A Randomised, Crossover, Clinical Study to Assess Nicotine Pharmacokinetics and Subjective Effects of the BIDI® Stick ENDS Compared with Combustible Cigarettes and a Comparator ENDS in Adult Smokers

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Potential competing interests: IMF is an independent consultant contracted to ENDS and tobacco product manufacturers to provide scientific and regulatory support for clinical and behavioral studies. RGNS is an independent consultant who provides statistical support to ENDS manufacturers. KG is an employee of, and WM is the President of, McKinney Regulatory Science Advisors, LLC who are contracted to provide scientific and regulatory support to ENDS and tobacco product manufacturers.

Abstract

Introduction: Nicotine pharmacokinetic (PK) assessments of electronic nicotine delivery systems (ENDS) are crucial to understand their ability to provide an alternative to cigarette smoking. Subjective effects data also strongly contribute to this understanding. The BIDI® Stick is a disposable ENDS product which contains 6% nicotine benzoate salt and various flavours. **Methods:** In this study we assessed nicotine PK and subjective effects of BIDI® Stick ENDS in adult smokers, compared to cigarettes and a comparator ENDS product. During each of eight (8) study visits, volunteer smoker subjects randomly used one of either their usual brand (UB) of cigarette, a BIDI® Stick ENDS, or a comparator ENDS (JUUL 5% with Virginia Tobacco flavour), during both defined (10 puffs, 30 seconds apart) and *ad libitum* puffing sessions. Blood samples were collected at various time points and subjective effects questionnaires were administered. **Results:** Plasma nicotine $C_{max\ 0\text{-}120}$ was not significantly different between BIDI® Stick ENDS with any flavour (range 15.3 (9.90) ng/ml for BIDI® Stick Winter to 17.6 (9.00) ng/ml for BIDI® Stick Classic) and UB cigarettes [16.2 (9.17) ng/ml]. $AUC_{0\text{-}120}$ and $T_{max\ 0\text{-}120}$ values were also not significantly different between BIDI® Stick ENDS and UB cigarettes, while subjective effects measures were also similar between BIDI® Stick ENDS and UB cigarettes. **Conclusions:** BIDI® Stick ENDS delivered nicotine to users comparably to their UB cigarette and also elicited similar subjective effects such as satisfaction and relief. Thus, the BIDI® Stick ENDS may be a satisfying alternative to cigarettes among current smokers and may support their transitioning away from cigarette smoking.

INTRODUCTION

Cigarette smoking is the leading preventable cause of morbidity and mortality worldwide, and is the primary causative factor in the deaths of more than 7 million smokers annually [1]. A number of serious human disorders are caused by cigarette smoking, including heart disease, lung disease and lung cancer, which arise due to a smokers' inhalation of toxic chemicals formed during the combustion of tobacco [2][3][4]. Cigarette smoke contains approximately 6,500 identified chemicals [3], and a number of these chemicals have a demonstrated association with the development of specific smoking-related diseases [5]. For smokers, the best possible means of reducing the risk to their health is to quit smoking [6], and large numbers of adult smokers report such a desire to stop smoking. However, the addictive nature of cigarette smoking means that quitting smoking is inherently difficult. Unfortunately, less than 10% of adult smokers actually manage to stop smoking annually [7].

Alternative forms of nicotine delivery that satisfy a smokers' desire for nicotine and reduce or eliminate exposure to tar and harmful toxicants found in cigarette smoke have been suggested since the 1970s as a means to reduce smoking-related health risks [8]. Regarding smokers who are either unable or unwilling to quit smoking, a number of public health bodies, such as Public Health England, the UK Royal College of Physicians, the New Zealand Ministry of Health and Health Canada, proposed that reduced-exposure products may provide a less harmful alternative to combustible cigarettes and support efforts to reduce the global burden of cigarette smoking [9][10][11]. E-cigarettes, also known as an Electronic Nicotine Delivery Systems (ENDS), generate an aerosol via electrical heating of an e-liquid that most commonly contains nicotine [12][13]. Since the heating temperature required to aerosolise e-liquids is much lower than the smoke-producing temperature developed during the combustion of tobacco leaves in conventional cigarettes, ENDS aerosols contain far fewer and substantially lower levels of harmful toxicants compared with cigarette smoke [14][15][16]. Therefore, exposure to cigarette smoke toxicants is either greatly reduced or absent in smokers who completely switch to ENDS [17][18][19][20][21][22]. In many instances, biomarkers of exposure are at levels seen with smoking abstinence [17][19] or in non-smokers. This exposure reduction has the potential to reduce the risk of tobacco-related disease in smokers who completely switch to using ENDS. Consequently, some public health bodies, including Public Health England, have proposed the use of ENDS as a potentially reduced-harm alternative to cigarette smoking for adult smokers [9], and particularly those who have been unable to quit by other means. Furthermore, a growing body of literature indicates that ENDS have the potential to support smoking cessation [23], particularly in those who use ENDS daily and non-intermittently [24][25].

It has been suggested that ENDS nicotine delivery is an important factor in determining their ability to facilitate smokers' switching away from cigarette smoking [26][27][28]. For example, nicotine-containing smoking cessation products such as nicotine gum that have higher nicotine content, deliver greater amounts of nicotine to users and produce greater satisfying and reinforcing effects are more effective in promoting smoking cessation [26][29][30][31], particularly among highly-dependent smokers [26][32][33]. Furthermore, greater nicotine delivery from ENDS is associated with greater reductions in urges to smoke as well as other beneficial subjective effects such as greater satisfaction, liking and reductions in withdrawal symptoms [34], as well as greater reductions in exposure to cigarette smoke toxicants [35][36].

