5 min (± 1 min) preinhalation; at 2, 4, 6, 8, and 10 min (± 1 min); at 15, 20, 40, and 60 min (± 2 min); and at 120, 180, 240, and 300 min (± 5 min) after the start of inhalation. The collection time of each blood sample was recorded.

For Part C, pre- and postdose venous plasma concentrations of nicotine were measured by performing venous blood sampling at 5 min (± 5 min) preinhalation and at 5 min (± 2 min) after the start of inhalation, of each hourly dose. The collection time of each blood sample was recorded.

Pharmacokinetic analyses were performed using Phoenix™ WinNonlin® Version 6.2 or higher.

Safety and Tolerability

For both Parts A and C, safety and tolerability were assessed by the study investigator. The incidence and nature of any adverse events

(AEs) and any concomitant medicines from the start of the study until 8 days (± 2 days) after the last administration were recorded by assessment of all spontaneously reported events and responses to neutral questioning, local tolerability, physical examination, and monitoring of vital signs (blood pressure, heart rate, respiration rate, and temperature).

Tolerability of the orally inhaled nicotine was an assessment of symptoms resulting from inhalation of the nicotine by participants. Any symptoms that were reported as worse than prior to dosing were recorded as AEs. Local tolerability was an assessment of the contact area of the novel nicotine inhaler with the participant's lips. Participants were asked how the device felt in their mouth or lips, which were also assessed visually. "Redness," "swelling," "stinging," "tingling," "numbness," and "other symptoms" were recorded and assigned a severity of "none," "mild," "moderate," or "severe." For Part A, local tolerability was assessed at 20 min predose and at 4 min postdose. For Part C, local tolerability was assessed at 20 min predose for the first dose only and at approximately 5 min postdose for each dose.

Statistical Analyses

Statistical analyses were performed using SAS® Version 9.2 or higher.

For Part A, participants were included in the pharmacokinetic population if they received all planned doses of nicotine, and descriptive statistics were used to summarize pharmacokinetic findings by dose level.

For Part C, participants were included if they received all planned doses up to and including the fourth hourly dose, and all blood sampling up to 5 min following the fourth hourly dose. Pharmacokinetic concentrations were presented by time for each dose.

Participants were included in the safety intent-to-treat population if they received one dose of nicotine.

Results

Study Population

In Part A, 18 participants were randomly assigned to one of three groups ($n = 6$ per group), and each participant received two single doses of nicotine via the novel inhaler device at two dose levels. A further 18 participants were assigned to Part C and received repeat doses of nicotine at one dose level. Baseline demographics of the participants are shown in [Supplementary Table S1](#).

Part A

All participants were included in the pharmacokinetic analysis. The mean (*SD*) weights of formulation inhaled from the novel nicotine inhaler device were 0.8340 (0.1092), 0.8579 (0.1098), and 0.7935 (0.1642) g, corresponding to an overall mean 0.2335, 0.4804, and 0.6665 mg nicotine, for the 0.22, 0.45, and 0.67 mg nicotine dose levels, respectively. The range of weights of formulation inhaled from the novel inhaler device were 0.6633–1.0803, 0.6936–1.0369, and 0.4224–0.9892 g, for the 0.22, 0.45, and 0.67 mg nicotine dose levels, corresponding to ranges of 0.1857–0.3025, 0.3884–0.5807, and 0.3548–0.8309 mg nicotine, respectively.

Part C

All participants were included in the pharmacokinetic analysis. The mean (*SD*) weight of formulation inhaled from the novel nicotine inhaler device 0.67 mg was 0.8424 (0.2051) g, corresponding to an overall mean 0.7076 mg nicotine administered each hour for 12 hr.

The weights of formulation inhaled were in the range of 0.1588–1.1991 g between participants, which corresponded to a range of 0.1334–1.007 mg nicotine.

