

EVALUATION OF THE ABUSE LIABILITY OF A NOVEL NON-TOBACCO SMOKELESS POUCH PRODUCT

Ed Carmines¹, Karen Carmines¹, Lise Fraissinet¹, Naama Levy-Cooperman², Zach Bader³, Mark Hanson⁴
Chemular Inc¹, Hudson, MI, Altreos Research Partners Inc², Toronto, CN, Altasciences³, Kansas City, KS, Black Buffalo Inc.⁴, Chicago, IL

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ABSTRACT

Black Buffalo Inc. has designed a novel alternative smokeless product that is based on a common non-tobacco food plant. The non-tobacco food plant leaf is cured and processed like tobacco but does not contain TSNAs or PAHs. Tobacco derived nicotine is added to the processed leaf. Black Buffalo's product is designed to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional smokeless pouch products. The potential abuse liability of Black Buffalo Wintergreen Pouches (BBP) was assessed and compared to own-brand cigarettes, Nicorette gum, and Copenhagen Long Cut Wintergreen (CLC). A randomized open label 5-way crossover in-patient clinical study was performed to evaluate the nicotine plasma levels and the subjective measures of effect. Subjects used 2 grams of CLC or one BB pouch, smoked their own cigarette or used one piece of nicotine gum under controlled conditions. Suppression of the urge to smoke was equivalent for all of the products but the time to effect was 5 minutes for own-brand cigarettes and 15 minutes for all of the other products. All of the oral products were less satisfying and less pleasant than own-brand cigarettes. Own-brand cigarette nicotine plasma levels peaked in 5.5 minutes with a maximum concentration of 19.6 ng/mL. BBP peaked at 30 minutes at a concentration of 7.1 ng/mL. CLC peaked at 30 minutes at a concentration of 13.2 ng/mL. Nicotine absorption from the Nicorette gum was slower (45 minutes peak) at a concentration of 6.6 ng/mL. The pharmacokinetic data demonstrate that nicotine absorption from BBP is less than own-brand cigarettes and CLC and similar to Nicorette gum. The results demonstrated that BBP has a lower abuse liability than own-brand cigarettes but is similar to CLC.

OBJECTIVE

Determine the potential abuse liability of Black Buffalo Wintergreen Pouch Product compared to own-brand cigarettes, Nicorette gum, and Copenhagen Wintergreen Long Cut.

THE PRODUCTS

Black Buffalo's (BB) tobacco alternative products were developed as an alternative to traditional moist smokeless tobacco (MST) products, with the intent of eliminating user exposure to the TSNAs and PAHs found in MST product. BB's products are made by applying food-grade flavors, pharmaceutical-grade tobacco-derived nicotine, salt, water, preservatives, humectants, and pH modifiers to a leafy vegetable food that has been flue-cured (i.e., dried using indirect heat), cut, and processed into a low-moisture biomass that resembles finely shredded tobacco.

The product does not contain any tobacco leaf or tobacco stem material, but it does contain tobacco-derived nicotine and is intended to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional MST products. The product is intended to be placed in the mouth between the cheek and gum for a period of time determined by the user (typically 30 to 60 minutes).