The BIDI® Stick is a disposable ENDS that contains an e-liquid with 6% nicotine in the form of a nicotine benzoate salt and a variety of flavours, which has been marketed in the United States as an alternative to cigarette smoking for adult smokers since 2014. While the nicotine pharmacokinetic profile of various types of ENDS products have been reported in the literature [13][37][38], including disposable ENDS [39], no studies have yet examined nicotine pharmacokinetics for disposable ENDS with a high concentration of nicotine salt in the e-liquid. In this paper, we describe findings from a clinical study assessing nicotine pharmacokinetics and subjective effects of the BIDI® Stick ENDS with various flavours, compared to combustible cigarettes and a comparator pod-based (JUUL) ENDS.

METHODS

This study was an open-label, randomised, crossover, clinical study in which healthy adult smokers were assigned to use one of eight (8) investigational products at each clinic visit and according to a pre-determined randomisation schedule. The study was conducted in July and August 2021 at the facilities of MTZ Clinical Research Sp. z.o.o., Warsaw, Poland, in accordance with the principles of International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. GCP compliance was assured by both a pre-study GCP audit by an independent auditor and by frequent monitoring visits during study conduct by an independent Clinical Research Associate. Ethics approval was received from the Ethics Committee of the District Medical Board in Warsaw (Resolution 15/21, 29th April 2021). All subjects received financial remuneration for their participation in the study, which was approved by the ethics committee. The study was registered on the ClinicalTrials.gov repository (identifier number NCT05072925).

Subjects

Subjects were adults aged 21-65 years inclusive and were current smokers of at least 10 factory-manufactured cigarettes a day with a Federal Trade Commission (FTC) tar yield of 8-10mg, had been smoking cigarettes for at least 12 months, and may have been dual users of ENDS. At a screening visit, which took place no more than 28 days before the first study visit, potential subjects provided written consent on an ethics committee-approved informed consent form. At this visit, a review of the potential subjects' medical history, a physical examination, clinical laboratory assessments, an electrocardiogram (ECG), vital signs measurements, a urine pregnancy test (female subjects only) and a chest X-ray were performed to ensure that potential subjects were healthy. Urinary cotinine (≥200ng/mL) and exhaled carbon monoxide (eCO; > 10ppm) were also assessed to confirm cigarette smoking status and a urine screen for drugs of abuse was performed. Subjects' cigarette smoking and nicotine product use history was captured, and the Fagerstrom Test for Cigarette Dependence (FTCD) [40] was administered.

Female subjects were ineligible if they were pregnant or breastfeeding and were required to practice a reliable method of contraception for the duration of the study. Exclusion criteria also included any clinically relevant medical or psychiatric disorder, abnormal findings in the physical examination, clinical laboratory assessments, ECG or chest X-ray, or a positive screen for drugs of abuse. Potential subjects who had a positive text for SARS-CoV-2 (COVID-19) or displayed any symptoms indicative of active SARS-CoV-2 infection were also excluded from the study.

Study Products

Six BIDI® Stick ENDS, each containing 6% nicotine benzoate salt and different flavours, were assessed in the study. The specific products assessed were BIDI® Stick Arctic, Classic, Zest, Regal, Winter and Solar. A comparator ENDS product, the JUUL pod system ENDS with 5% nicotine benzoate salt and Virginia Tobacco flavour, was also assessed. All subjects provided their usual brand (UB) of combustible cigarette for use as a reference cigarette.

Randomisation procedure

Randomisation sequences were prepared by MTZ Clinical Research Sp. z.o.o. and were produced using a block randomisation (Williams) procedure (18 subjects randomised to the 14 treatment sequences, size of block equal to 1) for 7 treatments in 7 periods (i.e., generation of a Latin-square design, where every treatment followed every other treatment the same number of times). Equal allocation of subjects to each sequence was ensured.

Study Procedures

At screening, subjects underwent numerous assessments outlined above to assure their health status. Subjects who passed all screening assessments and provided written informed consent visited the clinic site on eight (8) separate occasions, with each clinic visit separated by at least two (2) days. At the first of these visits, subjects underwent nicotine pharmacokinetic and subjective effects assessments with their usual brand (UB) of combustible cigarette. Prior to each subsequent visit, subjects were provided with a supply of either the BIDI® Stick ENDS or the JUUL ENDS they were to use at their next clinic visit according to the randomisation schedule, to use at home for a familiarisation period of at least two (2) days. At each clinic visit, subjects used their randomly assigned product and underwent nicotine pharmacokinetic and subjective effects assessments. Prior to each clinic visit subjects were instructed to abstain from the use of any nicotine-containing products for a period of at least 12 hours. Compliance with this instruction was assessed by measuring eCO with a cut-off level of 15 ppm. After the final clinic visit, subjects were discharged from the clinic after all nicotine pharmacokinetic and subjective effects assessments were completed. Subjects were contacted by telephone no longer than one (1) week after the final study visit to capture any post-study adverse events (AEs).

