

Nicotine Uptake in Naïve, Short-term and Experienced ENDS Users Compared to Nicotine Uptake in Smokers

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Abstract

There is growing support among the public health community, including the National Academies of Science, Engineering and Medicine and American Cancer Society, that ENDS products are likely to pose fewer health risks to an individual than combustible cigarettes. The US FDA Center for Tobacco Products recommends in draft guidance that human studies to support Premarket Tobacco Product Applications for ENDS include pharmacokinetic (PK) data examining the exposure to nicotine during ENDS use. Some studies indicate that experienced ENDS users reach levels of nicotine more similar to users of combustible cigarettes, albeit generally lower.

In this study, selected nicotine PK measures ($AUC_{nic\ 0-360}$, C_{max} , T_{max}) were investigated to assess nicotine exposure in naïve, short-term and experienced ENDS users over 6 hours with respect to the start of a 10-minute *ad libitum* product use period. The ENDS products were Vuse Solo Original and Vuse Solo Menthol. Data was compared to historical PK data from non-menthol and menthol cigarette smokers. Nicotine uptake ($AUC_{nic\ 0-360}$ and C_{max}) was significantly higher in both non-menthol and menthol cigarette smokers compared with Vuse Original and Vuse Menthol experienced users, respectively. Vuse Original and Vuse Menthol naïve users also had significantly lower nicotine uptake compared with experienced Vuse users. PK parameters in experienced and short-term Vuse Original and Vuse Menthol users were similar, with the exception of Vuse Original $AUC_{nic\ 0-360}$, which was significantly higher in experienced users compared to short-term users. T_{max} occurred significantly faster in the non-menthol and menthol cigarette smokers compared with the experienced Vuse Original and Vuse Menthol users. However, differences in T_{max} between the experienced versus short-term or naïve Vuse users were not statistically different.

Introduction

A substantial body of data has examined the nicotine pharmacokinetics (PK) from electronic nicotine delivery systems (ENDS) use¹. However, there have been limited comparisons of naïve and experienced users of the same product to date². The findings of previous studies suggest that nicotine uptake from ENDS use increases with experience. Naïve ENDS users, with limited product use experience, have been shown to achieve lower plasma nicotine concentrations than experienced ENDS users; whereas experienced ENDS users have plasma nicotine concentration values more comparable to, though generally lower than, those of combustible cigarette smokers.^{2,4}

The objectives of this clinical study were to:

- Assess nicotine PK parameters of Vuse Original and Vuse Menthol ENDS in Adopters (adult, exclusive ENDS users who also used Vuse ENDS daily for at least one month prior to screening).
- Compare the PK parameters of Vuse Original and Vuse Menthol in Adopters to historical nicotine PK parameters of non-menthol and menthol cigarettes, respectively, in adult smokers.
- Compare the PK parameters of Vuse Original and Vuse Menthol in Adopters to historical PK data of Vuse Original and Vuse Menthol in naïve users (limited ENDS product use) and in short-term users (adult smokers switched to ENDS use for 5 days), respectively.

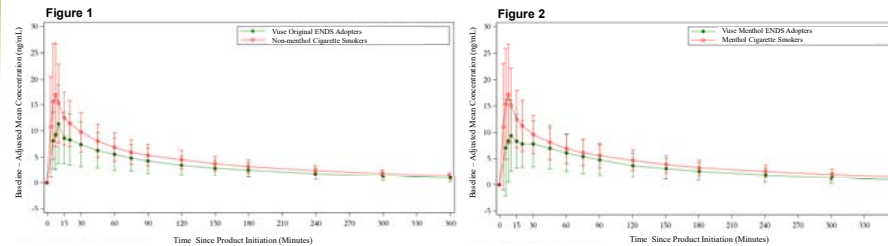
The historical PK data that was compared versus Vuse ENDS Adopters are as follows:

- Naïve users of Vuse Original⁵ and Vuse Menthol⁶ ENDS.
- Short-term users of Vuse Original and Vuse Menthol⁷ ENDS.
- Smokers of non-menthol cigarettes^{5,7}.
- Smokers of menthol cigarettes^{5,7}.

