

## Original Research Article

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# A pharmacokinetic study to examine nicotine delivery from e-cigarettes and a conventional cigarette in healthy subjects during a brief period of *ad libitum* use

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## ABSTRACT

**Background:** Smoking is a leading cause of numerous human disorders including lung cancer, chronic obstructive pulmonary disease, and atherosclerotic cardiovascular disease. Nicotine is primarily responsible for the addictive properties of cigarette smoking whereas other chemical constituents of the cigarette smoke are considered responsible for disease development. Electronic cigarettes (e-cigarettes) deliver a vapour containing nicotine and which is considered to contain significantly less chemical toxicants compared to cigarette smoke. This study will investigate nicotine delivery from a novel e-cigarette device and compare it to that from both a commercially-available e-cigarette and a combustible cigarette.

**Methods:** This study will examine nicotine pharmacokinetics in subjects while either smoking a cigarette or using one of 5 different e-cigarettes for up to 5 minutes *ad libitum*. The study is a single-centre, randomised controlled clinical study with a crossover design. Subjects of either gender will be aged 22–55 years (minimum legal smoking age in CA plus 1 year) and a verified smoking status (assessed by exhaled breath CO and urinary cotinine levels). Subjects will be judged to be healthy by medical history, physical examination, vital signs, ECG and clinical biochemistry tests. The primary objectives are to characterize the kinetics of nicotine absorption into the blood of subjects using different e-cigarettes or smoking a cigarette; and to compare nicotine delivery from different e-cigarettes with one another and with that from a conventional cigarette.

**Conclusions:** Data from this study will advance our scientific understanding of the pharmacokinetics of nicotine in smokers who use different types of e-cigarettes.

**Trial Registration:** NCT03178981 (clinicaltrials.gov registry, 6<sup>th</sup> June 2017).

**Keywords:** E-cigarette, Nicotine, Pharmacokinetics

## INTRODUCTION

Smoking is a contributing factor to numerous human disorders including lung cancer, chronic obstructive pulmonary disease and cardiovascular disease. The health risks associated with cigarette smoking are correlated with duration of smoking and degree of daily cigarette

consumption, and cessation reduces an individual's relative risks of tobacco-related disease.<sup>1,2</sup> Thus, tobacco-related health risks are assumed to be due to repeated and sustained exposure to a range of smoke toxicants.<sup>3</sup>

Smoke from conventional cigarettes is a complex mixture of more than 5,600 identified chemical constituents<sup>4</sup> in

both its particulate and vapour phases. Some of these chemicals have been identified as potential contributors to the harmful effects of cigarette smoke. Nicotine, a chemical also found naturally in tobacco leaf and which transfers into cigarette smoke, is primarily responsible for the addictive properties of cigarette smoking. Nicotine is rapidly absorbed into the bloodstream during cigarette smoking, from where it is rapidly distributed causing both systemic and central effects.<sup>5</sup> The pharmacokinetic profile of nicotine during cigarette smoking is a rapid rise and fall in plasma nicotine concentrations.<sup>6,7</sup>

E-cigarettes deliver a vapour which is considered to contain significantly less chemical toxicants compared to cigarette smoke.<sup>8,9</sup> The use of e-cigarettes in helping smokers either reduce or quit smoking has been proposed as having the potential to play a major role in tobacco harm reduction, and this potential is further supported by

data from large cross-sectional and longitudinal survey studies in the U.K.<sup>10-13</sup> The cross-sectional data also suggest that e-cigarettes are a more effective aid to smoking cessation than more traditional NRT products.<sup>12</sup> Most recently, Zhu et al provided strong evidence from population surveys with nationally-representative samples that e-cigarette use in the U.S. was associated with an increased smoking cessation rate.<sup>14</sup>

### Study objectives

The primary aim of this study is to characterise the pharmacokinetic profile of nicotine during a brief ad libitum use period of different variants of the Raptor e-cigarette (Table 1). Nicotine pharmacokinetics will be compared to those seen during smoking of a single conventional cigarette or use of a market comparator e-cigarette.