Nicotine Pharmacokinetics

During the first clinic visit (Visit 2), subjects smoked their UB combustible cigarette during two (2) use sessions. In the first session, subjects smoked a single combustible cigarette by taking 10 puffs with each puff 30 seconds apart (controlled puffing). Blood samples (4 mL) were obtained for plasma nicotine analysis at -5, 3, 5, 7, 10, 15, 30, 45, 60, 75, and 120 minutes relative to the first puff on the cigarette. In the second session, which began immediately after the last (120 minute) blood draw, subjects were allowed to take *ad libitum* puffs on their UB cigarette for a period of 60 minutes. During this *ad libitum* session, subjects were allowed smoke as many cigarettes as they liked. A blood sample for nicotine PK analysis was drawn at the end of the session (i.e., at 180 minutes). At subsequent visits, subjects used their assigned ENDS product following the same procedures.

Blood samples (4 ml) for plasma nicotine analysis were drawn into dipotassium ethylenediaminetetraacetic acid (K_2 EDTA) vacutainer tubes via an intravenous catheter port. No later than 90 minutes after collection, samples were centrifuged at 1500 RPM at 4°C for 10 minutes. The plasma fraction was transferred to two (2) sterile polypropylene screw cap tubes and stored frozen at -20°C within 120 minutes of collection. Plasma samples were shipped on dry ice to a commercial bioanalytical laboratory (Altasciences Company Inc., Laval, Quebec, Canada). Nicotine levels were assessed with a validated reversed-phase HPLC with MS/MS method, using an AB Sciex API 5000 quadrupole mass spectrometer and a Turbo V ion source with ES probe and operating in positive ion mode. The lower limit of quantification (LLOQ) for this assay was 0.200 ng/ml, and the upper limit of quantification (ULOQ) was 100.000 ng/ml.

Subjective Effects Assessments

At the end of the *ad libitum* puffing session, subjects completed the 21-item Product Evaluation Scale (PES)[41] for which responses were recorded on a 7-point Likert scale ranging from 'Not at all' to 'Extremely'.

Statistical Analyses

Since this study was the first to examine nicotine pharmacokinetics in subjects using BIDI® Stick ENDS, no formal power calculations were performed. The sample size is typical of other studies reported in literature examining the pharmacokinetics and subjective effects of different tobacco/nicotine products [37] and a sample size of 18 subjects was determined adequate to meet the study objectives.

Descriptive statistics for PK parameters, including baseline-adjusted maximum plasma nicotine concentration between 0 and 120 minutes ($C_{max\ 0\text{-}120}$); time to maximum plasma nicotine concentration following defined puffing ($T_{max\ 0\text{-}120}$); and baseline-adjusted area under the plasma nicotine concentration-time curve at 120 minutes ($AUC_{0\text{-}120}$) were summarised for each study product. $AUC_{0\text{-}120}$ was calculated using a linear trapezoidal method. Following baseline adjustment, any $AUC_{0\text{-}120}$ values which fell below zero were excluded from both descriptive and inferential statistics.

For inferential statistical analyses, linear mixed models were used to test differences in log-transformed $C_{max\ 0\text{-}120}$ and $AUC_{0\text{-}120}$ values between BIDI® Stick ENDS, JUUL, and UB cigarettes. Subject was included as a random effect. The sequence of product used was initially specified as a random effect, but the models produced non-positive definite G matrices and so this variable was removed as a random effect. Model parameter estimates were exponentiated back to their original scale and used to create 90% confidence intervals for the ratio of geometric, least-squares means. Statistically significant differences between test products were determined if the 90% confidence interval range did not include the value 1.00. Proportional odds generalised linear mixed models were used to test differences in T_{max} values between BIDI® Stick ENDS, JUUL, and UB cigarettes. The subject and sequence order of the product used were specified as random effects. Statistical significance was determined for 90% odds ratio confidence intervals that did not contain the value 1.00.

The PES was analysed by assessing four composite subscales: (1) “satisfaction”; (2) “psychological reward”; (3) “aversion”; and (4) “relief” [41]. PES subscale scores were summarised using descriptive statistics for each study product and post-hoc pairwise comparisons between study products were made using linear mixed effects models with the subject specified as a random effect.
Statistical analyses were performed using SAS Version 9.4 (Cary, NC, USA) with alpha = 0.05 (2-tailed).

Safety Assessments

Safety and tolerability were assessed by collecting information concerning the incidence, nature and severity of any AEs experienced by subjects. Vital signs (blood pressure and heart rate) were also routinely monitored during study visits.

RESULTS

Study Population

Of 41 subjects who were screened, 18 (43.9%) met all of the inclusion criteria and none of the exclusion criteria and were enrolled into the study. Seventeen subjects attended the clinical site for all eight (8) study visits and used their randomly assigned study product in the product use sessions; one subject was discontinued after Visit 2 (UB cigarette smoking) due to a number of adverse events (headache, nausea, coughing) which occurred following the nicotine pharmacokinetic session. Brief demographic details of the 18 subjects are provided in Supplementary Table 1. Subjects’ mean (SD) age was 39.2 (9.21) years, approximately two-thirds were male, and all were of Caucasian race. On average, subjects FTCD score was 5.8 (1.66) and subjects usually smoked on average 15.8 (3.56) cigarettes per day and had been smoking for an average of 19.3 (7.66) years. Two subjects had prior experience of ENDS use, but neither these nor any other subjects were currently using ENDS.