Results

- Generally healthy, adult Vuse ENDS Adopters (N=47) were enrolled in the study.
- Vuse ENDS Adopters' mean age was 34 years (range: 23 to 60 years); most were male (61.7%) and White (85.1%); 21% were Hispanic or Latino.
- Vuse ENDS Adopters experience using a cig-a-like ENDS product was 1.4 ± 1.5 years (mean \pm SD), with 79% using a cig-a-like product daily.
- Four subjects experienced adverse events (AEs) assessed as related to product. These AEs were mild in severity except one, which was moderate and resulted in product discontinuation but not study withdrawal. No deaths and no SAEs were reported.

Baseline-Adjusted Plasma Nicotine Concentrations are Higher in Cigarette Users Compared to ENDS Adopters



Baseline-Adjusted Plasma Nicotine Concentrations are Lowest for Naïve ENDS Users; Similar in ENDS Adopters and Short-term ENDS Users

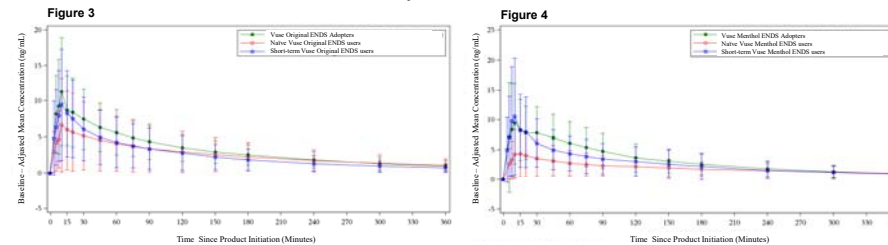


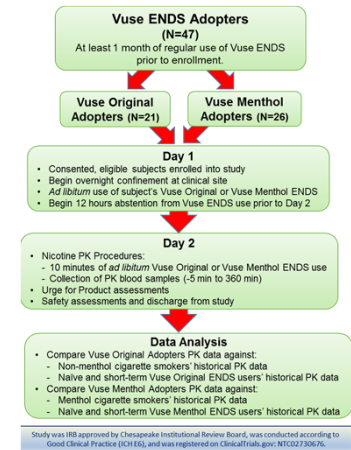
Table 1. Baseline-Adjusted Plasma Nicotine Uptake Parameters are Highest in Cigarette Users

Parameter	Geometric Means							
	Vuse Original			Non-Menthol Cigarette Smokers* (n=122)	Vuse Menthol			Menthol Cigarette Smokers* (n=138)
	ENDS Adopters (n=21)	Naïve Users* (n=45)	Short-term ENDS Users* (n=37)		ENDS Adopters (n=23)**	Naïve Users* (n=62)	Short-term ENDS Users* (n=38)	
$AUC_{nic\ 0-360}$ (ng*min/mL)	1013.9	653.2 (p=0.0182)	640.3 (p=0.0315)	1464.6 (p=0.0094)	990.2	545.1 (p=0.0014)	753.6 (p=0.1922)	1476.1 (p=0.0125)
C_{max} (ng/mL)	10.6	4.8 (p=0.0001)	7.0 (p=0.1013)	17.0 (p=0.0038)	9.0	3.4 (p<0.0001)	8.2 (p=0.6548)	17.2 (p=0.0002)
T_{max} ** (minutes)	10.0	15.1 (p=0.1248)	15.0 (p=0.0845)	7.5 (p=0.0028)	14.9	15.1 (p=0.4673)	10.0 (p=0.1002)	7.5 (p<0.0001)

*Historical data; **Median for T_{max} . Pair-wise comparisons were made versus the corresponding Adopters group using t-test or Wilcoxon signed rank test (for T_{max}). Comparisons were significant when p<0.05; ***Only data from subjects with an evaluable PK profile were included in the statistical analysis of nicotine uptake parameters.

Materials and Methods

Figure 5



Conclusions

- Nicotine uptake* from cigarettes in smokers was higher than nicotine uptake from ENDS products in experienced, short-term, and naïve users.
- Plasma nicotine PK profiles and PK parameters were similar between short-term users (5 days experience) and adopters (at least 30 days experience) of the same ENDS product.
- Naïve ENDS users had the lowest nicotine uptake* relative to short-term and experienced users of the same ENDS product.
- In summary, naïve ENDS users had lower nicotine uptake* than ENDS Adopters and Short-term ENDS users. Both ENDS Adopters and Short-term ENDS users had PK profiles more comparable to, though generally lower than, those of combustible cigarette smokers.

* Based on $AUC_{nic\ 0-360}$, C_{max}

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