**Table 1: Investigational products.**

Product number	Form	Product and manufacturer	Nicotine yield/content	Other ingredients
1	Combustible tobacco cigarette	Camel Silver RJ Reynolds	0.7 mg/cig <sup>†</sup>	N/A
2	E-cigarette	Vype Raptor British American Tobacco	3 mg/ml <sup>#</sup>	Water, glycerol, propylene glycol, berry flavor
3	E-cigarette	Vype Raptor British American Tobacco	5 mg/ml <sup>#</sup>	Water, glycerol, propylene glycol, berry flavor
4	E-cigarette	Vype Raptor Maxx British American Tobacco	5 mg/ml <sup>#</sup>	Water, glycerol, propylene glycol, berry flavor
5	E-cigarette	Vype Raptor Maxx British American Tobacco	8 mg/ml <sup>#</sup>	Water, glycerol, propylene glycol, berry flavor
6	E-cigarette	MarkTen <sup>®</sup> XL Summer Fusion <sup>\$</sup> NU MARK LLC	2.5% nicotine by weight	Water, propylene glycol, glycerol, flavoring

<sup>†</sup>International Organisation for Standardisation nicotine yield. <sup>#</sup>nicotine content of liquid solution; <sup>\$</sup>commercially-available product in the US.

### Investigational products

Details of the investigational products to be used in this study. The target values for nicotine content are manufacturing specifications and the actual results may vary due to product variation, but these values will be within an appropriate range.

### METHODS

#### Study registrations

This study was registered on the clinicaltrials.gov registry on 6<sup>th</sup> June 2017 and given the registration number NCT03178981.

#### Study design

The study will be a single-centre, part-randomised, open-label, six-period crossover study conducted in 18 healthy

male and female volunteers, who are regular smokers of conventional cigarettes and who may occasionally use e-cigarettes. Subjects must have been smoking regularly for at least one year and must not be trying or planning to quit. The study will be carried out at a single site in Burbank, California and 18 subjects will be expected to complete the study. This study will be conducted in compliance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and US laws, including those relating to the protection of subjects' personal data.

Participants will receive full and adequate oral and written information in non-technical terms about the nature, purpose, potential risks and any possible benefits of study participation. Participants will be given time to consider all the information, the opportunity to ask questions and will be required to read, sign and date informed consent forms that summarise the discussion before participating in any procedures related to the study.

The protocol (Version 1 dated 9<sup>th</sup> May 2017) and the informed consent form (ICF) were submitted for review to the Chesapeake IRB on 2<sup>nd</sup> June 2017 and given the identifier Pro00021905. Full IRB approval was granted on 12<sup>th</sup> June 2017. All substantial protocol amendments will be approved by the Chesapeake IRB and they will be informed of minor amendments to the protocol which do not require their approval.

The study has a part-randomised crossover design to enable nicotine pharmacokinetic data to be obtained from all subjects for all products. During their first study visit, subjects will smoke a conventional cigarette. The conventional cigarette selected for this study has an ISO nicotine yield of 0.7 mg/cigarette, which is representative of a common cigarette nicotine yield where the study will be conducted. During the subsequent 5 visits, subjects will use a different e-cigarette at each visit in a randomly-allocated sequence.

Financial compensation for the inconvenience to and effort of participants will be offered as part of the study, but the sponsor does not wish this approach to incentivise participants to smoke. Stipends will, therefore, be calculated independently by the clinic according to the usual rates for this type of clinical study and will be approved by the IRB.

The age of each subject will be verified using appropriate identification documentation prior to inclusion in the study to ensure subject age restrictions specified in this protocol are followed.

### **Study participants**

#### *Selection of study population*

18 male or female subjects who smoke at least 10 commercially-available cigarettes per day will be enrolled. Subjects will have smoked for at least 1 year prior to screening. Subjects in this study will be a minimum of 22 years of age, based on the legal minimum age of 21 to obtain nicotine/tobacco products in California and the 1-year smoking history requirement. Subjects' smoking status will be verified using urinary cotinine and exhaled breath CO tests.