Nicotine Pharmacokinetics

During use of all study products in the controlled puffing session, plasma nicotine levels rose rapidly (Figure 1). The mean (SD) maximum plasma nicotine concentration reached following this session ($C_{max\ 0\text{-}120}$) was 16.2 (9.17) ng/ml for subjects' UB combustible cigarette (Table 1). $C_{max\ 0\text{-}120}$ values were not significantly different (Tables 1 and 2) for each of the BIDI® Stick ENDS assessed compared both each other and with UB cigarettes and ranged from 15.3 (9.90) ng/ml for BIDI® Stick Winter to 17.6 (9.00) ng/ml for BIDI® Stick Classic. $C_{max\ 0\text{-}120}$ for the comparator ENDS product (JUUL Virginia Tobacco) was 6.8 (4.13) ng/ml, which was significantly lower than that for either the UB cigarettes or any of the BIDI® Stick ENDS (Table 2). Similar to $C_{max\ 0\text{-}120}$, area under the plasma nicotine concentration-time curve between 0 and 120 minutes ($AUC_{0\text{-}120}$) values for any of the BIDI® Stick ENDS were not significantly different than that for UB cigarettes, while $AUC_{0\text{-}120}$ for the comparator (JUUL) ENDS product was significantly lower than that for both the UB cigarettes and any of the BIDI® Stick ENDS (Tables 1 and 2). Time to maximum plasma nicotine concentration values for the defined puffing session ($T_{max\ 0\text{-}120}$) ranged from 6.0 minutes for both the BIDI® Stick Regal and Winter ENDS (SDs 1.58 and 1.41, respectively) to 6.7 (2.74) minutes for the UB cigarettes (Table 1). $T_{max\ 0\text{-}120}$ for the JUUL comparator ENDS was 5.9 (1.73) minutes. There were no statistically significant differences in $T_{max\ 0\text{-}120}$ between any of the study products.

During the *ad libitum* use session, plasma nicotine levels rose again for all study products (Figure 1). While no formal statistical analysis was performed, $C_{max\ 120\text{-}180}$ was highest for BIDI® Stick Arctic ENDS and lowest for UB cigarettes and JUUL Virginia Tobacco (Figure 1 and Table 1).

Subjective Effects

Analysis of the composite scores for the PES "relief", "satisfaction" and "aversion" subscales showed no statistically significant differences between any of the study products (Table 3). For the 'psychological reward' subscale, a significant difference between study products was observed only between subject's UB cigarette and the BIDI® Stick Winter ENDS. The individual item "was it enough nicotine" item, which is a component of the "relief" subscale was assessed individually. Mean score for this item were highest for the UB cigarette and lowest for JUUL Virginia Tobacco ENDS (Table 3). UB cigarette was significantly higher than BIDI® Stick Arctic and JUUL Virginia Tobacco, while the JUUL ENDS was significantly lower than BIDI®Stick Regal, Solar and Zest.

Safety Assessments

No serious adverse events occurred during the study. A small number of adverse events occurred in some subjects, including headaches, dizziness and events related to blood draws (e.g., bruising). These were all classed as either mild or moderate and quickly resolved without treatment.

DISCUSSION

The primary finding from this clinical study was that the BIDI® Stick ENDS delivered nicotine to users in a manner comparable to that from subject's UB combustible cigarette. In terms of C_{max}, AUC and T_{max}, these parameters were not significantly different for any flavour of BIDI® Stick ENDS compared to the combustible cigarette. Such a finding is unique in the literature for a disposable e-cigarette, although refillable tank-type ENDS devices and pod-based e-cigarettes have been found to deliver nicotine in a manner similar to [12][13][27][28] or exceeding [42] that from combustible cigarettes. It has been proposed that providing sufficient nicotine delivery with either a greatly reduced, or absence of, exposure to harmful toxicants would be tolerated by smokers and thus may better serve tobacco harm-reduction efforts by shifting smokers down the continuum of risk towards a less harmful tobacco product [8][10] or helping them to stop smoking [27]. Furthermore, it has been acknowledged by the U.S. Food and Drug Administration that cigarette-like nicotine delivery from the heated tobacco product IQOS is potentially beneficial to smokers trying to switch since they are more likely to completely switch away from and not resume combustible cigarette smoking [10][43], while a recent study concluded that an ENDS was most likely to help smokers reduce toxicant exposure and cigarette consumption when it was capable of delivering nicotine at levels similar to that of a cigarette [35]. In addition, it was proposed following a comparison of the nicotine delivery between U.S. and European versions of the JUUL ENDS that since nicotine delivery from the European version was not as effective it may have more limited potential in helping smokers stop smoking [28]. Effective nicotine delivery from non-inhaled smoking cessation products is also suggested to provided better assistance in smoking cessation [26][30][31][32][33] . Overall therefore, our finding of comparability between nicotine delivery from BIDI® Stick ENDS and combustible cigarettes supports that the BIDI® Stick ENDS may facilitate smokers switching to a form of nicotine intake with reduced exposure to harmful toxicants.

It has been suggested that high nicotine delivery from ENDS may be harmful if it leads to greater dependence [42], although a recent study {m/44/} reported no differences in dependence between users of low, medium and high strength nicotine e-liquids in either pod-based or disposable ENDS which presumably give rise to different nicotine exposures. Furthermore, from our nicotine pharmacokinetic and subjective effects findings it is unlikely that dependence on BIDI® Stick ENDS would be greater than that of combustible cigarettes, and this is supported by the literature which suggests lower dependence on ENDS compared to cigarettes [44], although that analysis did not take e-liquid nicotine concentration into account and likely arose from an analysis of users of a diverse range of nicotine concentrations. A recent study also examined dependence among smokers who switched to using the JUUL ENDS, demonstrating no difference in dependence between 3% and 5% nicotine concentrations, as well as demonstrating that regardless of nicotine concentration used, dependence on JUUL use was lower than dependence on cigarette smoking [17]. While it is unlikely therefore that dependence on using BIDI® Stick ENDS would be higher than dependence on cigarette smoking, and may in fact be lower, this requires further assessment.

