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Plasma Nicotine Pharmacokinetics of Oral Nicotine Pouches Across Varying Flavours and Nicotine Content*

by

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SUMMARY

Background: In recent years several nicotine products have been introduced that aim to offer smokers an alternative to cigarettes. As well as having fewer toxicants than combustible cigarettes, such nicotine products must be able to deliver nicotine efficiently. The aim of this study was to determine and compare the pharmacokinetics of nicotine absorption from nine oral tobacco-free smokeless nicotine pouches with varying nicotine content and flavours.
Methods: In a randomised, open-labelled, controlled, crossover clinical study, nicotine pharmacokinetics and product-liking were compared between nine nicotine pouches (*Velo*, BAT; 4- or 7-mg nicotine per pouch and in eight flavours). During a 10-day confinement period, 42 healthy adult participants, who were current smokers of combustible cigarettes, used a single study product once each day during a 45-min use period following overnight nicotine abstinence.
Results: Maximum plasma nicotine concentration and area under curve for nicotine concentration *versus* time 180 min after the start of study product use were significantly greater for the 7-mg than for the 4-mg *Velo* pouches ($p < 0.0001$). These values did not differ between flavours among the 7-mg *Velo* nicotine pouches after adjustment for multiple comparisons (both $p > 0.003$). The median time to maximum plasma nicotine concentrations and mean product-liking scores were similar regardless of nicotine content and flavour.
Conclusions: Regardless of flavour, nicotine pouches with the same nicotine content and formulation produce similar pharmacokinetic parameters and can deliver nicotine efficiently. Nicotine pouches could be a satisfying alternative for smokers switching from conventional cigarettes.
[Contrib. Tob. Nicotine Res. 32 (2023) 130–139]

KEYWORDS

Nicotine; nicotine pouches; flavours; switching.

ZUSAMMENFASSUNG

Hintergrund: In den letzten Jahren sind diverse Nikotinprodukte eingeführt worden, die Rauchern eine Alternative zu Zigaretten bieten sollen. Abgesehen davon, dass sie weniger Giftstoffe enthalten als klassische Zigaretten, sollten solche Nikotinerzeugnisse Nikotin auch wirksam abgeben können. Ziel der vorliegenden Studie waren die

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Bestimmung und der Vergleich der Pharmakokinetik der Nikotinaufnahme von neun oralen, tabakfreien, rauchlosen Nikotinbeuteln mit unterschiedlichem Nikotingehalt und in verschiedenen Geschmacksrichtungen.
Methoden: In einer randomisierten, offenen, kontrollierten, klinischen Crossover-Studie wurden jeweils die Pharmakokinetik des Nikotins sowie die Produktvorlieben bei neun verschiedenen Nikotinbeuteln verglichen (*Velo*, BAT; 4 mg oder 7 mg Nikotin je Beutel und in acht Geschmacksrichtungen). Während eines 10-tägigen Isolationszeitraums konsumierten 42 gesunde erwachsene Probanden, die aktuell brennbare Zigaretten rauchten, nach einer nächtlichen Nikotinabstinenz einmal täglich für eine Konsumdauer von 45 Minuten ein einziges Studienprodukt.
Ergebnisse: Die maximale Nikotinplasmakonzentration und die Fläche unter der Nikotinkonzentrations-Zeit-Kurve über einen Zeitraum von 180 Minuten nach dem Beginn des Konsums des Studienproduktes waren bei den *Velo*-Beuteln mit 7 mg im Vergleich zu denen mit 4 mg signifikant größer ($p < 0{,}0001$). Nach Bereinigung um Mehrfachvergleiche variierten diese Werte innerhalb der *Velo*-Nikotinbeutel mit 7 mg nicht zwischen den Geschmacksrichtungen (beide $p > 0{,}003$). Die mediane Zeit bis zum Erreichen der maximalen Nikotinplasmakonzentration und die durchschnittliche Bewertung der Produktvorlieben waren unabhängig von Nikotingehalt und Geschmacksrichtung ähnlich.
Schlussfolgerungen: Nikotinbeutel mit demselben Nikotingehalt und derselben Formulierung weisen, unabhängig von der Geschmacksrichtung, ähnliche pharmakokinetische Parameter auf und können Nikotin wirksam abgeben. Sie könnten daher eine zufriedenstellende Alternative für Raucher sein, die das Rauchen herkömmlicher Zigaretten aufgeben möchten. [Contrib. Tob. Nicotine Res. 32 (2023) 130–139]