#### **Inclusion criteria**

The inclusion criteria are; current smokers of conventional factory-made cigarettes who have either tried or are occasional users of e-cigarettes. Subjects must be smoking  $\geq 10$  cigarettes per day and must have done so for at least one year. Smoking status will be confirmed with urinary cotinine and n exhaled breath CO tests at screening, as well as by tobacco use questionnaire; males or non-pregnant, non-lactating females, and between 22 and 55 years of age inclusive; women of child-bearing potential who are using acceptable methods of contraception. Women of non-childbearing potential may

be included if they are either surgically sterile or postmenopausal for more than 1 year and must have a negative urine pregnancy test result during screening; male subjects must use an approved method of birth control during the entire study. These subjects must not donate sperm during this time; in good health based on medical history, ECG, vital signs, blood biochemistry, haematology, urinalysis and physical examination; body mass index between 18 and 30 kg/m<sup>2</sup> inclusive; weight between 60 and 120 kg (males) and between 50 and 100 kg (females); no clinically significant abnormalities in blood pressure values; negative results for the urinary drug of abuse screening and alcohol test; given their written informed consent to participate in the study and to abide by the study restrictions.

#### **Exclusion criteria**

Exclusion criteria may be applied at screening or at any time during the study. Exclusion criteria are; a history of, or clinically active significant, neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological disease or other major disorders; any clinically significant abnormal laboratory safety findings at screening and prior to first product use; previously diagnosis of any form of malignancy; allergies which in the opinion of the principal investigator should preclude participation; an episode of acute illness (e.g. upper respiratory tract infection, viral infection, etc.) requiring treatment within 4 weeks prior to Admission; use of prescription or over-the-counter bronchodilator medication (e.g. inhaled or oral  $\beta$ -adrenergic agonists) to treat a chronic condition within the 12 months prior to Admission; recent history of or current drug or alcohol abuse; an inability to communicate well with the investigator/study staff; participation in another clinical research study in the last 2 months; treatment with prescription medications within 21 days or over-the-counter medication within 24 hours of the planned first product use occasion, except for those stated in the Inclusion criteria. For all subjects, prescribed use of blood pressure (e.g. beta blockers) and lipid lowering (e.g. statins) medications are permitted; use of drugs or substances (except tobacco) known to be strong inducers or inhibitors of any CYP enzymes within a 28 day period prior to first product use; any treatment with smoking cessation medications within 30 days of the planned first product use occasion; any other clinically significant medical history including conditions which might affect drug absorption, metabolism or excretion; female subjects, who are pregnant or become pregnant during the course of the study; loss or donation of more than 450ml of blood within the 2 months preceding the first product administration; self-reported non-inhalers. Subjects who are observed as non-inhalers at screening by the clinic staff will be excluded; trying to stop smoking or to stop using e-cigarettes, or considering stopping in the next two months. All subjects will be informed that they are free to quit smoking/using e-cigarettes and withdraw from the

study at any time; being unwilling or unable to comply with the study requirements; subjects who in the opinion of the principal investigator should not participate in the study for any other reason.

### ***Withdrawal from the study***

Any subject may discontinue from the study at any time and for any reason, either at the discretion of the Investigator, the sponsor or at the request of the subject. The reason for such a premature discontinuation will be clearly documented. The Investigator may withdraw a subject from the study at any time if he considers that their health is compromised by remaining in the study or the subject is not sufficiently cooperative.

### ***Smoking advice and support***

Subjects will be able to ask for advice to stop using tobacco/nicotine products and will be provided with a smoking cessation helpline number.

### ***Investigational products***

The raptor device is a novel e-cigarette that consists of a reusable section (containing a battery), a mouthpiece cover, and disposable cartridges which contain a nicotine e-liquid. The e-liquid also contains glycerol, propylene glycol, water, and a fruit flavour.