An interesting facet of our analyses of pharmacokinetic data is the finding of no difference in nicotine pharmacokinetics between BIDI® Stick ENDS containing different flavours. A small number of studies have assessed the impact of ENDS flavours on nicotine pharmacokinetics; one study reported an impact of flavours on C_{max} although the data appeared skewed by an abnormally high C_{max} for a cherry flavour which was likely due to the cherry e-liquid having a lower pH than the other liquids and much smaller differences were seen between other flavours with a similar pH [45], a small impact of certain flavours [45][46][47], or no impact [48][49]. Our study data show that a comprehensive range of flavoured BIDI® Stick ENDS do not differentially impact nicotine pharmacokinetics or abuse liability/dependence measures when compared to tobacco flavoured BIDI® Stick ENDS.

In addition to comparable nicotine delivery to cigarettes, we observed comparable subjective effectsfollowing the use of BIDI® Sticks ENDS. Plasma nicotine C_{max} in ENDS users correlates with satisfaction [34], while other subjective effects related to ENDS use are better indicators of the potential for ENDS to act as a viable alternative to cigarette smoking [50][51]. This is likely of great importance when considering the harm reduction potential of ENDS. In this regard, a multidimensional framework for nicotine-containing products has been developed [50] which takes into account toxicity/harmfulness, appeal and dependence. Using this framework, it has been suggested that the "sweet spot" for a nicotine product occurs when appeal and dependence are maximised and toxicity/harmfulness are minimised. Several studies have demonstrated reduced toxicant levels in ENDS emissions compared to cigarette smoke [9][14][15][16]. In line with these findings, emissions testing of BIDI® Stick ENDS demonstrated toxicant levels which were both significantly less than those in cigarette smoke and comparable to emissions from other ENDS (data not shown). This supports a profile of lower toxicity and harmfulness of using BIDI® Stick ENDS compared with cigarette smoking. Given this potential lower toxicity, along with evidence of comparable abuse liability/dependence potential of the BIDI® Stick ENDS (based on nicotine delivery and subjective effects) and comparable appeal of the BIDI® Stick ENDS (based on subjective effects findings), this suggests that the BIDI® Stick ENDS has an appropriate balance of toxicity, appeal and dependence and is a viable alternative to cigarette smoking. BIDI® Stick ENDS therefore will likely have a positive impact on net population health [50].

Interpretation of the findings from this study may be subject to some limitations. Firstly, the study was conducted in a cohort of smokers in Poland, whereas BIDI® Stick ENDS are currently only marketed in the

U.S. Thus, our nicotine PK and subjective effects data may not reflect those of a U.S. smoker using BIDI® Stick ENDS. However, this limitation is mitigated by the study inclusion criteria, which ensured that only smokers of high-yield cigarettes were eligible for entry into the study, and this approach was taken to more closely match the higher yield cigarettes more commonly smoked by US smokers [52][53]. Furthermore, in the study a comparator ENDS (JUUL Virginia Tobacco) was included and our nicotine pharmacokinetic findings for both combustible cigarettes and JUUL Virginia Tobacco closely match those previously reported in similar studies in U.S. smokers [46][54]. Secondly, while our studies included a period in which study subjects were allowed to use the study products prior to their nicotine pharmacokinetic and subjective effects assessments, this period was short. It has been described that nicotine delivery from ENDS may change over time as users become acclimatised to the devices [36][55][56], and therefore, our findings may not reflect nicotine delivery in an acclimatised BIDI® Stick ENDS user.

CONCLUSIONS

In summary, nicotine pharmacokinetic assessments showed that the BIDI® Stick ENDS delivered nicotine to users in a manner comparable to their UB combustible cigarette. Subjective effects data, including satisfaction and relief were also comparable between cigarette and BIDI® Stick ENDS. These findings support the BIDI® Stick ENDS as a satisfying alternative for current smokers and may support their transitioning away from harmful cigarette smoking.

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Competing Interests

IMF is an independent consultant contracted to ENDS and tobacco product manufacturers to provide scientific and regulatory support for clinical and behavioral studies. RGNS is an independent consultant who provides statistical support to ENDS manufacturers. KG is an employee of, and WM is the President of, McKinney Regulatory Science Advisors, LLC who are contracted to provide scientific and regulatory support to ENDS and tobacco product manufacturers.

Figure 1. Mean Baseline-Adjusted Plasma Nicotine Concentration by Time. N = 17-18 in each

case. Horizontal black bars show periods of product use, which occurred between 0 and 5 minutes (defined use) and between 120 and 180 minutes (*ad libitum* use). Errors bars have been omitted for clarity; for variability estimates refer to Table 1. UB, usual brand; VT, Virginia Tobacco.