RESUME

Toile de fond: Au cours des dernières années, plusieurs produits contenant de la nicotine ont été présentés dans le but de proposer aux fumeurs un substitut à la cigarette. En plus de contenir moins de substances toxiques que les cigarettes combustibles, ces produits doivent être en mesure de délivrer de la nicotine avec efficacité. L'objet de la présente étude fut de déterminer et de comparer la pharmacocinétique de l'absorption de la nicotine de neuf sachets de nicotine sans tabac, à ingérer et non pas à fumer et affichant des teneurs en nicotine et des saveurs variées.
Méthodes: Dans le cadre d'un essai clinique croisé, sur échantillon contrôlé, ouvert et randomisé, la pharmacocinétique de la nicotine et l'appréciation pour le produit firent l'objet d'un comparatif entre neuf sachets de nicotine (*Velo*, BAT; 4- ou 7-mg de nicotine dans chaque sachet, disponible en huit saveurs). Durant une période de confinement de 10 jours, 42 adultes en bonne santé et fumeurs actuels de cigarettes combustibles consommèrent un seul produit étudié, une fois par jour, pendant une durée de 45 minutes suivant une nuit d'abstinence à la nicotine.
Résultats: La concentration maximale de nicotine dans le plasma et l'aire sous la courbe de concentration de nicotine en fonction d'un temps de 180 minutes après le début de la consommation du produit furent, de façon significative, supérieures pour les sachets *Velo* dosés à 7-mg par rapport aux sachets *Velo* dosés à 4-mg ($p < 0{,}0001$). Ces valeurs ne varièrent pas selon les saveurs parmi les sachets de nicotine *Velo* dosés à 7-mg après ajustement en vue de comparaisons multiples ($p > 0{,}003$ dans les deux cas). Le temps médian écoulé avant d'atteindre les concentrations maximales de nicotine dans le plasma et les scores moyens d'appréciation du produit furent similaires, quelle que soit la saveur ou la teneur en nicotine.
Conclusions: Indépendamment de la saveur, les paramètres pharmacocinétiques des sachets de nicotine affichant la même teneur en nicotine et la même formulation s'avèrent similaires et ces produits peuvent, de façon efficace, délivrer de la nicotine. Les sachets de nicotine pourraient constituer un substitut satisfaisant pour les fumeurs désireux d'abandonner les cigarettes conventionnelles. [Contrib. Tob. Nicotine Res. 32 (2023) 130–139]

INTRODUCTION

Cigarette smoking is a leading avoidable contributor to morbidity and mortality, playing a causal role in lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease, among other diseases (1). Smoking cigarettes is addictive, primarily due to nicotine – a naturally occurring alkaloid in tobacco leaves (2) that has effects on mood and relaxation through its activity at neuronal nicotinic receptors in the brain (3). Nicotine in cigarette smoke is rapidly absorbed through the lungs and transferred to the bloodstream (4), which distributes it around the body. As a result, the pharmacokinetic profile of nicotine during cigarette smoking is distinguished by a swift rise in blood nicotine levels (5), and the consequent desirable effects are rapid (3). Prominent regulatory agencies and health-care bodies, such as the Royal College of Physicians and Public Health England, consider nicotine to be relatively harmless at the levels of exposure attained during cigarette smoking, as compared to the significant harm caused by other components of cigarette smoke (6–8). Instead, the harmful effects of smoking are due to the long-term inhalation of 8,700 or more identified chemicals (9), including many with a known link to the development of specific diseases (10). The individual health risk associated with cigarette smoking is correlated with the length of smoking history and the number of cigarettes smoked each day, such that smoking cigarettes for longer and with greater frequency leads to increased risk of disease (11, 12).
Quitting smoking substantially reduces the risk of an individual developing a smoking-related disease. However, while large proportions (> 50%) of smokers report a desire to stop smoking, and many make cessation attempts each year (13), fewer than 1 in 10 smokers successfully quit smoking each year (13, 14). As a result, an alternative approach based on tobacco harm reduction (THR) has been put forward (15). The principle of THR is to encourage smokers, who would not otherwise quit smoking, to switch from smoking combustible cigarettes to using alternative non-combustible/smokeless nicotine and tobacco products with decreased levels of toxicant emissions, such as e-cigarettes (6). While not entirely risk free, such switching could

significantly reduce smokers' exposure to harmful toxicants (6, 7, 16, 17) and potentially an individual's risk of developing a smoking-related disease (18, 19).

Oral nicotine pouches (NPs) are alternative tobacco-free nicotine products that have the potential for THR. They are similar in form and usage to Swedish snus, a smokeless tobacco product, representative brands of which have been recognised by the U.S. Food and Drug Administration as a modified-risk tobacco product that has been epidemiologically proven to offer significantly reduced risks of disease compared to cigarettes. Introduction to the market is expected to benefit the health of the population as a whole (20). Both snus and NPs are placed under the upper lip, allowing the nicotine to be absorbed through the oral mucosa. Whereas snus contains tobacco, NPs contain a cellulose matrix with pharmaceutical grade nicotine (21–23). Therefore, when compared to snus, NPs do not contain tobacco and consequently have lower levels in key harmful and potentially harmful tobacco product and tobacco smoke constituents (23).

Recent *in vitro* toxicology studies have reported that NP extracts have significantly less biological activity than an equivalent reference snus product across multiple flavour variants and nicotine content (24, 25). As well as having lower toxicity, alternative non-combustible/smokeless nicotine and tobacco products must be able to deliver nicotine to smokers efficiently to be successfully adopted as part of a THR strategy (6, 26). Recent studies indicate that NPs may deliver nicotine sufficiently to smokers seeking satisfactory alternative products (27, 28), but to date there is little information of the effects of nicotine content and flavours on nicotine pharmacokinetics for these products.