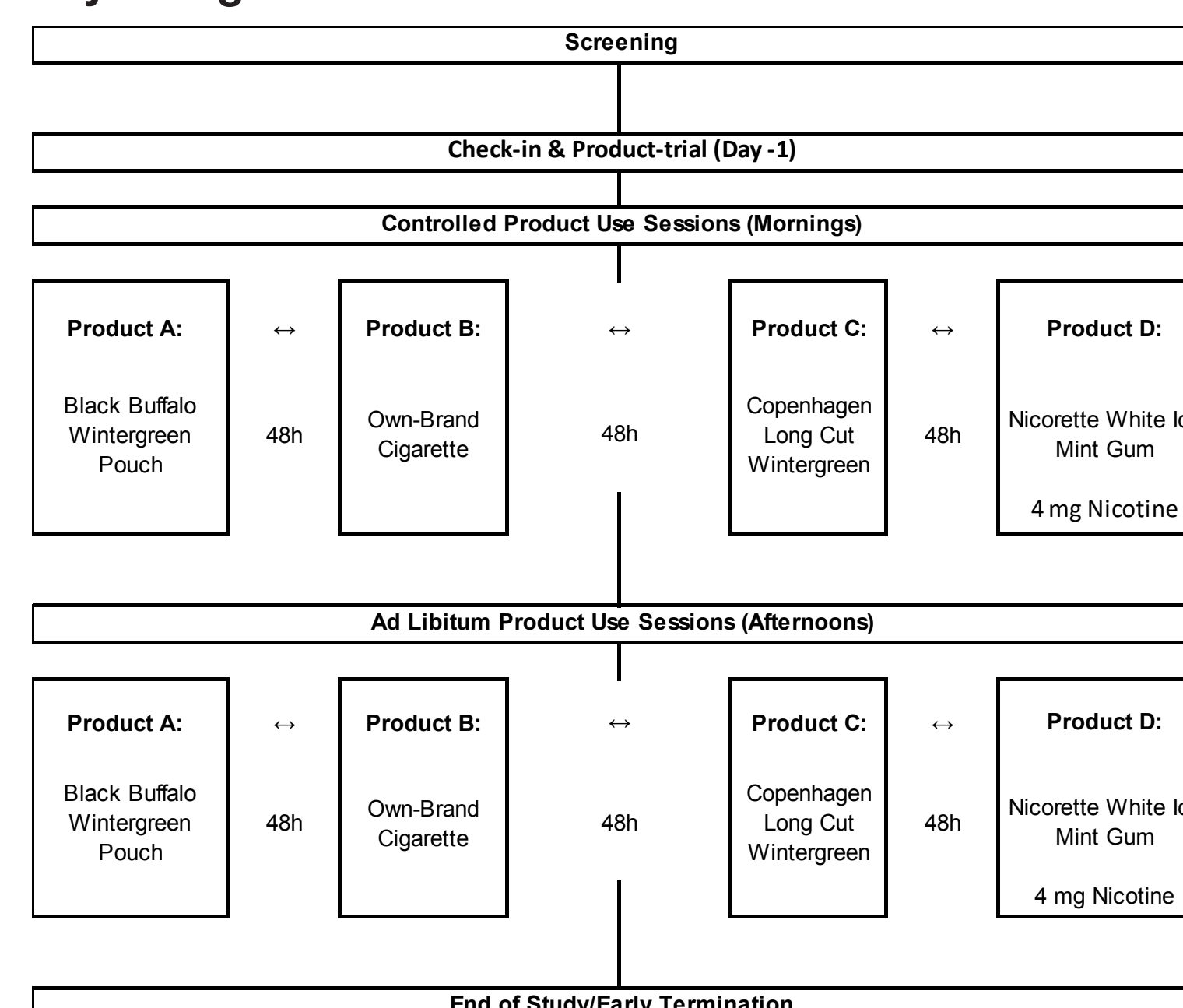
METHODS

This was a randomized, open-label, 5-way crossover study designed to evaluate the abuse liability, pharmacokinetics (PK), and product use behavior associated with Black Buffalo Wintergreen Pouch, subjects' own-brand cigarettes, Copenhagen Wintergreen Long Cut, and nicotine polacrilex gum in healthy adult male and female smokers who have experience using smokeless products.

- Subjects had to have a history of smoking an average of ≥ 10 cigarettes daily for at least 1 year
- Subjects must have used a mint-flavored, smokeless tobacco product (loose or pouch), at least 20 times in their lifetime and at least once (loose or pouch) in the past 30 days (prior to study start)
- Subjects must have tested positive for urine cotinine (≥ 200 ng/mL) at Screening

Subjects participated in a standard screening visit and a Confined Assessment Phase, which included a Product Trial Session on Day -1 and Product Use Sessions, which consisted of morning Controlled Product Use Sessions and 4-hour afternoon Ad Libitum Product Use Sessions (Figure 1). Each study day of product use was separated by approximately 48 hours. During the Controlled Product Use Sessions, pharmacodynamic (PD) measures (using the Tobacco/Nicotine Withdrawal Questionnaire and Direct Effect of Products Questionnaire) and PK plasma samples were collected at various time points. During the Ad Libitum Product Use Sessions, PD measures (QSU-Brief measure and the "Use the Product Again" visual analog scale [VAS]) were administered prior to (QSU-Brief only) and at the end of each Ad Libitum Product Use Period. Product use behaviors (i.e., the number of pouches, cigarettes, or pieces of gum consumed, and the duration of use) were collected throughout each Ad Libitum Product Use Session. Subjects smoked 1 cigarette for 10 minutes (single puff every 30 seconds), chewed one piece of nicotine gum (chew and park for 30 minutes) or placed the oral products in their mouth between the lip and gum for 30 minutes.