All study cigarettes and e-cigarettes will be provided by the Sponsor free of charge. Brief product details shown in Table 1. This study is unblinded due to the obvious differences between cigarettes and the different e-cigarette variants to be used in the study. However, within each raptor device the staff and subjects are blinded to the nicotine content.

The different products will be identifiable to the clinic staff and investigator by study identification codes forming part of study-specific labels applied to the product packaging. The products will be stored in a locked, limited-access area at room temperature.

### ***Randomisation***

Each subject will be assigned a screening number beginning with 1001 at the time of registering for the study.

After completing the testing of the study cigarette at Visit 1, eligible subjects will be assigned a randomisation number beginning with 2001. The randomisation will determine the order in which the subjects will test the study e-cigarettes at Visits 2-6. The randomisation code for the e-cigarettes will be produced using a computer-generated pseudo-random permutation procedure using SAS version 9.3.

### ***Compliance***

To ensure product use compliance in the clinic, all products will be administered under the supervision of the PI or suitably qualified staff. All subjects will receive training by clinic staff on how to operate the different e-cigarettes.

### ***Concomitant medication***

Medications considered necessary for the welfare of the subject, and which are not expected to interfere with the evaluation of study treatments, may be taken at the discretion of the Investigator.

Subjects will not take any prescription or over-the-counter medication (including herbal medications) during the study until completion of all study visits, unless the Principal Investigator has given their prior consent. For female subjects, hormonal contraceptives are acceptable. For all subjects, prescribed use of blood pressure (e.g. beta blockers) and lipid lowering (statin) medications and occasional use of over the counter allergy relief medication and painkillers (paracetamol) are permitted. Subjects will be made aware that they must inform the Investigator before taking any new treatment during their participation in the trial.

If any medication is required, the name, strength, frequency of dosing and reason for its use will be documented in the subject's source documents.

Subjects should avoid medication that interferes with the cyclo-oxygenase pathway (anti-inflammatory drugs such as aspirin and ibuprofen) within 14 days of the first test product administration until discharge at the end of the study.

Subjects should also not use any drugs or substances (except tobacco) known to be strong inducers or inhibitors of CYP enzymes (formerly known as cytochrome P450 enzymes) within 30 days prior to first product use.

### ***Study procedures***

#### ***Screening visit***

Subjects will undergo screening assessments no more than 30 days in advance of the first product administration. Enrolment in the study is defined as the signing of the informed consent.

The following information and procedures will be recorded and performed as part of the screening assessments:

- Inclusion and exclusion criteria
- Complete medical history

- Demography (including gender, ethnic origin, age, height, weight and BMI)
- Prior and concomitant medication
- Vital signs (blood pressure and pulse rate, body temperature)
- 12-lead ECG
- Physical examination by the study physician
- Urine drug of abuse including alcohol screen
- Urine pregnancy test for female subjects
- Tobacco and e-cigarette use history questionnaires, including urinary cotinine screen and exhaled breath CO measurements, and Fagerstrom Test for Cigarette Dependence.
- Current brand of cigarettes smoked.
- Biochemistry, haematology and urinalysis.

At the screening visit, subjects will be allowed to familiarise themselves with the e-cigarette test products. This will include them using each e-cigarette.

#### *Product use phase: study visit 1*

Subjects will attend the clinic on the day of each product administration having refrained from using tobacco or nicotine products for 12 hours prior to the visit. At this visit, subjects will be asked to smoke the combustible cigarette. Subjects will remain in the clinic throughout the smoking and measurement period until all study visit procedures have been completed (approximately 2 hours). The following information and procedures will be recorded and performed as part of each visit assessment:

- Vital signs (heart rate and blood pressure) on admission.
- Review of any adverse events and concomitant medications since the previous visit.
- Review of compliance with non-use of tobacco products, using an exhaled breath CO screen.
- Pregnancy test for females.
- Administration of the test product (regular cigarette).
- Blood samples for nicotine pharmacokinetic analysis will be drawn pre-administration (-5) and at the following times after the first puff: 1, 3, 5, 6, 7, 9, 15, 45, and 60 minutes.
- Product satisfaction questionnaire.
- Vital signs before discharge.