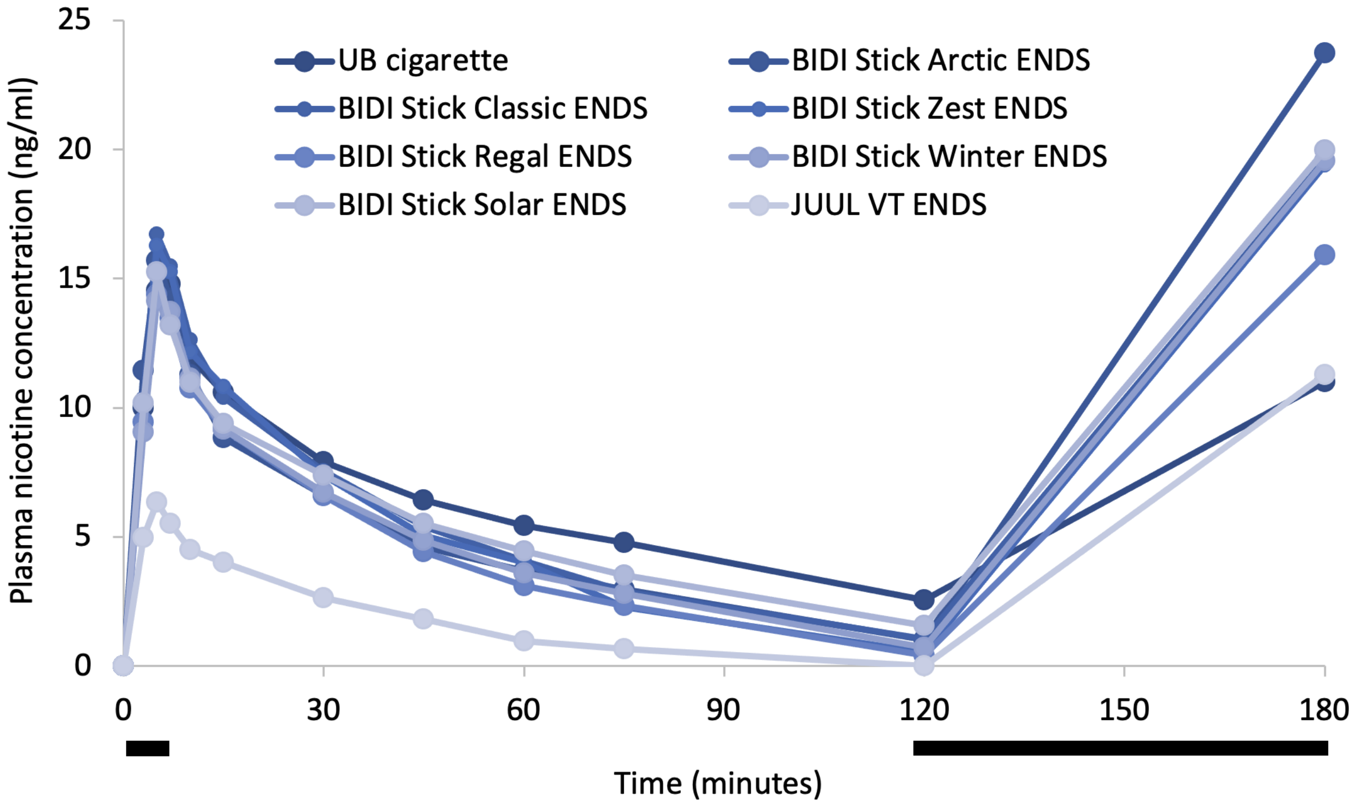

Table 1. Nicotine Pharmacokinetic Parameters for BIDI Stick© ENDS and Comparator Products. N = 17-18 in each case. UB, usual brand; SD, standard deviation; VT, Virginia Tobacco; min, minimum; max, maximum.

	UB Cigarette	BIDI® Stick Arctic	BIDI® Stick Classic	BIDI® Stick Regal	BIDI® Stick Solar	BIDI® Stick Winter	BIDI® Stick Zest	JUUL VT
$C_{max\ 0\text{-}120}$ (ng/mL)								
Mean (SD)	16.2 (9.17)	16.8 (9.71)	17.6 (9.00)	15.6 (8.72)	16.0 (11.73)	15.3 (9.90)	17.2 (10.30)	6.8 (4.13)
Geometric mean (SD)	14.0 (1.74)	13.5 (2.18)	15.5 (1.68)	13.4 (1.80)	12.6 (2.07)	13.1 (1.76)	14.7 (1.77)	5.7 (1.89)
Median	13.9	16.6	13.3	13.7	11.1	12.0	11.6	5.7
Min, max	4.7, 40.6	1.4, 36.8	7.1, 33.9	3.8, 37.0	2.6, 41.2	4.4 to 44.6	5.4 to 42.7	1.8 to 14.78
$AUC_{0\text{-}120}$ (min*ng/mL)								
Mean (SD)	742.2 (330.05)	624.0 (217.00)	618.0 (290.33)	561.12 (351.77)	628.6 (412.57)	587.2 (334.23)	635.4 (288.25)	293.6 (173.39)
Geometric mean (SD)	671.8 (1.61)	589.0 (1.43)	565.0 (1.54)	384.3 (3.45)	455.1 (3.20)	484.4 (2.04)	572.6 (1.65)	202.1 (3.55)
Median	665.5	610.9	607.2	590.0	532.9	530.9	584.1	284.7
Min, max	233.4, 1448.4	321.1, 1118.8	251.5, 1491.0	7.7, 1412.1	7.4, 1679.2	75.2, 1206.6	146.3, 1312.7	4.5, 588.2
$T_{max\ 0\text{-}120}$ (minutes)								
Mean (SD)	6.7 (2.74)	6.2 (1.39)	6.11.41)	6.0 (1.58)	6.1 (1.58)	6.0 (1.41)	6.8 (2.51)	5.9 (1.73)
Median	6	7	5	5	7	5	7	5
Min, max	3, 15	5, 10	5, 10	3, 10	3, 10	5, 10	5, 15	3, 10
$C_{max\ 120\text{-}180}$ (ng/ml)								
Mean (SD)	11.0 (5.30)	23.7 (12.67)	19.6 (10.43)	15.9 (13.29)	20.0 (11.73)	19.6 (14.67)	19.4 (10.21)	11.3 (10.85)
Geometric mean (SD)	10.04 (1.53)	18.61 (2.09)	17.32 (1.67)	12.44 (2.54)	16.96 (1.82)	16.86 (2.03)	17.56 (1.78)	8.52 (2.37)
Median	9.3	28.8	18.4	11.4	20.1	15.0	16.3	6.8
Min, max	4.9, 25.6	3.5, 38.4	8.5, 42.7	0.9, 48.9	7.4, 44.2	4.9, 50.1	5.3, 40.6	1.7, 41.2