In this study, we have determined and compared the pharmacokinetics of nicotine absorption among current cigarette smokers using nine different *Velo* NPs including a single product with a nicotine content of 4 mg and eight NPs with different flavours (e.g., fruit and mint/menthol), at a nicotine content of 7 mg. We have also assessed product-liking for the NPs. Based on our findings, we discuss the THR potential of NPs in delivering nicotine efficiently and providing a choice of flavours to smokers seeking an alternative to smoking.

METHODS

Study design

The present randomised, controlled, crossover clinical study was conducted at a single site in Kansas City, KS, USA. The study was registered on the U.S. ClinicalTrials.gov registry (NCT04846088). Approval was given by an Institutional Review Board (IRB; Ethics (WIRB Copernicus Group, Puyallup, WA, USA; study reference number 1305801) before study commencement. The study was conducted in accordance with the U.S. Code of Federal Regulations (CFR) governing Protection of Human Subjects (21 CFR Part 50), Financial Disclosure by Clinical Investigators (21 CFR Part 54), and IRBs (21 CFR Part 56). It was also carried out in accordance with the protocol and under the principles of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP) E6 (R2). All participants provided written informed consent before enrollment and before undergoing any study procedures, including screening. At any time, they were free to quit smoking, withdraw their consent, or withdraw from the study.

Participants

Forty-two healthy male or female participants who met the inclusion criteria were enrolled in the study within 45 days of their screening visit to ensure that a minimum of 36 participants completed the study. An attempt was made to recruit a balance of sexes with no less than 40% of either sex represented and to recruit at least 15–20% black/African American participants to reflect the reported percentage of U.S. smokers in this group. Participants were aged 22–65 years inclusive and generally healthy as determined by clinical laboratory evaluations (including haematology, clinical chemistry, urinalysis, serology, urine drug and urine/breath alcohol screen), medical history, physical examination including oral examination, vital signs assessment and 12 lead electrocardiograms. All participants were current smokers with a minimum 1-year smoking history and who were smoking at least 10 per day of filtered non-menthol or menthol cigarettes between 83 and 100 mm in length as their primary source of tobacco use. Exhaled carbon monoxide and urine cotinine were assessed to confirm cigarette smoking status. Participants also self-reported use of smokeless tobacco products (e.g., moist snuff or snus) at least once or twice in their lifetime before screening. Female participants underwent a serum pregnancy test at screening and a urine pregnancy test at check-in to the clinical site. Women of childbearing potential were required to use an accepted form of contraception for 30 days before and after the study.

The main exclusion criteria were:

- pregnancy or breastfeeding (women only);
- self-reported non-inhalation of cigarette smoke;
- self-reported previous or current use of any *Velo* or *Dryft* NPs;
- presence of gum bleeding and/or abscess, open mouth sores or oral ulcers at screening or check-in;
- history of significant allergic reaction to any substance including mint, wintergreen or spearmint flavouring;
- whole-blood donation within 56 days of screening or blood plasma donation within 7 days of screening or between screening and check-in;
- delaying a decision to quit using tobacco or nicotine products in order to participate in the study or self-reporting a quit attempt within 30 days of screening;
- or current use of any smoking cessation aid.

Investigational products

The study products were nine *Velo* portioned oral NPs including a 4-mg/pouch of nicotine with one flavour (*Velo* Wintergreen) and 7-mg/pouch of nicotine with eight flavours (*Velo* Max Wintergreen, Spearmint, Peppermint, Citrus Burst, Black Cherry, Coffee, Dragon Fruit, and Cinnamon). The contents of each *Velo* or *Velo* Max pouch

include a powdered cellulosic substrate, pharmaceutical grade tobacco-derived nicotine, pH adjusters, sweeteners, and other ingredients specific to each flavour. The powdered mixture is pouched in a porous wrapping material referred to as "fleece".

Study procedures

All participants were screened against the inclusion and exclusion criteria and completed a questionnaire on their tobacco product use. Within 45 days of screening, they were admitted to the clinic on Day 1 of the study and were confined to the site for approximately 10 days until the last assessments had been made. On admission, participants' eligibility was reconfirmed and they underwent vital signs assessments, physical and oral examinations, and a urine pregnancy test (females only). At the end of the study, they underwent clinical laboratory testing, physical and oral examinations, vital signs assessments, and a urine pregnancy test (females only).

On Day 1, all participants took part in a product familiarisation session lasting at least 45 min in which they tried the *Velo* Max 7-mg nicotine and peppermint flavour study NP. Throughout the study, participants were required to abstain from using any nicotine product for at least 12 h before the product use session the following morning. In each product use session, participants used a single study product as specified by predetermined randomisation sequences. Within 30 min of the start of the session, participants were asked to rinse their mouth with approximately 50 mL water and were then instructed to place a single *Velo* pouch in their mouth anywhere between their gum and their upper lip and allow the pouch to absorb saliva and moisten. Participants moved the pouch from one side of the mouth to the other approximately every 10 min, and the pouch remained in the mouth for a period of 45 min.