#### *Product use phase: visits 2-6*

During study visits 2-6, subjects will use their randomly-assigned e-cigarette for pharmacokinetic and product satisfaction analysis. During these visits, subjects will undergo the same procedures as those described for study visit 1 but using the e-cigarette product assigned for that visit. This process will repeat until each subject has used the 5 different e-cigarette products. The e-cigarette cartridges will be weighed at the beginning and end of these visits to determine the loss of mass from the cartridge during use.

#### *Follow-up visit*

The Investigator will obtain information on any new adverse events and new/changes to concomitant medication since the last product use visit. Provided there are no adverse events which require further attention, the subject's participation in the study will be complete. This will be performed by a phone call to the subjects with a visit scheduled only if necessary. If a visit is necessary, vital signs will be taken and a symptom-driven physical examination performed.

#### *Study termination*

If, in the opinion of the Principal Investigator, clinical observations in the study suggest that it may be unwise or unsafe for any of the subjects to continue, the Principal Investigator may terminate part of or the entire study. In addition, the sponsor may terminate part of or the entire study for safety or administrative reasons. A written statement fully documenting the reasons for study termination will be provided to the IRB.

#### *Assessments*

##### *Blood sampling for the analysis of nicotine*

Blood samples (5 ml) will be taken from a cannula placed in a forearm vein, at the following times: -5, 1, 3, 5, 6, 7, 9, 15, 45 and 60 minutes. Blood samples will be collected into a K<sub>2</sub>EDTA vacutainer tube.

No later than 30 minutes after collection, samples will be centrifuged at 2500 RPM and at 4°C for 15 minutes. The plasma will be transferred to 2 polypropylene screw cap tubes and stored frozen at -20°C (± 10°C) or below within 60 minutes from collection.

Plasma samples will be shipped in batches on dry ice for analysis to a commercial bioanalytical laboratory (Altasciences, Laval, QC, Canada). Nicotine bioanalysis will be conducted in accordance with appropriate standards including GLP.

#### *Safety assessments*

##### *Adverse events*

The condition of each subject will be monitored throughout the study from screening until the follow-up contact. Any adverse events and remedial action will be recorded in the subject's source documents. The nature, time of onset, duration and severity will be documented, together with an investigator's opinion of the relationship to product administration.

Adverse event definitions, assignment of severity and causality, and procedures for reporting serious adverse events are defined in the protocol.

### Physical examination and health screens

A physical examination will be performed at screening. The examination will include: ears, nose and throat, ophthalmological, dermatological, cardiovascular, respiratory, gastro-intestinal, central nervous system, lymph nodes, musculo-skeletal. Blood samples will be obtained for biochemistry and haematology analysis and a urine sample obtained for urinalysis. A 12-lead ECG will be performed.

### Smoking and nicotine use tests

Subjects will undergo an exhaled breath CO (eCO) assessment to determine their smoking status. eCO must be  $>10$  ppm for subjects to be enrolled into the study. Subjects will also be asked to provide a urine sample for a cotinine screen and they will only be enrolled into the study if their urine cotinine level is greater than 200 ng/ml.

### Pregnancy test

To be entered into and to complete the study, female subjects must have a negative urine pregnancy test at screening and at each subsequent visit.

### Urine drugs of abuse screen

Subjects will be asked to provide urine samples for drugs of abuse screen at screening. Urine samples will be screened for the presence of the following drugs of abuse: marijuana, cocaine, amphetamines, morphine/opiates and benzodiazepine.

### Determination of sample size

18 subjects will be recruited this study. This was determined using the power and sample size function for a paired t-test in MINITAB v 17.1.0, with a power value of 0.8, alpha = 0.05 and standard deviations from a previous study (5.1 ng/ml plasma nicotine for difference between cigarette and e-cigarette, 1.5 ng/mL plasma nicotine for differences between e-cigarettes). This sample size will detect a minimum difference in  $C_{max}$  values of 3.6 ng/mL between a conventional cigarette and e-cigarettes, and a difference of 1.1 ng/mL between e-cigarettes.