Study Assessments: Pharmacokinetic Analysis

Arterial PK of a Single Nicotine Dose (Part A)

The mean arterial plasma nicotine level rose sharply following administration of each of the three doses of nicotine using the novel inhaler device. Nicotine was detected in arterial blood at the first postinhalation sampling time point (at 2 min after the start of inhalation); the mean (*SD*) arterial plasma nicotine concentrations at 2 min postinhalation were 1.10 (0.78), 2.06 (0.92), and 2.59 (1.18) ng/mL for the 0.22, 0.45, and 0.67 mg doses, respectively (Figure 1). The postdose arterial plasma nicotine level had fallen to below the lower limit of quantification (1.00 ng/mL) in most participants by 120, 180, and 360 min for the 0.22, 0.45, and 0.67 mg doses, respectively.

Insufficient data were available over the validated range of plasma nicotine concentration (1–50 ng/mL) to allow accurate determination of arterial plasma nicotine half life.

The highest mean (*SD*) arterial plasma nicotine concentrations recorded at the study time points were 1.99 (0.62) ng/mL at 8 min for the 0.22 mg dose, and 3.66 (1.17) and 4.23 (1.14) ng/mL at 6 min for both 0.45 and 0.67 mg doses, respectively. Mean (*SD*) arterial C_{max} following administration of the novel nicotine inhaler device 0.22, 0.45, and 0.67 mg were 2.113 (0.671), 3.733 (1.131), and 4.380 (1.186) ng/mL, respectively (Table 1). Similarly, mean AUC_{last} and AUC_{all} were higher with increasing doses of nicotine. In contrast, median (range) arterial T_{max} decreased with increasing nicotine doses (Table 1).

Comparison of arterial mean plasma nicotine concentrations in Part A with venous mean plasma nicotine concentrations in Part B

(reported elsewhere [Moyses et al.¹⁹]), following administration of a single dose of 0.45 mg nicotine via the novel inhaler device (Figure 2), suggests that an early peak arterial plasma nicotine concentration is followed by a peak in venous plasma nicotine concentration. The venous plasma nicotine concentration in Part B is seen to continue to be higher than the arterial plasma nicotine concentration in Part A for the remainder of the postdose period.

Venous PK of Repeated Nicotine Doses (Part C)

The mean pre- and postdose venous plasma nicotine concentrations increased steadily throughout the 12-hr dosing period in Part C of the study and appeared to approach a steady state oscillation between approximately 8 and 10 ng/mL at the later time points (after 9 hr) (Figure 3). The highest mean (*SD*) pre- and postdose venous plasma nicotine concentrations were measured at dose 11—i.e., 8.31 (3.05) and 10.40 (3.68) ng/mL, respectively.

Safety and Tolerability

Part A

A total of 56 treatment-emergent AEs (TEAEs) were reported by 16 (89%) participants. Of these, 47 were considered as related to study medication. The most common TEAEs related to the study medication were oral paraesthesia, throat irritation, headache, dizziness, dry throat, and cough (Supplementary Table S2). There were 27 reports of local tolerability symptoms; all were reported as mild, with tingling the most commonly reported symptom (12/18 participants).

Two TEAEs were assessed as moderate, one of which was assessed as related to study medication (tingling of the lips and tongue, which was reported immediately after administration of 0.67 mg of nicotine via the novel device and resolved within 9 min).