After product use and blood sampling was completed, participants were allowed to smoke their own brand of combustible cigarettes *ad libitum* until the 12 h abstinence period prior to the next product use session.

Blood sampling for nicotine pharmacokinetics

Venous blood samples were collected by direct venepuncture or through an indwelling cannula. Blood samples (4 mL) were taken at −5, 2, 5, 10, 15, 30, 45, 60, 90 and 180 min relative to product administration into K_2-EDTA vacutainer tubes. To ensure anticoagulation, the tubes were inverted 10 times and centrifuged within 60 min (1,500 g, 4 °C, 10 min). The plasma was stored in two aliquots at −20 °C. The time from blood sample collection to plasma storage did not exceed 90 min.

Nicotine analysis was done by Altasciences (Laval, Quebec, Canada) using liquid chromatography with tandem mass spectrometry detection as previously described (28). In brief, nicotine was extracted from 0.15 mL plasma by protein precipitation and analysed using a Waters XBridge C18 column on an AB Sciex API 5000 quadrupole mass spectrometer in positive ion mode for the detection of nicotine.

Analyst® software version 1.6.3, was used to acquire and review chromatograms. The internal standard was nicotine-D_4, and nicotine was quantified over a theoretical concentration range of 0.2–100.0 ng/mL. For the analysis only non-smokers prepared the spiking solutions, calibrant and quality control samples.

Furthermore, blank samples were injected before the pre-test to check for the presence of nicotine in the system. In addition to blank and zero standards, all runs had a set of 11 non-zero standards and 4 levels of Quality Control samples prepared with analyte-free human plasma. Incurred Sample Reanalysis evaluation was assessed concurrently to the sample analysis with at least 10% of the first 1000 analysable study samples and 5% of the remaining samples reassayed and compared to their original values. The sample analysis was conducted in accordance with U.S. Food and Drug Administration Guidance for Industry, (29) and European Medicines Agency Guideline on Bioanalytical Method Validation (30).

Subjective effects assessments

At the end of the pharmacokinetic session (180 min relative to the start of product use), participants completed a single product-liking questionnaire to evaluate the subjective effect of study product use. Answers were given as a numeric rating score from 0 to 10, with 0 corresponding to "strong disliking", 5 corresponding to "neither like nor dislike" and 10 corresponding to "strong liking".

Safety assessments

Adverse events (AEs) were defined as any untoward medical occurrence or condition experienced by a participant after signing the informed consent form until completion of the study, irrespective of whether it was considered to be related to the use of study products. An AE could be any unfavourable and unintended sign (e.g., abnormal laboratory finding), symptom or disease, without any judgment about causality.

All AEs, whether volunteered, elicited or noted on the physical examination/oral examination at the end of the study, were recorded throughout the study. The start and stop date and time of all AEs was captured. Participants who presented with unresolved or new AEs at study conclusion or early termination were followed up until the AE had resolved or stabilised. A product-emergent adverse event (PEAE) was defined as an AE that was not present prior to study product use or an AE that was present but worsened in intensity or frequency after study product use.

A serious adverse event (SAE) was defined as any medical occurrence that resulted in death or was life-threatening, required inpatient hospitalisation or prolongation of an existing hospitalisation, resulted in persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions, was a congenital anomaly or birth defect or was a severe medical event that required medical or surgical intervention to prevent one of the above outcomes.

Sample size and statistical methods

Using data from prior studies, it was estimated that 36 participants would be needed to have at least an 80% chance

Table 1. Demographic data of study participants collected at screening.

Variable	Number of participants	%	Mean (SD)
Age (years)	42	—	40.4 – 11.38
Sex			
Male	28	66.7	—
Female	14	33.3	—
Weight (kg)	42	—	81.17 – 17.02
Height (cm)	42	—	173.5 – 9.2
BMI (kg/m^2)	42	—	26.8 – 4.45
Race			
White	33	78.6	—
Black / African American	9	21.4	—
Ethnicity			—
Hispanic or Latino	6	14.3	—
Not Hispanic or Latino	36	85.7	—

Abbreviations: BMI: body-mass index; SD: standard deviation.

of obtaining a 95% confidence interval with a half-width of up to 20% of the means for the primary endpoints. The target number of participants to be recruited into this study was 42 participants, which allowed for approximately a 14% dropout rate with a goal of 36 participants completing the study.

