Characterization of Nicotine Pharmacokinetics from Use of Reduced Nicotine Content Cigarette Prototypes in Adult Smokers

Mingda Zhang, Jeffery Edmiston, Donna Smith
Altria Client Services LLC, Richmond, VA, USA

SRNT 26th Annual Meeting
March 11-14, 2020, New Orleans, LA, USA

http://sciences.altria.com | Altria

This scientific research is presented by Altria Client Services LLC (ALCS). ALCS affiliate companies are tobacco product manufacturers.

ABSTRACT

In March 2018, FDA issued an advance notice of proposed rulemaking (ANPRM) on a nicotine standard for conventional cigarettes to make them minimally- or non-addictive. Currently there are limited data available on the relationship between the nicotine content in tobacco and human nicotine pharmacokinetics (PK).

METHODS: We developed five prototype reduced nicotine cigarettes (RNCs) with nicotine levels between 1.3 to 11.1 mg nicotine per gram tobacco and one prototype conventional nicotine cigarette (CNC). Using these prototypes, we conducted a randomized 6-way crossover clinical study to investigate nicotine PK among 57 healthy adult cigarette smokers following controlled use of a single cigarette (10 puffs taken at 30s intervals). The study also examined product use parameters and increase in blood carboxyhemoglobin saturation (CO boost) during 30 minutes of *ad libitum* product use.

RESULTS: Both maximum plasma nicotine concentration (C_{max}) and area under the nicotine concentration curve (AUC) following the use of the RNC prototypes (1.34-7.08 ng/ml and 1.48-7.99 ng*hr/ml, respectively) were lower than with the CNC prototype (9.33 ng/ml and 10.39 ng*hr/ml, respectively). Overall, the average number of puffs, puff duration, number of cigarettes smoked during the brief *ad libitum* product use conditions, and cigarette butt length, were similar between the RNC and CNC prototypes. There was no significant difference in CO boost among the study cigarettes.

CONCLUSIONS: Smokers' exposure to nicotine is closely correlated with the nicotine content of the study cigarettes. We found no significant differences in use parameters or CO boost when participants smoked the study cigarettes with different nicotine levels during 30 minutes of *ad libitum* use conditions. The lowest nicotine content (1.3 mg/g) tested in the study was higher than the level of particular interest to the FDA (0.3-0.5 mg/g). Tobacco leaf at lower nicotine levels was not available to make RNC prototypes in the 0.3-0.5 mg/g range.

BACKGROUND

FDA issued an advance notice of proposed rulemaking (ANPRM) entitled "Tobacco Product Standard for Nicotine Level of Combusted Cigarettes" in 2018 indicating that it was considering a product standard to set a maximum nicotine level in cigarettes so that they are "minimally addictive or non-addictive" [1]. Through the ANPRM, the Agency is seeking additional scientific data and research relevant to the empirical basis for regulatory decisions related to a nicotine tobacco product standard.

The SPECTRUM research cigarettes manufactured under parameters specified by the NIDA [2] have become standard cigarettes for reduced nicotine cigarette (RNC) clinical studies. There is only one peer-reviewed publication on nicotine pharmacokinetics (PK) using the SPECTRUM nicotine research cigarettes involving 12 participants [3]. Since the SPECTRUM cigarettes were not available for the study, we developed and manufactured small quantities of prototype reduced nicotine research cigarettes at nicotine levels similar to those of the widely used SPECTRUM cigarettes. However, we were not able to make cigarettes at the nicotine level of 0.4 mg/g for this study. These research cigarettes have major sensory deficits compared to commercial cigarettes.

CONCLUSIONS

- The nicotine exposure with use of the reduced nicotine test cigarettes closely reflect the nicotine content in the cigarettes, consistent with previously published results from a study using the SPECTRUM nicotine research cigarettes [3].
- The CO boost during *ad libitum* use, from either the first cigarette or after the whole 30-minute session, was comparable across cigarettes at various nicotine levels, suggesting no major difference in puffing intensity and hence exposure to CO.
- The overall product use behavior including average puffs per cigarette, puff duration, and number of cigarettes smoked during the *ad libitum* session were similar among the study products, including both the reduced nicotine content test cigarettes and the conventional nicotine content reference cigarette.

