Characterization of Nicotine & NNN Pharmacokinetics from Use of a Novel Heated Tobacco Capsule Prototype in Adults Who Smoke

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ABSTRACT

Heated tobacco products (HTPs) may offer a potentially reduced-risk alternative to adults 21+ who smoke cigarettes (AS) and are unable or unwilling to quit. In this study, we characterized the nicotine pharmacokinetics (PK) and subjective measures of a novel heated tobacco capsule (HTC) prototype in AS. The HTC prototype consists of a hand-held battery-operated device and a disposable tobacco-containing capsule that is inserted into the device. We conducted a randomized, crossover study to characterize nicotine PK of prototype capsules containing one menthol and 3 non-menthol tobacco blend variants, relative to the subject's usual brand cigarette (UBC) in 20 menthol and 24 non-menthol AS. To facilitate acclimation with the novel HTC prototype, subjects were allowed to use up to 5 capsules for each prototype tobacco blend variant during a product trial, and up to 2 capsules for each prototype the day prior to the PK session. The PK assessments were conducted during a single use session of the HTC prototype or UBC. Subjects also completed questionnaires on "urges to smoke", "craving cigarettes", and rated the products for "pleasant" and "satisfying" using visual analog scales (VAS). The geometric mean plasma nicotine Cmax values were 14.2 ng/mL for the menthol and ranged from 8.8 to 10.6 ng/mL for the non-menthol HTC prototypes, compared to 24.0 ng/mL for the menthol and 14.5 ng/ml for the non-menthol UBCs, respectively. The "pleasant" and "satisfying" VAS scores for the prototype non-menthol HTCs used in this study were statistically significantly lower compared to the UBC. Reductions in "craving a cigarette" were significantly lower for the prototype menthol HTC compared to UBC. Overall, the nicotine uptake during use of the HTC prototypes suggests they have the potential to be acceptable substitutes for cigarettes.

BACKGROUND

The growing consensus among public health authorities is that tobacco products exist on a continuum of risk. Use of combustible tobacco products, such as conventional cigarettes carries increased health risks, while use of noncombustible tobacco products, such as HTP, is associated with relatively lower risks.[1] Many adult cigarette smokers (~55%) are interested in less harmful tobacco products.[2] Heated tobacco products may offer a reduced risk alternative to adults 21+ who smoke cigarettes and are unable or unwilling to quit. The test products used in this study were novel HTC prototypes intended for adult smokers as an alternative to combustible cigarettes.

STUDY PRODUCT

Prototype HTC

Study Product	Nicotine Yield[a] (mg/unit)[b]	NNN Yield[a] (ng/unit)[b]
HTC Menthol Prototype (HTC-M)	1.29	9.4
HTC Non-Menthol Prototype 1 (HTC-NM1)	1.29	8.85
HTC Non-Menthol Prototype 2 (HTC-NM2)	1.26	18.0
HTC Non-Menthol Prototype 3 (HTC-NM3)	1.83	27.1
1R6F[c]	1.94	215

[a] Based-on machine smoking under Intense puffing protocol (55 cc puff volume, 2 s puff duration and 30 s puff interval. No vent blocking was performed for the HTC prototypes.)
[b] 1 unit = 1 capsule for HTC Prototype or 1 stick for conventional cigarette
[c] For reference only (tested at ~9 puffs), the actual cigarettes used in this study were self-supplied subjects' usual brand cigarettes (Reference product), which were not tested for nicotine and NNN.