### Statistical analysis

A detailed statistical analysis plan will be prepared before database closure and agreed by the sponsor and the investigational site. Any changes in the planned statistical methods will be documented in the clinical study report.

### Pharmacokinetic data

The following pharmacokinetic (PK) parameters will, where possible, be derived from the plasma

concentrations of nicotine, using non-compartmental procedures.

**Table 2: Pharmacokinetic data.**

Parameter	Definition
$C_{max}$	Maximum observed plasma concentration
$t_{max}$	Time of maximum observed plasma concentration
$AUC_{0-last}$	Area under the curve from time zero to the last sample collection (60 min)

Additional PK parameters may be determined where appropriate.

Blood nicotine levels will be plotted as mean concentration level in relation to time, with and without 95% CI of the mean for each product at each timepoint.

Area under the curve ( $AUC_{0-last}$ ) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing, known as the Linear Up-Log Down method.  $AUC_{0-last}$  is defined as the area under the curve from  $t=0$  sample collection time-point until the last collection, usually at the 60 min time point.

All nicotine plasma concentration data and derived PK parameters will be listed by subject and summarised by product. Summary tables will be overall as well as by gender.

Differences between products will be compared using change of nicotine concentration from baseline,  $C_{max}$  and AUC. Overall and gender specific summary tables of all study endpoints will be produced.

### Adverse events management

The condition of each subject will be monitored throughout the study from the Screening Visit until the follow-up contact. Any adverse events and remedial action will be recorded in the subject's source documents. The nature, time of onset, duration and severity will be documented, together with the investigator's opinion of the relationship to product administration. Any clinically significant abnormalities identified during the course of the study will be followed-up until they return to normal or can be clinically explained.

Any AE assessed as related to the IP will be assessed for its expectedness. An AE will be regarded as 'unexpected' if its nature or severity is not consistent with information already known about the IP, and which is not listed in the current Investigator's Brochure.

The PI will review each event, grade its severity and assess its relationship to the product consumption and/or the study procedures. The date of onset, time of onset,

and outcome of each event will be noted. If any of the above AEs are serious, special procedures will be followed. The Investigator will report all SAEs to the Sponsor's medical contact within 24 hours. Written reports will then be submitted within 48 hours, whether or not the serious events are deemed related to study procedures or products. The IRB will be notified of these reports.

### **Assessing study conduct**

Quality control and quality assurance will be performed according to the sponsor's standard operating procedures. A designated professional Clinical Research Associate (CRA) employed by an independent CRO will conduct monitoring visits throughout the study. These visits will be for the purposes of verifying adherence to the protocol and GCP, and that accurate and complete data are recorded in the source documents and test product inventory forms. A monitoring plan will be drawn up with the CRA and the Sponsor at least two weeks prior to study start and prior to the conduct of the Site Initiation Visit.

SPC has four main applications, which are as below.<sup>8</sup>

1. To achieve process stability
2. To provide the guidance on how the process may be improved by reducing variation
3. To assess the performance of a process
4. To provide information to assist management decision.

### **DISCUSSION**

The development and marketing of novel nicotine and tobacco products with, relative to conventional cigarettes, reduced levels of toxicants in their emissions is a potential way to reduce the harms associated with cigarette smoking.<sup>3</sup> This study will allow us to determine nicotine pharmacokinetic parameters for a novel, developmental e-cigarette and a cigarette. Such data are important since effective nicotine delivery is considered to be a potential determinant of both the uptake and continued use of alternatives to cigarette smoking by current smokers.<sup>15,16</sup>

**Funding:** This study will be funded by British American Tobacco (Investments) Limited.

**Conflict of interest:** IF, AE, OMC, JM, CJP and IMF are current employees of British American Tobacco (Investments) Limited. MN is the President of Los Angeles Clinical Trials, a CRO contracted to provide services to the study. MN is also the PI for this study.

**Ethical approval:** The study was approved by the Chesapeake Institutional Review Board

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