Raw nicotine concentrations and derived baseline-adjusted concentrations were determined by compartmental methods using Phoenix® WinNonlin® version 8.0 (Certara, Princeton, NJ, USA). The primary endpoint nicotine pharmacokinetic parameters maximum plasma nicotine concentration (C_{max}) and area under the nicotine concentration-*versus*-time curve from time zero to 180 min after the start of study product use ($AUC_{nic\ 0–180}$) were adjusted for baseline plasma nicotine concentration under the assumption that nicotine elimination follows first-order kinetics. Negative concentrations resulting from baseline adjustment were forced to zero. The secondary pharmacokinetic endpoint time to maximum plasma nicotine concentration (T_{max}) was also calculated based on the baseline-adjusted plasma nicotine concentrations. Observed plasma nicotine concentration values below the lower limit of quantification were set at half the lower limit of quantification, and missing data were considered as missing at random and not imputed. Demographic and pharmacokinetic parameters presented here are for the pharmacokinetic population, which included 41 participants who used at least one study product and it had sufficient data to derive at least one pharmacokinetic parameter.

The pharmacokinetic parameters C_{max} and $AUC_{nic\ 0–180}$ were summarised using descriptive statistics for each study product. These statistics included the number of non-missing data points, mean, standard deviation (SD), coefficient of variation, minimum, median, and maximum. Additionally, geometric means, geometric SD, and geometric coefficient of variation calculated for C_{max} and $AUC_{nic\ 0–180}$ are reported. For T_{max} only non-missing data points, minimum, median, and maximum values are reported.

Statistical comparisons of C_{max} and $AUC_{nic\ 0–180}$ between study products were performed using paired *t*-tests on a log-transformed scale. For T_{max}, comparisons were made using a sign test on the original data scale. For all pharmacokinetic parameter comparisons, Bonferroni adjustment was used during the statistical analyses. With a total of 24 comparisons (8 product comparisons × 3 parameters), a *p*-value less than 0.002 (0.05/24) would indicate statistically significant difference.

For the product-liking subjective effects measure, the overall product-liking numeric rating score was summarised by product using descriptive statistics (non-missing data points, mean, SD, minimum, quartile 1, quartile 3, and maximum).

RESULTS

Participant demographics

A total of 42 participants met eligibility requirements and were enrolled into the study. The majority of randomised participants (95.2%) completed the study according to the protocol. All 42 participants (100%) completed Day 1, 41 participants (97.6%) completed Days 2 and 3, and 40 participants (95.2%) completed Days 4 through 9. Two participants voluntarily withdrew from the study early, for a family emergency on Day 4 (1 participant) and due to the number of blood draws on Day 1 (1 participant).

Basic participant demographic data are summarised in Table 1. The male:female ratio was 68:32; 80.5% of the participants were white and 19.5% were black/African American.

Nicotine pharmacokinetics

Mean plasma nicotine concentration-time curves for the *Velo* NPs are shown in Figure 1, while descriptive data and statistical comparisons of the pharmacokinetic parameters are summarised in Table 2 and Table 3, respectively. For each study product, the mean plasma nicotine concentration increased throughout use, reaching a peak at the end of the 45-min product use period. Mean coefficient of variation

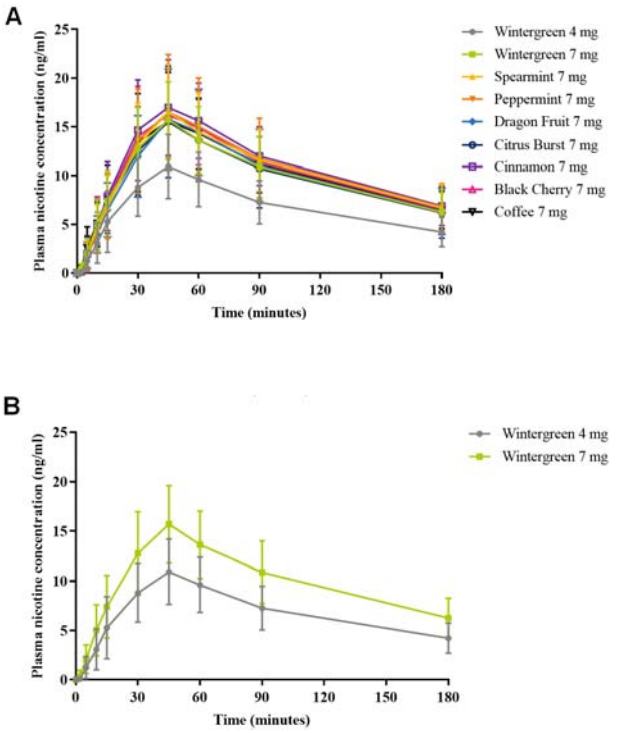

Figure 1. Baseline-adjusted plasma nicotine concentrations over time. Figure shows the baseline adjusted mean nicotine concentrations with bars showing standard deviation for each timepoint. (A) shows the plasma nicotine profiles of the 7-mg nicotine-containing pouches. (B) shows the plasma nicotine profiles of the wintergreen-flavoured nicotine pouches.

(CV) maximum nicotine concentration (C_{max}) with baseline-adjustment was lowest for the *Velo* Wintergreen 4-mg pouch (11.224 ng/mL (28.7%)) and was similar for the *Velo* Max 7-mg pouches regardless of flavour, ranging from 16.220 ng/mL (33.3%) for *Velo* Max Citrus Burst 7-mg to 17.888 ng/mL (26.2%) for *Velo* Max Cinnamon 7-mg (Table 2).