OBJECTIVES

- **Primary Objectives:**
  - To characterize the rate and extent of nicotine exposure after a single use of 1 menthol (Menthol Group) and 3 non-menthol (Non-Menthol Group) prototype HTCs under single ad libitum-use conditions relative to subjects' usual brand menthol (**UBC-M**) and non-menthol (**UBC-NM**) combustible cigarettes in adult smokers
  - To compare subjective effects while using 1 menthol prototype HTC and 3 non-menthol prototype HTCs relative to subject's respective combustible cigarettes in adult smokers
- **Secondary Objectives:**
  - To characterize the rate and extent of NNN exposure* after a single use of 1 menthol (Menthol Group) and 3 non-menthol (Non-Menthol Group) prototype HTCs under single ad libitum-use conditions relative to subjects' menthol and non-menthol combustible cigarettes in adult smokers
  - To characterize puffing topography of 4 prototype HTCs in adult smokers (*data not shown)*

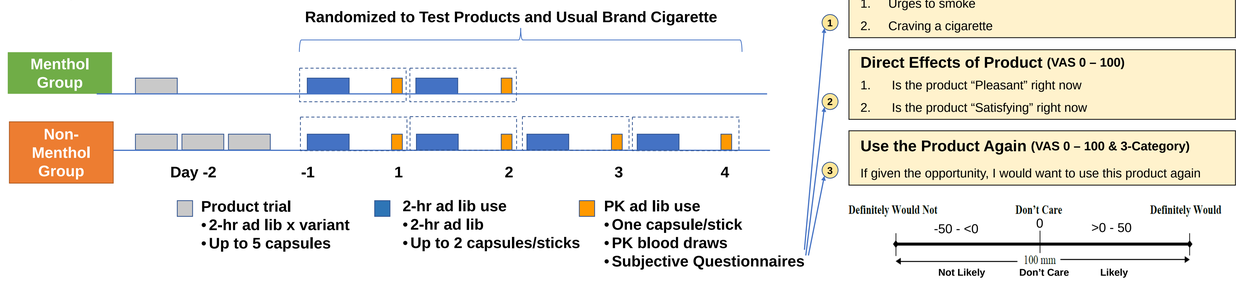
* by measuring plasma levels of NNN

METHODS

Study Design

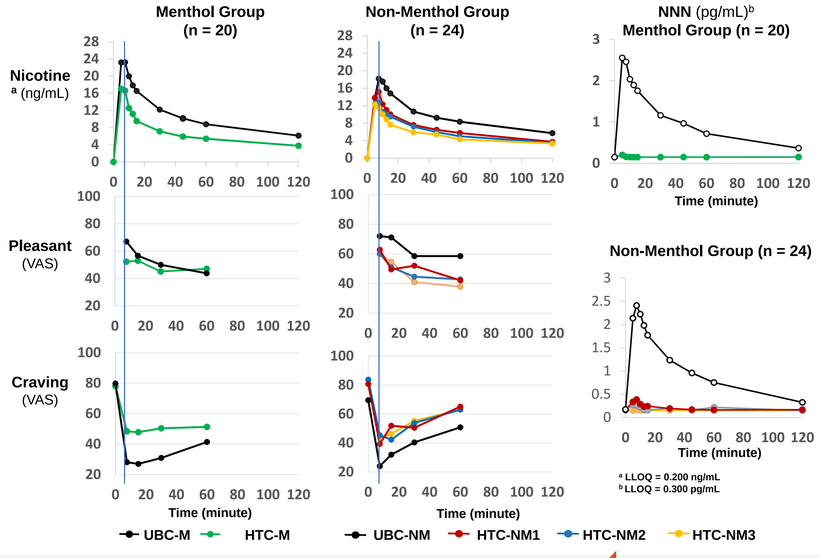
- A randomized, 2-groups (Menthol & Non-Menthol) crossover in-clinic study
- Study Population
  - Healthy adult males and female dual users (21-65 years of age)
  - Smoked 10-30 cig/day in past year
- Study Product Use
  - 2-hour ad libitum product trial in clinic at check-in
  - 2-hour ad libitum use the day prior to PK assessment
  - 7-min ad libitum use during PK assessment
- PK & Subjective Effects Assessment
  - Blood samples taken from 5 min prior to and 180 min after the start of product use
  - Subjective Effects questionnaire administered at 5 min prior to and at 7.5, 15, 30 and 60 min after the start of product use

Study Event



RESULTS

Mean Nicotine & NNN Concentrations (Baseline-Adjusted), Pleasant & Craving VAS Scores Over Time