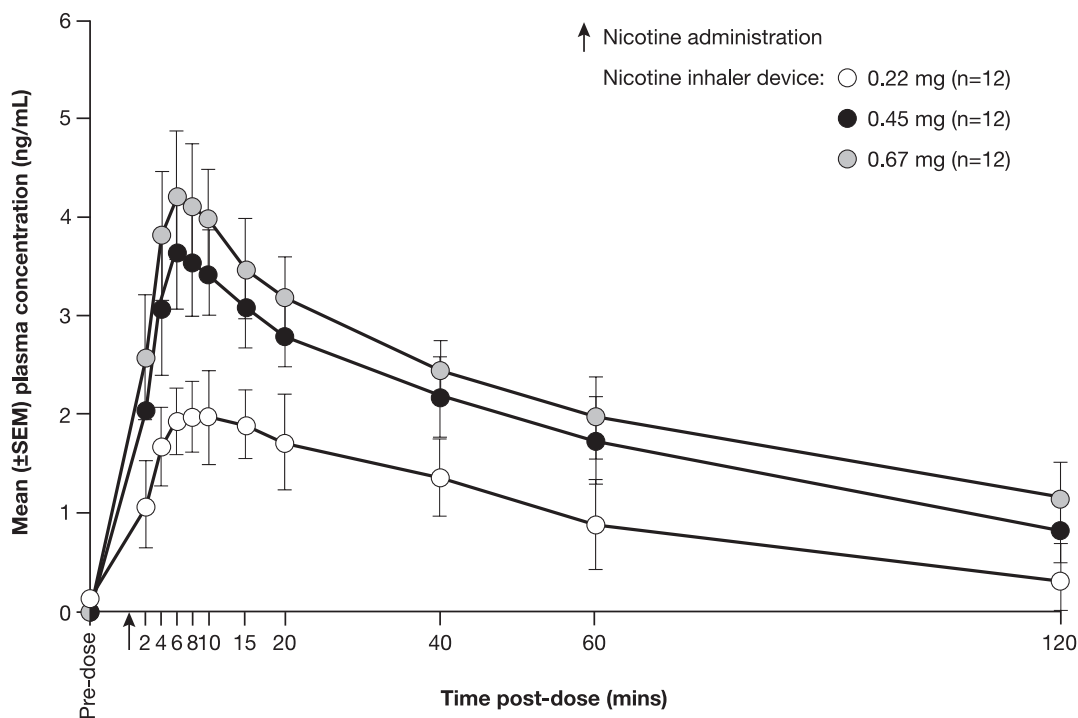


Figure 1. Mean arterial plasma nicotine concentration by treatment (linear scale): Part A ($N = 18$)^{*} up to 120 min after single administration of the novel nicotine inhaler device. SEM = standard error of the mean.^{*}Participants in each group ($n = 6$ per group) received two single doses of nicotine (a single dose at two of the three dose levels).

Table 1. Summary of Arterial Pharmacokinetic Parameters by Treatment: Part A

	Nicotine inhaler device		Nicotine inhaler device
	0.22 mg	0.45 mg	0.67 mg
C_{max} , ng/mL	2.113 (0.671)	3.733 (1.131)	4.380 (1.186)
T_{max} , median (range), min	10.0 (6.0–20.0 ^a)	7.0 (6.0–10.0)	6.0 (4.0–10.0)
AUC_{last} , min-ng/mL	118.6 (127.3)	241.7 (152.6)	296.9 (124.6)
AUC_{all} , min-ng/mL	145.7 (132.5)	274.4 (146.5)	334.4 (124.2)

All values are mean (SD) unless stated otherwise. AUC_{all} = area under the plasma concentration–time curve from time zero to the end of the sample collection period; AUC_{last} = area under the concentration–time curve from time zero to the time of the last quantifiable concentration; C_{max} = maximum plasma nicotine concentration; T_{max} = time to maximum plasma nicotine concentration.

^a T_{max} was in the range 6.0–10.0 min for 10 participants. T_{max} values of 15 and 20 min were observed in the remaining two participants.