STRENGTHS & LIMITATIONS

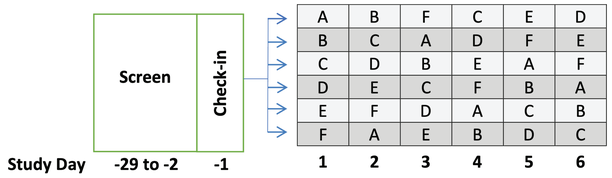
Strengths of this study include the randomized crossover design with subjects confined in a clinical research facility, a large number of subjects (57), and testing cigarettes at 6 different nicotine levels. Because the confined study design eliminated participants' access to non-study cigarettes, the observed results are not confounded by non-compliance to study product use as commonly observed in ambulatory studies [4]. Limitations of the study include the use of non-standard research cigarette prototypes custom-made in small quantities, and with major sensory deficits, which introduces the uncertainty on the generalizability of the observed results; the lowest nicotine level tested was 1.3 mg/g tobacco because we were unable to make cigarettes at 0.4 mg/g nicotine level; and the *ad libitum* sessions only consisted of 30 minutes which might not be long enough to detect changes in use behavior. In addition, results from this study were obtained while participants were confined in a clinical setting which may not reflect actual use behavior in real world situations.

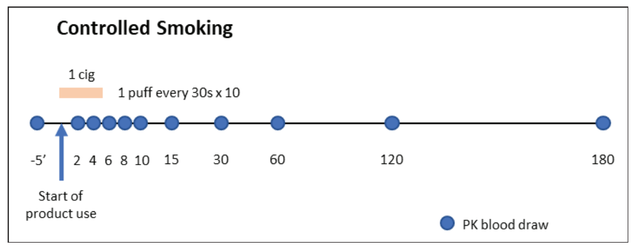
METHODS

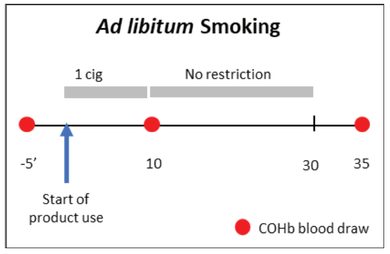
Study Design

This study utilized a single-blind, randomized, 6-way crossover design to evaluate PK, and product use behavior, associated with study products including five RNCs and one CNC with nicotine content between 1.3 to 15.8 mg/g filler among healthy adult cigarette smokers of 21-65 years of age. All subjects were self-affirmed exclusive smokers of manufactured non-menthol combustible cigarettes having an average consumption of 5-30 cigarettes per day (CPD) for at least 12 months and no other type of tobacco- or nicotine- containing product use in the 30 days prior to Check in.

Subjects who met all inclusion and none of the exclusion criteria during screening checked into the clinic on Day -1 and abstained from use of any tobacco- or nicotine-containing products until the first study product use on Day 1. On each study day (Days 1–6), subjects received 1 of the 6 study products (A to F) according to the randomization schedule and used the assigned product in two episodes separated by 6 hours: once in the morning under controlled use conditions (i.e., 10 puffs of one assigned cigarette taken at approximately 30-second intervals) and once in the afternoon under *ad libitum* use conditions (i.e., *ad libitum* use of one assigned cigarette for 10 minutes plus 20 additional minutes of *ad libitum* use without restriction on the number of cigarettes). PK blood samples for plasma nicotine were taken at approximately 5 minutes prior to and 2, 4, 6, 8, 10, 15, 30, 60, 120 and 180 minutes following the start of the 1st product use episode. Carboxyhemoglobin (COHb) blood samples were taken at approximately 5 minutes prior to, and at approximately 15 and 35 minutes following the start of the 2nd product use episode. Number of puffs, duration of each puff (first cigarette only), number of cigarettes smoked, and cigarette butt length were recorded by site staff for the 2nd product use episode.







Study Products

		Nicotine Content (mg/g filler)	Nicotine Yield (mg/cig, ISO)	CO Yield (mg/cig, ISO)
Product A	RNC - Test	1.3	0.07	9.6
Product B	RNC - Test	2.3	0.12	10.1
Product C	RNC - Test	5	0.27	10.2
Product D	RNC - Test	7.8	0.37	10.9
Product E	RNC - Test	10.4	0.51	10.6
Product F	CNC - Reference	15.3	0.62	10.4

Outcome Variables

Primary

-Maximum plasma nicotine concentration (C_{max}), time to C_{max} (T_{max}), and area under the nicotine concentration curve (AUC) measured following each product use under controlled use conditions.