Table 2. Statistical Comparison of Nicotine Pharmacokinetic Parameters. N = 10-17 in each case. [a]Back-transformed (exponentiated) linear mixed model parameter estimates used to create 90% CI ratios of geometric least squares means between study products. [b] Odds ratios 90% CIs. Statistical significance is concluded if the CIs do not contain 1.00. UB, usual brand; LS, least square; CI, confidence interval. Values which were significantly different are in bold type.

	BIDI® Stick Arctic	BIDI® Stick Classic	BIDI® Stick Regal	BIDI® Stick Solar	BIDI® Stick Winter	BIDI® Stick Zest	JUUL VT
$C_{max\ 0\text{-}120}$ LS Means (90% CI)[a]							
BIDI Stick® Classic ENDS	0.89 (0.71,1.12)	--	--	--	--	--	--
BIDI Stick® Regal ENDS	1.01 (0.80,1.27)	1.13 (0.90,1.43)	--	--	--	--	--
BIDI Stick® Solar ENDS	1.07 (0.85,1.35)	1.20 (0.95,1.51)	1.06 (0.84,1.33)	--	--	--	--
BIDI Stick® Winter ENDS	1.05 (0.83,1.33)	1.18 (0.93,1.49)	1.04 (0.82,1.31)	0.98 (0.78,1.24)	--	--	--
BIDI Stick® Zest ENDS	0.94 (0.75,1.19)	1.06 (0.84,1.33)	0.93 (0.74,1.18)	0.88 (0.70,1.11)	0.89 (0.71,1.13)	--	--
JUUL VT ENDS	**2.44 (1.93,3.08**)	**2.74 (2.17,3.45)**	**2.42 (1.91,3.05)**	**2.28 (1.81,2.88)**	**2.32 (1.84,2.93)**	**2.59 (2.06,3.27)**	--
UB Cigarette	1.00 (0.72,1.38)	1.12 (0.81,1.55)	0.99 (0.71,1.37)	0.93 (0.67,1.29)	0.95 (0.68,1.32)	1.06 (0.77,1.47)	**0.41 (0.30,0.57)**
$AUC_{0\text{-}120}$ LS Means 90% (CI)[a]							
BIDI Stick® Classic ENDS	0.92 (0.73,1.16)	--	--	--	--	--	--
BIDI Stick® Regal ENDS	0.97 (0.78,1.21)	1.05 (0.84,1.33)	--	--	--	--	--
BIDI Stick® Solar ENDS	0.96 (0.78,1.19)	1.04 (0.83,1.32)	0.99 (0.79,1.24)	--	--	--	--
BIDI Stick® Winter ENDS	1.04 (0.84,1.29)	1.13 (0.89,1.42)	1.07 (0.86,1.33)	1.08 (0.87,1.34)	--	--	--
B BIDI Stick® Zest ENDS	0.94 (0.75,1.17)	1.02 (0.8,1.29)	0.96 (0.77,1.21)	0.97 (0.78,1.22)	0.90 (0.72,1.13)	--	--
JUUL VT ENDS	**1.86 (1.47,2.35)**	**2.02 (1.58,2.58)**	**1.91 (1.51,2.43)**	**1.93 (1.53,2.45)**	**1.79 (1.41,2.27)**	**1.98 (1.56,2.52)**	--
UB Cigarette	0.81 (0.66,0.99)	0.88 (0.7,1.1)	0.83 (0.68,1.03)	0.84 (0.68,1.04)	0.78 (0.63,0.96)	0.86 (0.7,1.07)	**0.44 (0.35,0.55)**
$T_{max\ 0\text{-}120}$ (Odds Ratios 90% (CI)[b]							
BIDI Stick® Classic ENDS	0.79 (0.25,2.42)	--	--	--	--	--	--
BIDI Stick® Regal ENDS	0.70 (0.23,2.16)	0.89 (0.29,2.76)	--	--	--	--	--
BIDI Stick® Solar ENDS	0.84 (0.27,2.58)	1.07 (0.35,3.30)	1.20 (0.39,3.71)	--	--	--	--
BIDI Stick® Winter ENDS	0.65 (0.21,2.02)	0.83 (0.27,2.58)	0.93 (0.30,2.90)	0.78 (0.25,2.41)	--	--	--
BIDI Stick® Zest ENDS	1.40 (0.46,4.29)	1.79 (0.58,5.49)	2.01 (0.65,6.19)	1.67 (0.54,5.13)	2.15 (0.70,6.65)	--	--
JUUL VT ENDS	0.59 (0.19,1.82)	0.75 (0.24,2.33)	0.84 (0.27,2.62)	0.70 (0.23,2.18)	0.90 (0.29,2.81)	0.42 (0.13,1.30)	--
UB Cigarette	1.08 (0.36,3.27)	1.38 (0.45,4.19)	1.54 (0.51,4.71)	1.29 (0.42,3.91)	1.66 (0.54,5.06)	0.77 (0.26,2.32)	1.84 (0.60,5.65)