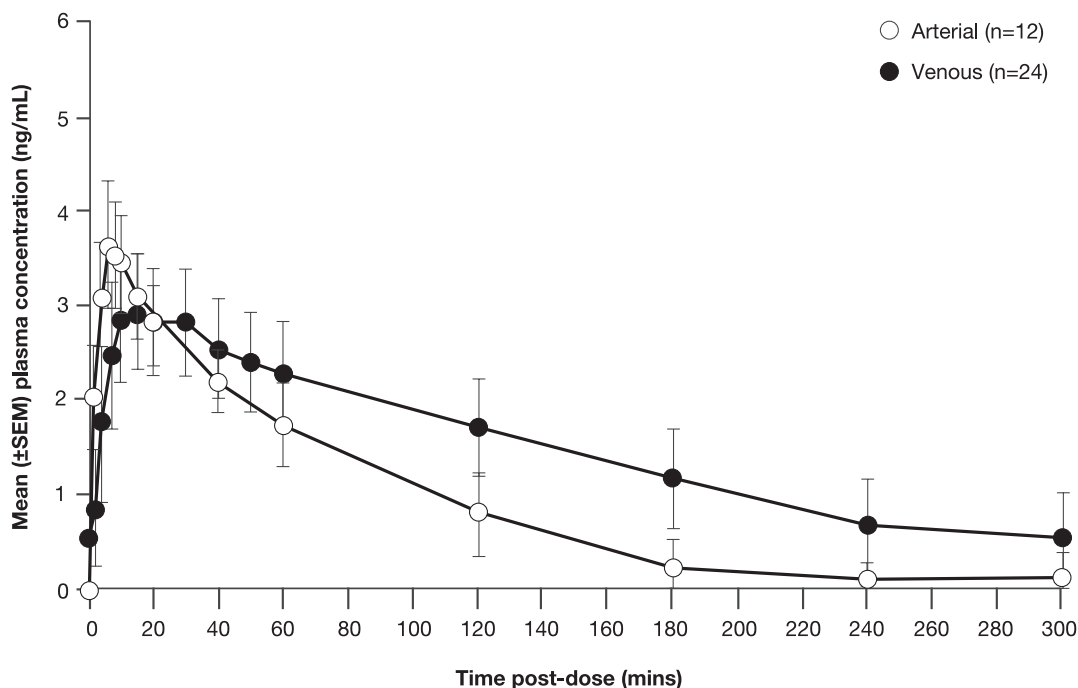


Figure 2. Comparison of mean arterial versus venous plasma nicotine concentrations over time after a single administration of the nicotine inhaler device 0.45 mg (linear scale) in Parts A ($N = 18$)^{*} and B[†] ($N = 24$). SEM = standard error of the mean. ^{*}Participants in each group ($n = 6$ per group) received two single doses of nicotine (a single dose at two of the three dose levels). [†]Participants received one single dose of nicotine at 0.45 mg. Data from Part B are reported elsewhere.¹⁹

Part C

A total of 104 TEAEs were reported by 17 (94%) participants. Of these, 97 were considered as related to the novel inhaler device and the most commonly reported were oral paraesthesia, throat irritation, and headache (Supplementary Table S2). One participant reported mild stinging 5 min postdose following administration of the first three doses of nicotine via the novel device. There were 34 (16%) reports of mild tingling and 14 (6%) reports of mild numbness.

Two TEAEs were assessed as moderate, one of which was assessed as related to study medication (emesis, which was reported 20 min after the 11th hourly administration of 0.67 mg nicotine via the novel device and resolved within 1 hr).

There were no AEs reported as severe, no serious AEs, or deaths throughout the study and no participants discontinued treatment owing to an AE.

There were no clinically significant changes in mean vital signs over time for the duration of the study. In Part A, one participant exhibited a change at the physical examination (decreased sensation in the right little finger and palm) which was assessed as clinically

significant but considered to be a non-TEAE as it occurred before the first dose.

Discussion

We present data from two parts of a four-part clinical study assessing a novel nicotine inhaler device. We studied both the arterial PK of a single dose of nicotine at three dose levels (Part A) and the venous PK of repeat doses of nicotine (Part C). The results indicate that nicotine rapidly enters the systemic circulation following administration using the novel inhaler device and that repeated hourly inhalations lead to an increasing venous plasma nicotine concentration that approaches a steady state oscillation after 9 hr.

In Part A of the study, arterial blood sampling times enabled the pharmacokinetic profile of nicotine administered using the novel inhaler device to be clearly defined. The mean arterial plasma concentration rose sharply following administration of each of the three doses of nicotine with the presence of nicotine detected in arterial blood at the first sampling time point (at 2 min) after the start of