Similarly, mean (CV) $AUC_{nic\ 0–180}$ values were lowest for the *Velo* Wintergreen 4-mg pouch (1212.535 ng × min/mL (27.4%)) and both highest for all the *Velo* Max 7-mg pouches and similar between flavours, ranging from 1752.167 ng × min/mL (31.2%) for *Velo* Max Citrus Burst 7-mg and 1965.491 ng × min/mL (22.1%) for *Velo* Max Cinnamon 7-mg (Table 2).

Statistical comparison of C_{max} and $AUC_{nic\ 0–180}$ showed that both parameters were significantly different between the *Velo* Wintergreen 4-mg and *Velo* Max Wintergreen 7-mg NPs, but not between the *Velo* Max Wintergreen 7-mg NP and any of the other 7-mg study products (Table 3). Median T_{max} values were identical at 46 min for all *Velo* NPs assessed, regardless of nicotine content or flavour (Table 2) and were not statistically significantly different between any of the study products (Table 3).

Subjective effects

Data for the product-liking subjective effect assessment are presented in Table 4. Broadly speaking, mean scores for product-liking were similar for all *Velo* NPs assessed, regardless of flavour and nicotine content. Mean (SD) product-liking scores ranged from 5.1 (2.28) for the *Velo* Max Black Cherry 7-mg pouch to 6.1 (2.88) and 6.1 (2.43) for the *Velo* Max Coffee and *Velo* Max Dragon Fruit 7-mg pouches, respectively.

Adverse events

There were no serious or severe product-emergent adverse events (PEAEs) and no participants were withdrawn from the study for safety reasons. A total of 90 PEAEs were experienced by 28 (66.7%) of the 42 participants. Of these PEAEs, seven in total were reported by six participants (14.3%) following the use of *Velo* Max Peppermint during the product familiarisation session, this being the only product used during this session.

During the test sessions, the incidence of participants with PEAEs ranged from 25.0% for *Velo* Max Black Cherry 7-mg to 7.3% for *Velo* Max Wintergreen 7-mg. PEAE

Table 2. Summary of baseline-adjusted nicotine pharmacokinetic parameters. Data are presented as mean (coefficient of variation) for C_{max} and $AUC_{nic\ 0–180}$, and median (minimum and maximum) for T_{max}.

Product	Nicotine per pouch (mg)	C_{max} (ng/mL)	$AUC_{nic\ 0–180}$ (ng × min/mL)	T_{max} (min)
Velo Wintergreen	4	11.224 (28.7%)	1212.535 (27.4%)	46.0 (30.00–73.00)
Velo Max Wintergreen	7	16.807 (23.6%)	1773.454 (25.1%)	46.0 (30.00–90.00)
Velo Max Spearmint	7	16.991 (27.9%) [1]	1862.770 (25.2%) [1]	46.0 (30.00–90.00) [1]
Velo Max Peppermint	7	17.476 (32.5%) [1]	1894.044 (30.6%) [1]	46.0 (30.00–90.00) [1]
Velo Max Citrus Burst	7	16.220 (33.3%) [1]	1752.167 (31.2%) [1]	46.0 (15.00–90.00) [1]
Velo Max Black Cherry	7	17.322 (28.0%) [1]	1872.012 (25.9%) [1]	46.0 (30.00–90.00) [1]
Velo Max Coffee	7	16.354 (28.9%) [1]	1829.397 (23.7%) [1]	46.0 (15.00–90.00) [1]
Velo Max Dragon Fruit	7	16.648 (29.8%) [1]	1775.659 (28.8%) [1]	46.0 (30.00–90.00) [1]
Velo Max Cinnamon	7	17.888 (26.2%)	1965.491 (22.1%)	46.0 (30.00–90.00)

Abbreviations: C_{max}: maximum plasma nicotine concentration; $AUC_{nic\ 0–180}$: area under the plasma nicotine concentration-time curve between 0 and 180 min from the start of product use; T_{max}: time of maximum plasma nicotine concentration and is the median of the actual recorded blood collection time. Non-missing data points = 41 in each case.

[1] N = 40: Two participants voluntarily withdrew from the study, one participant on Day 1 and the second on Day 3.

Table 3. Statistical comparisons of nicotine pharmacokinetic parameters.