Table 3. Product Evaluation Scale Scores. N = 17-18 in each case. Test products in the same row that do not share superscripts significantly differ (p<0.05) based on a linear mixed model. Pairwise comparisons were tested from the omnibus linear mixed model. The enough nicotine individual item is a component of the 'relief' subscale. All items were answered on seven-point response scales from 1 ("not at all") to 7 ("extremely"). UB, usual brand; Min, minimum; max, maximum; VT, Virginia Tobacco; SD, standard deviation.

	UB Cigarette	**BIDI® Stick Arctic**	**BIDI® Stick Classic**	**BIDI® Stick Regal**	**BIDI® Stick Solar**	**BIDI® Stick Winter**	**BIDI® Stick Zest**	**JUUL VT**
Relief								
Mean (SD)	4.67 (1.13)^{a}	4.44 (1.19)^{a}	4.36 (1.13)^{a}	4.66 (1.25)^{a}	4.65 (1.17)^{a}	4.15 (1.10)^{a}	4.61 (1.29)^{a}	4.24 (1.18)^{a}
Median	4.70	4.60	4.60	4.80	4.80	4.00	4.60	4.20
Min to max	2.80 to 7.00	2.20 to 7.00	2.20 to 6.00	2.00 to 7.00	2.20 to 6.20	2.20 to 6.00	2.20 to 7.00	2.60 to 7.00
Satisfaction								
Mean (SD)	4.56 (1.47)^{a}	4.76 (1.45)^{a}	4.24 (1.44)^{a}	4.74 (1.21)^{a}	5.00 (1.37)^{a}	4.50 (1.77)^{a}	4.97 (1.22)^{a}	4.22 (1.37)^{a}
Median	4.13	5.50	4.50	4.50	5.00	5.25	5.00	4.00
Min to max	2.25 to 7.00	2.50 to 7.00	1.00 to 6.00	2.25 to 7.00	2.25 to 7.00	1.00 to 6.75	2.00 to 7.00	2.00 to 6.75
Psychological Reward								
Mean (SD)	4.54 (1.12)^{b}	4.06 (1.34)^{ab}	3.98 (1.48)^{ab}	4.06 (1.31)^{ab}	4.06 (1.03)^{ab}	3.53 (1.43)^{a}	4.05 (1.47)^{ab}	4.04 (1.27)^{ab}
Median	4.60	4.00	4.00	4.20	4.20	4.00	4.00	3.60
Min to max	2.80 to 7.00	1.80 to 6.00	1.00 to 7.00	2.00 to 7.00	2.20 to 5.40	1.00 to 5.40	1.00 to 7.00	2.00 to 6.80
Aversion								
Mean (SD)	2.24 (1.49)^{a}	2.10 (0.94)^{a}	2.13 (1.10)^{a}	2.49 (1.17)^{a}	1.96 (1.12)^{a}	2.03 (1.15)^{a}	2.49 (1.52)^{a}	2.12 (1.03)^{a}
Median	1.88	2.00	1.75	2.50	1.50	1.50	2.25	2.00
Min to max	1.00 to 7.00	1.00 to 4.00	1.00 to 4.50	1.00 to 5.00	1.00 to 4.00	1.00 to 4.00	1.00 to 5.00	1.00 to 4.00
Was it Enough Nicotine Item								
Mean (SD)	5.39 (1.29)^{d}	4.47 (1.62)^{abc}	4.76 (1.52)^{abcd}	5.12 (1.54)^{ad}	5.00 (1.27)^{abd}	4.65 (1.54)^{abcd}	4.88 (1.58)^{abd}	4.06 (1.85)^{c}
Median	5.00	4.00	5.00	5.00	5.00	5.00	5.00	4.00
Min to max	3.00 to 7.00	1.00 to 7.00	1.00 to 7.00	2.00 to 7.00	3.00 to 7.00	1.00 to 7.00	1.00 to 7.00	1.00 to 7.00

Supplementary Table 1. Demographic details for study subjects. Values are presented as means ±standard deviation. [a]Fagerström Test for Cigarette Dependence (FTCD) score at screening. [b]Selfreported daily cigarette consumption at screening. Abbreviation: BMI, body mass index; Min, minimum; max, maximum.

Characteristic	Metric	Values
Age (years)	Mean (SD) Min, max	39.2 (9.21) 26, 55
Sex (male:female)	N(%):N(%)	11(61.1):7(38.9)
Race Caucasian	 N (%)	 18 (100)
Weight (males; kg)	Mean (SD)	79.3 (4.22)
Weight (females; kg)	Mean (SD)	66.6 (11.64)
BMI (kg/m^2)	Mean (SD)	24.9 (3.09)
FTCD score[a]	Mean (SD)	5.8 (1.66)
Cigarette consumption[b]	Mean (SD) Min, max	16.6 (4.82) 10, 30
Time since smoking initiation (years)	Mean (SD)	19.3 (7.66)

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