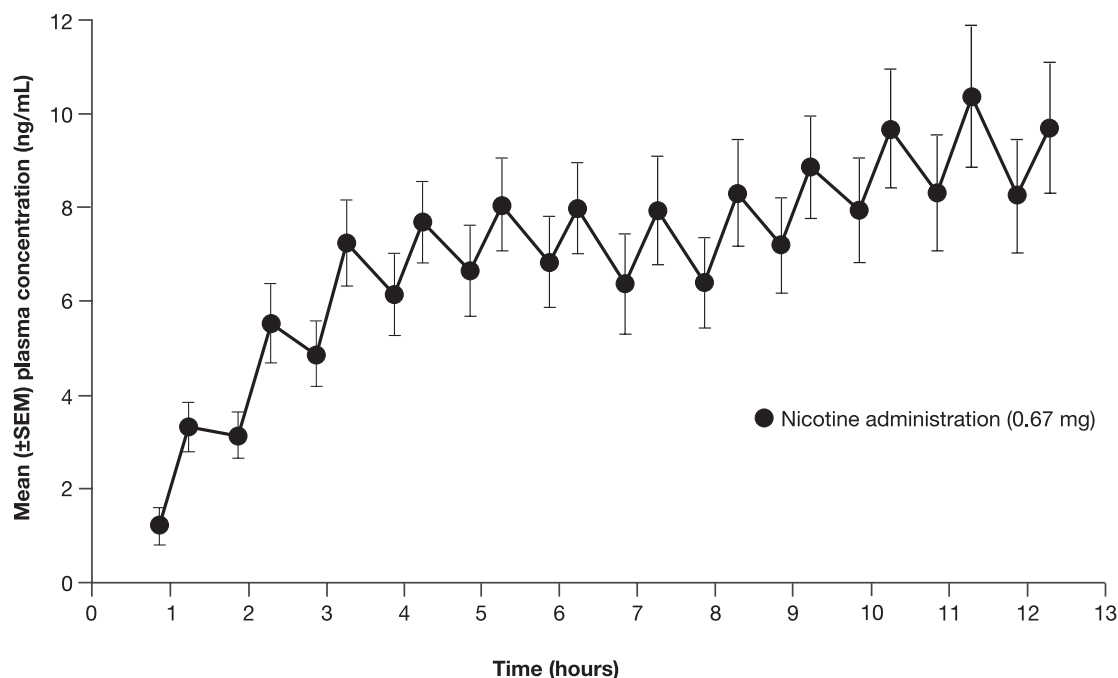


Figure 3. Mean venous plasma nicotine concentration over time (linear scale): Part C ($N = 18$) after repeated administration of the novel nicotine inhaler device (0.67 mg). SEM = standard error of the mean.

inhalation (which took approximately 2 min to complete). For the 0.45 mg dose, the mean arterial nicotine plasma level of 2.06 ng/mL recorded at 2 min was over half the subsequent C_{max} . The speed at which nicotine was apparent in arterial blood suggests that there was a degree of pulmonary absorption with the novel inhaler device as oromucosal delivery alone results in a significantly slower rise in plasma nicotine concentration.⁷ Mean arterial nicotine plasma C_{max} increased from 2.113 to 4.380 ng/mL with an increase in nicotine dose from 0.22 to 0.67 mg. The increase in C_{max} was accompanied by a corresponding decrease in median T_{max} (from 10.0 to 6.0 min). The median arterial T_{max} for the 0.67 mg nicotine dose was similar to that reported for 1.0 mg nicotine delivered via a nasal spray (6.0 vs. 5.0 min, respectively),²¹ where the difference may reflect the bolus regimen used with the nicotine nasal spray.

AUC_{all} values ranged from 145.7 to 334.4 min-ng/mL, possibly due to the variability in individual patterns of inhalation within the study dosing regimen of one puff every 15 s. The lack of observed dose proportionality between the 0.45 and 0.67 mg doses could be due to variation in the depths of inhalation between individuals and with different strengths. Such observations have been reported previously and are thought to be due to increased throat scratch experienced with inhalation of nicotine at higher concentrations.²²

In Part C of the study, both the pre- and postdose venous plasma nicotine concentrations increased steadily throughout the 12-hr dosing period. The highest pre- and postdose plasma nicotine concentrations were measured at dose 11 of the 12 doses administered. Venous plasma nicotine concentrations after repeat dosing of 0.67 mg nicotine (Part C) appeared to be more variable than arterial concentrations after single dosing (Part A). The cumulative effect of repeatedly dosing before venous plasma nicotine concentrations had returned to baseline is likely to have contributed to the observed variation. Following hourly administration of 0.67 mg of nicotine using the novel inhaler device, venous plasma nicotine concentrations appeared to approach a steady state oscillation between

approximately 8 and 10 ng/mL at the later time points of the study. This is considerably lower than the range of venous plasma nicotine concentration recorded after smoking a cigarette containing 1.2 mg nicotine every hour (approximately 20–50 ng/mL).²³