Comparison		*p* value		
Reference product	Comparator product	C_{max}	$AUC_{nic\ 0–180}$	T_{max}
Velo Max Wintergreen 7-mg	Velo Wintergreen 4-mg	< 0.0001 [1]	< 0.0001 [1]	0.63
Velo Max Wintergreen 7-mg	Velo Max Spearmint 7-mg	0.19	0.13	0.99
Velo Max Wintergreen 7-mg	Velo Max Peppermint 7-mg	0.19	0.12	0.26
Velo Max Wintergreen 7-mg	Velo Max Citrus Burst 7-mg	0.67	0.45	0.65
Velo Max Wintergreen 7-mg	Velo Max Black Cherry 7-mg	0.10	0.10	0.36
Velo Max Wintergreen 7-mg	Velo Max Coffee 7-mg	0.83	0.35	0.50
Velo Max Wintergreen 7-mg	Velo Max Dragon Fruit 7-mg	0.63	0.85	0.42
Velo Max Wintergreen 7-mg	Velo Max Cinnamon 7-mg	0.015	0.003	0.81

[1]Value indicates statistical significance.
Comparisons of C_{max} and $AUC_{nic\ 0–180}$ were performed using paired *t*-tests on a log-transformed scale. T_{max} comparisons were made using a sign test on the original data scale. Bonferroni adjustment for multiple comparisons was performed such that a *p* value of < 0.002 indicated statistical significance. Abbreviations: C_{max}: maximum plasma nicotine concentration; $AUC_{nic\ 0–180}$: area under the plasma nicotine concentration-time curve between 0 and 180 min from the start of product use; T_{max}: time of maximum plasma nicotine concentration.

occurrences during the test sessions ranged from 15 following use of *Velo* Max Peppermint 7-mg to 5 following the use of *Velo* Max Wintergreen 7-mg and *Velo* Max Spearmint 7-mg. Overall, the PEAE experienced most commonly was hiccups, reported by 5 participants (12.2%) after use of *Velo* Max Cinnamon 7-mg, 3 participants (7.5%) after use of *Velo* Max Black Cherry 7-mg, 3 participants (7.5%) after use of *Velo* Max Peppermint 7-mg, and 1 participant each after use of *Velo* Max Dragon Fruit 7-mg, *Velo* Max Wintergreen 7-mg, *Velo* Wintergreen 4-mg (2.4% each), and *Velo* Max Coffee 7-mg (2.5%). Of the participants who experienced at least one PEAE, most experienced PEAEs which were mild in severity (52.4%) while the remaining experienced PEAEs were moderate in severity (14.3%). A total of 21 participants (50.0%) experienced 57 product use-related PEAEs (categorised as either related or possibly related).

DISCUSSION

The present randomised crossover clinical study examined nicotine pharmacokinetics and product-liking among cigarette smokers who used 9 different *Velo* NPs during 9 separate 45 min use sessions. We found that the increase in plasma nicotine concentration, both in terms of C_{max} and $AUC_{nic\ 0–180}$, was greater when participants used *Velo* Max NPs containing a higher nicotine content (7-mg) compared to a *Velo* NP containing lower nicotine content (4-mg). However, median T_{max} values did not differ between the NPs with different nicotine content. Importantly, we also found that when participants used *Velo* Max NPs with the same 7-mg nicotine content but with different flavours, C_{max}, $AUC_{nic0–180}$ and T_{max} were not significantly impacted. Lastly, product-liking was similar across all *Velo* NPs assessed regardless of nicotine content and flavour.

In the past years, several studies have been published on NP pharmacokinetics. RENSCH *et al.* (31) described data from a study similar to the one reported here and examined nicotine pharmacokinetics in smokers when they either smoked a combustible cigarette or used a single NP containing approximately 3–4 mg nicotine for a 30-min period. C_{max} values ranged from approximately 9–12 ng/mL, and these values were similar to those seen in our study for the *Velo* Wintergreen 4-mg pouch (C_{max} was approximately 11 ng/mL). In addition, MCEWAN *et al.* (27) also described data from a study similar to the present one where the nicotine pharmacokinetics were studied in smokers using several commercially available NPs with nicotine content ranging from 6–10 mg nicotine for a 60-min period. In this

Table 4. Summary of overall product-liking questionnaire scores.

Product	Nicotine per pouch (mg)	Number of participants	Mean (SD)	Median	Min, max	Q1, Q3
Velo Wintergreen	4	41	5.8 (2.22)	6	0, 10	4, 7
Velo Max Wintergreen	7	41	5.9 (2.25)	6	1, 10	4, 8
Velo Max Spearmint	7	40	5.6 (2.30)	6	0, 10	5, 7
Velo Max Peppermint	7	40	5.3 (2.13)	6	0, 10	4, 7
Velo Max Citrus Burst	7	40	6.0 (2.52)	6	0, 10	4, 8
Velo Max Black Cherry	7	40	5.1 (2.28)	5	0, 10	4, 7
Velo Max Coffee	7	40	6.1 (2.88)	6.5	0, 10	5, 8
Velo Max Dragon Fruit	7	40	6.1 (2.43)	6	0, 10	5, 8
Velo Max Cinnamon	7	41	5.5 (2.67)	6	0, 10	4, 7

The numerical score scale was from 0 to 10, with 0 corresponding to “strong disliking”, 5 corresponding to “neither like nor dislike” and 10 corresponding to “strong liking”.
Abbreviations: SD: standard deviation; Min: minimum; Max: maximum; Q1: first quartile; Q3: third quartile.