Secondary

-Number of puffs and duration of each puff (first cigarette only), number of cigarettes smoked, and cigarette butt length under ad libitum use conditions, and;

-CO boost, as measured by COHb saturation, before, during and after the ad libitum use episode.

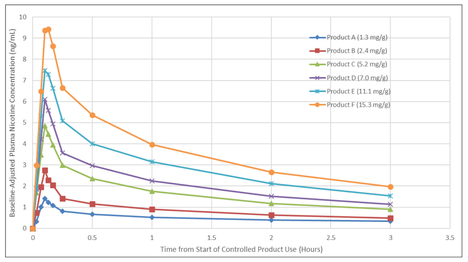
RESULTS

Study Population

- Subjects randomized: 57 (55 completed)
  - Male: 32
  - Female: 25
  - White: 54
  - Non-white: 3
- Average age: 43.1 (±11.9) years
- Mean numbers of cigarettes per day: 16.1 (±4.8)
- Mean years of smoking history: 25.0 (±12.9)

Pharmacokinetic Measures

Mean Baseline-adjusted Plasma Nicotine Concentration-Time



Baseline-Adjusted Plasma Nicotine PK Parameters

Product	C_{max}† (ng/mL)	AUC† (ng*hr/mL)	T_{max}‡ (hr)
Product A	1.34 (1.13-1.59)	1.48 (1.28-1.71)	0.115
Product B	2.43 (2.04-2.88)	2.29 (1.99-2.65)	0.100
Product C	4.64 (3.90-5.52)	4.69 (4.06-5.41)	0.101
Product D	5.62 (4.73-6.68)	5.86 (5.07-6.76)	0.101
Product E	7.08 (5.96-8.42)	7.99 (6.92-9.23)	0.133
Product F	9.33 (7.85- 1.09)	10.39 (9.00-11.99)	0.133

†Geometric LS Mean values (confidence intervals); ‡ median

The differences in C_{max} and AUC were statistically significant for all product comparisons, and closely reflect the nicotine content in the cigarettes.

The differences in T_{max} were not statistically significant with the exception of that between Product B and F (p=0.0445).

Product Use Behaviors

The mean number of puffs per cigarette was slightly greater, whereas the mean puff duration was slightly shorter, for the 1st cigarette during *ad libitum* use compared to those during controlled use across all products.

The mean number of cigarettes smoked and cigarette butt length during *ad libitum* use were similar across all products.

	Product	A	B	C	D	E	F
Puffs Per Cigarette	Controlled	9.9	10.0	10.0	10.0	10.0	9.9
	Ad Libitum	10.8	10.6	10.7	12.0	11.6	11.7
Puff Duration (second)	Controlled	2.6	2.8	2.7	2.8	2.7	2.6
	Ad Libitum	2.4	2.5	2.4	2.4	2.3	2.2
Number of Cigarettes	*Ad Libitum*	4.0	3.9	4.1	3.8	3.7	3.8
Cigarette Butt Length (mm)	*Ad Libitum*	36.4	36.8	36.2	37.5	36.1	36.7

CO Boost

Mean CO Boosts After *Ad Libitum* Product Use Were Similar Across All Study Products

Mean (±SD) CO Boost (Absolute Change in % COHb Saturation) During *Ad Libitum* Use*						
Product	A	B	C	D	E	F
1st Cigarette	1.16 ± 0.90	1.02 ± 0.42	1.10 ± 0.44	1.02 ± 0.40	1.13 ± 0.46	1.01 ± 0.37
30' Ad Libitum	3.93 ± 2.17	3.72 ± 2.13	3.63 ± 1.64	3.59 ± 2.02	3.58 ± 2.12	3.51 ± 1.86

*COHb data were not available for 31 subjects due to a sample processing error; therefore, the results are based on available data from the remaining 24 to 26 subjects

REFERENCES

1. U.S. Food and Drug Administration (2018): 21 CFR. p. 11818-11843.
2. National Institute on Drug Abuse: https://www.drugabuse.gov/nicotine-research-cigarette-drug-supply-program3
3. Kamens, H.M., et al. (2019): Nicotine Tob Res,. https://doi.org/10.1093/ntr/ntz045
4. Zhang, M., et al. (2020): Intl J Clin Res Trials. https://doi.org/10.15344/2456-8007/2020/141