The qualitative pharmacokinetic profile of the novel device is similar to that of a cigarette with higher, earlier peak arterial concentrations relative to venous levels, although at lower absolute nicotine concentrations than seen with a cigarette. This is in contrast to pharmacokinetic data on the Nicorette[®] nicotine inhaler, which shows an earlier venous peak and a low, delayed arterial peak consistent with predominantly nonpulmonary delivery.²⁴ Hence, the closer pharmacokinetic surrogacy of the novel device may translate into greater acceptability and efficacy relative to currently available NRT products, although this will require confirmation from randomized efficacy trials. A variety of electronic cigarettes are also available, which utilize electrical heating to vaporize nicotine for inhalation. Pharmacokinetic studies of electronic cigarette-naïve populations have shown very low levels of systemic nicotine,¹⁴ although a small study of experienced users with electronic cigarettes carrying increased voltage and higher concentration nicotine solutions demonstrated that PK comparable with those of cigarettes are obtainable.¹⁷ With the achievement of a similar profile in a device-naïve population in the current study, it is plausible that the novel device may have broader efficacy than standard, widely available, electronic cigarettes.

This was a small, short-duration study that was not designed to fully evaluate safety. However, reports of AEs were recorded systematically and the trial was conducted according to GCP. Administration of nicotine via the novel device was well tolerated by the participants in both study parts and the TEAEs reported were consistent with those reported in a previous study.²⁵ There were no severe or serious AEs, and no subjects discontinued treatment owing to an AE. The majority of local AEs were mild in nature. However, the safety profile of the novel nicotine inhaler will need to be confirmed in larger, longer term trials.

The comparison of arterial and venous plasma nicotine concentrations following administration of a single dose of 0.45 mg nicotine via the novel inhaler device in Parts A and B, respectively (Figure 2), is derived from results from different participants. Analysis of results from simultaneous arterial and venous blood samples from the same participants would provide more accurate information. Furthermore, the novel inhaler utilizes a breath-actuated valve and the quantity of nicotine inhaled may have varied between users. The precise pattern of nicotine delivery and absorption using the novel inhaler device would require confirmation in further studies using labeled nicotine. An additional limitation of the study was highlighted on comparison of the mean venous plasma nicotine concentrations delivered from the novel inhaler device 0.45 mg in Parts B and D. The plasma nicotine concentration curves were very similar; however, the peak nicotine concentration in Part D was 3.52 ng/mL compared with 3.28 ng/mL in Part B. Although the device was primed before use in all study parts, it was thought that administration of the fourth dose from the device in Part D allowed greater saturation of the wick compared with administration of the first dose in Part B and consequently delivered a higher dose of nicotine than in Part B. This first-dose anomaly was regarded as consistent across the three strengths of formulation used. The administration of a single dose and repeat doses from the novel inhaler device in Part A and Part C, respectively, may have resulted in lower plasma concentrations of nicotine being achieved in Part A than Part C.

Conclusions

The data indicate that nicotine is rapidly delivered into the systemic circulation following inhalation using the novel inhaler device with an arterial pharmacokinetic profile consistent with a degree of pulmonary absorption.

The novel nicotine inhaler device is comparable with a cigarette both in appearance and mode of use. It offers a rapid nicotine delivery that is as fast as the nicotine nasal spray but offers the possibility of improved tolerability. It has the potential to address many behavioral and sensorial aspects of smoking that can make quitting difficult, and it is also likely to be of considerable interest in a tobacco harm reduction approach to smoking.

Supplementary Material

Supplementary Tables S1 and S2 and Figure S1 can be found online at <http://www.ntr.oxfordjournals.org>

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Declaration of interests

CM and AH are employees of Kind Consumer Limited. AR has no conflicts of interest to disclose.

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