case, C_{max} values ranged from 11.9–18.4 ng/mL with three of these NPs containing between 6–10 mg nicotine having a similar C_{max} to the *Velo* Max NPs containing 7 mg nicotine. However, this study also suggested that the physical design characteristics of these different NPs produced by different companies may have an effect on the nicotine pharmacokinetics and subjective effects. This might also explain a further pharmacokinetic study in smokers that used a 4-mg nicotine-containing NP with 60-min use time which reported a C_{max} of 8.5 ng/mL and thus is lower than the level reported for the 4-mg nicotine NP reported in this study, even with a longer usage time (28). Finally, a study by LUNELL *et al.* (21) assessed NP nicotine pharmacokinetics in snus users when they used an NP containing either 3, 6 or 8 mg nicotine or used snus products containing 8 or 18 mg nicotine, for a 60-min period. Mean C_{max} for a 3-mg NP (7.7 ng/mL) was slightly lower than that seen for the 4-mg *Velo* NP assessed in our study (approximately 11 ng/mL) while the mean C_{max} for the 6-mg (14.7 ng/mL) and the 8-mg (18.5 ng/mL) NPs (21) were similar to those in our study for the 7-mg NPs assessed (range approximately 16–18 ng/mL). T_{max} values for all of the studies discussed including the present study were closely associated with the end of the product use time period (21, 23, 27, 31). Due to methodological differences in how the AUC-values were estimated, these cannot be compared.

A similar product to NPs is snus, a smokeless tobacco product which is accepted to present a lower risk to users than smoking combustible cigarettes (20, 32, 33). Examination of the literature concerning snus gives insight into the potential of NPs to be a reduced-risk alternative to tobacco products as NPs are similar in physical form to snus but do not contain tobacco.

In a study among snus users, LUNELL *et al.* (21) compared nicotine pharmacokinetics between NPs and snus, reporting that the AUC was greater for an NP with 6 mg nicotine than for snus with 8 mg nicotine, indicating that NPs may be able to provide nicotine more efficiently than snus. In addition, extraction of nicotine during use seems to be more effective from NPs (58% on average over 60 min) (21, 23, 28) compared with 33% on average from snus (23). Therefore, NPs deliver slightly higher amounts of nicotine compared to snus, a product recognised as a reduced risk alternative to smoking that reduces exposure to harmful toxicants (33, 34) and produces beneficial changes in biomarkers of potential harm in smokers who switch to exclusive use of snus (35).

It should be noted that the pharmacokinetic studies discussed here controlled participants' NP product usage time and that consumers will adjust usage times to suit their preferences.

An interesting facet of our data is the lack of an impact of flavour on nicotine pharmacokinetics of NPs. This was also noted in the study by RENSCH *et al.* (31) where no significant impact of NP flavour on nicotine pharmacokinetics was reported. It has been suggested that menthol may increase the absorption of nicotine and toxicants associated with pouched tobacco products such as Swedish snus. This is described as increased rate of permeation and was studied in a porcine oral mucosa model by SQUIER *et al.* (36), which showed a significant increase in nicotine permeation in the presence of 0.08% menthol. However, the data from this study show that, contrary to this, there is no notable difference in nicotine absorption during use of NPs containing menthol, which is found in the tested Wintergreen, Spearmint, and Peppermint flavoured NPs, as compared to the other flavours tested.

The present study has some limitations. First, it was conducted among cigarette smokers in the U.S.; thus, the findings might not be generalisable to other groups (e.g., users of other nicotine products such as snus), or to other countries where patterns of tobacco and nicotine product use might vary. Second, the data were gathered from use of a single NP product for a fixed amount of time on a single day after overnight abstinence from nicotine. For normal everyday use plasma nicotine concentrations will be influenced by product use duration, as well as by factors such as product nicotine content, proportion of nicotine extracted from the product during use, average daily consumption, and the way in which the product is used by the consumer.

Average daily consumption is a particularly important factor in assessing daily nicotine exposure and blood plasma concentrations. Regarding NPs, an average daily consumption of 8.6 pouches per day among solus NP users has been reported, compared with 14 cigarettes per day reported among solus smokers in the same study (23). However, further studies are needed to establish daily nicotine exposure and the resulting plasma nicotine concentrations associated with NP use, as well as consumer behaviour when using NPs, in order to better inform of their tobacco harm reduction potential (37).

CONCLUSION

In conclusion, the present data provide important insight into nicotine delivery and pharmacokinetics in current smokers during use of NPs with varying nicotine content and various flavours. We demonstrate that *Velo* NPs deliver nicotine to a degree comparable with cigarette smoking but with slower uptake and that flavours do not have an impact on NP nicotine uptake.

Further, we also demonstrate that the use of *Velo* NPs was associated with a strong degree of product-liking. Overall, data from our study are broadly similar to those reported by others and support the idea that tobacco-free NPs deliver similar levels of nicotine to those achieved during cigarette smoking and may therefore provide a suitable alternative form of nicotine delivery for current smokers. Further studies are required to investigate the potential role of NPs in THR.

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CONFLICT OF INTEREST

At the time of the study all authors were current employees of British American Tobacco (Investments) Limited except SBW and TJ who were employees of Reynolds American Inc.

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