Nicotine PK Parameters

(Geometric Mean: C_{max} and AUC, median: T_{max})

Test Product	C_{max} (ng/mL)	T_{max} (min)	AUC (ng*min/mL)
HTC-M	14.2*	4.6	828.6*
UBC-M	24.0	7.4	1497.7
HTC-NM1	8.8*	5.0	671.1*
HTC-NM2	10.3*	7.5	762.0*
HTC-NM3	10.6*	7.5	794.3*
UBC-NM	14.5	8.5	1094.4

* p<0.05 compared to UBC-M or UBC-NM, respectively

Study Population Demographics

Trait	Menthol Group	Non-Menthol Group
Female Male	12 8	12 12
Black White Other	11 6 1	6 18 0
Age (yrs)	37.6 (26–53)	37.5 (24–56)
Body Mass Index (kg/m^2)	28.6 (22.7–33.4)	30.6 (29.9–39.9)
Cigarette Per Day	13.4 (10-25)	18 (10-30)

Subjective Effects Measures

Test Product	Tobacco/Nicotine Withdrawal (Maximum Reduction from Baseline)		Direct Effects of Product (Maximum VAS Scores)		Use Product Again Number and (% in each category)		
	Urge to Smoke	Craving a Cigarette	Pleasant	Satisfying	Not Likely	Don't Care	Likely
HTC-M	41.50	40.80*	62.75	60.35	7 (35)	1 (5)	12 (60)
UBC-M	55.45	60.1	70.35	67.85	5 (25)	0	15 (75)
HTC-NM1	45.04	43.61	65.93*	67.42*	5 (23)	2 (9)	15 (68)
HTC-NM2	47.42	39.6	65.83*	66.71*	11 (45)	0	12 (55)
HTC-NM3	46.25	46.38	71.04*	70.92*	11 (48)	1 (4)	11 (48)
UBC-NM	45.75	48.38	86.54	84.46	2 (9)	0	21 (91)

* p<0.05 compared to UBC-M or UBC-NM, respectively

SUMMARY & CONCLUSION

Summary
- The plasma nicotine C_{max} of all HTC prototypes tested were statistically significantly lower than subjects' usual brand cigarettes for both menthol and non-menthol groups.
- The plasma nicotine T_{max} for all HTC prototypes tested were comparable to cigarettes.
- On average, subjects rated similar for the menthol HTC Prototype on pleasantness and satisfaction as to their usual brand cigarette, whereas subjects rated the non-menthol HTC prototypes lower on pleasantness and satisfaction than their usual brand cigarette
- The HTC prototypes reduced the urges to smoke (both the menthol and non-menthol) and craving cigarettes (non-menthol) to levels similar to those from their usual brand cigarettes
- Approximately 50 -75% of subjects indicated they would likely to use the HTCs again
- The plasma NNN C_{max} AUC were 93% and 88% for the menthol HTC prototype and 86 - 92% (C_{max}), 74 – 78% (AUC) for the non-menthol HTC prototypes lower than the respective usual brand cigarettes.

Conclusion
- Overall, the data suggests these prototypes may be acceptable alternatives for cigarettes and switching completely will substantially reduce exposure to NNN.

STRENGTH & LIMITATIONS

Strengths
- Product use under specified condition allows for assessment of test and reference products under well characterized conditions
- Subjective measures were evaluated using-questionnaires that are frequently referenced in literature

Limitations
- Product use in an in-clinic setting may not reflect how consumers typically use the products in a real-world setting
- Clinical procedures occurring concurrently with subjective measurements may skew the subjective responses. However, it is reasonable to compare between the test and reference products since both were tested under similar conditions

REFERENCES

1. Gottlieb S, Zeller M. A Nicotine-Focused Framework for Public Health. N Engl J Med. 2017; 377(12):1111-1114.
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3. U.S. Department of Health and Human Services. Applications for Premarket Review of New Tobacco Products. 2011 September. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/
4. O'Connell G, Pritchard J, Prue C, Thompson J, Verron T, Graff D, and Walele T. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med. 2019; 14(6): 853–861.