Figure 1. Study Design



A total of 30 subjects were randomized and 25 completed the study. All subjects reported smoking approximately one pack of cigarettes a day and had been smoking for approximately 20 years.

After controlled use:

- All of the oral products were considered less pleasant than own-brand cigarettes (Figure 2). There were no differences among the oral products. The time to the median effect was 5 minutes for own-brand cigarettes, 15 minutes for Black Buffalo Wintergreen Pouch Product, 15 minutes for Nicorette Gum and 30 minutes for Copenhagen Wintergreen Long Cut (Table 1).
- Suppression of the urge to smoke was equivalent for all of the products (Figure 3; Table 1) but the time to effect was 5 minutes for own-brand cigarettes and 15 minutes for all of the other products.
- Like pleasantness, all of the oral products were less satisfying than own-brand cigarettes (Figure 4).

Nicotine plasma levels were measured after controlled use of the products. Table 4 shows the amount of nicotine in each product and the effective nicotine dose for each product. Figure 5 shows the baseline adjusted plasma nicotine concentrations of each product and Table 3 shows the derived Nicotine parameters.

4-HOUR AD LIBITUM USE

During the 4-hour ad libitum session subjects (Table 4):

- Used a mean of 5.3 Black Buffalo Pouches for an average of 51 minutes
- Used 2.2 Copenhagen Long Cut portions for an average of 89 minutes
- Smoked a mean of 5.9 own-brand cigarettes for an average of 39 minutes
- Chewed 3.1 pieces of Nicorette gum for an average of 61 minutes

Subjects were asked if they would be willing to use the product again and rated their response on a 100-point VAS ("If given the opportunity, I would want to use this product again," where scores could range from 0 (Definitely would not) to 100 (Definitely would), and where 50 (Don't care) was the neutral point. Own-brand cigarettes were rated the highest with a score of 85 followed by Black Buffalo Pouch (67), Nicorette gum (64) and Copenhagen Long Cut (56) (Table 5).

ADVERSE EXPERIENCES

There were no adverse experiences reported following use of Black Buffalo Pouches and 4 minor adverse experiences reported following use of Copenhagen Long Cutpouches, cigarettes, or pieces of gum consumed, and the duration of use) were collected throughout each Ad Libitum Product Use Session. Subjects smoked 1 cigarette for 10 minutes (single puff every 30 seconds), chewed one piece of nicotine gum (chew and park for 30 minutes) or placed the oral products in their mouth between the lip and gum for 30 minutes.

	Controlled Product Use (Morning Sessions)						Ad Libitum Product Use (Afternoon Sessions)
Assessment	Assessment Time Points (Minutes)						
Tobacco/Nicotine Withdrawal Questionnaire	pre	5	15	30	60	90	
Direct Effects of Product Questionnaire		5	15	30	60	90	
QSU-Brief							Pre- and 10minutes post-use
Use the Product Again VAS							Pre- and 10minutes post-use

Table 1. Primary Endpoints of Urges to Smoke and Pleasant VAS

Measure Parameter Statistic	Black Buffalo Pouch (N=28)	Own-Brand Cigarette (N=26)	Copenhagen Long Cut (N=26)	Nicorette Gum 4 mg (N=27)
Urges to Smoke VAS				
Emax(controls)				
Median	17.0	15.0	28.0	23.0
TE ₅₀ (minutes)				
Median	15.0	5.0	15.0	15.0
Pleasant VAS				
Emax(controls)				
Median	56.0	92.0	54.0	52.0
TE ₅₀ (minutes)				
Median	15.00	5.00	30.00	15.00

Figure 2. Is the Product Pleasant Right Now?

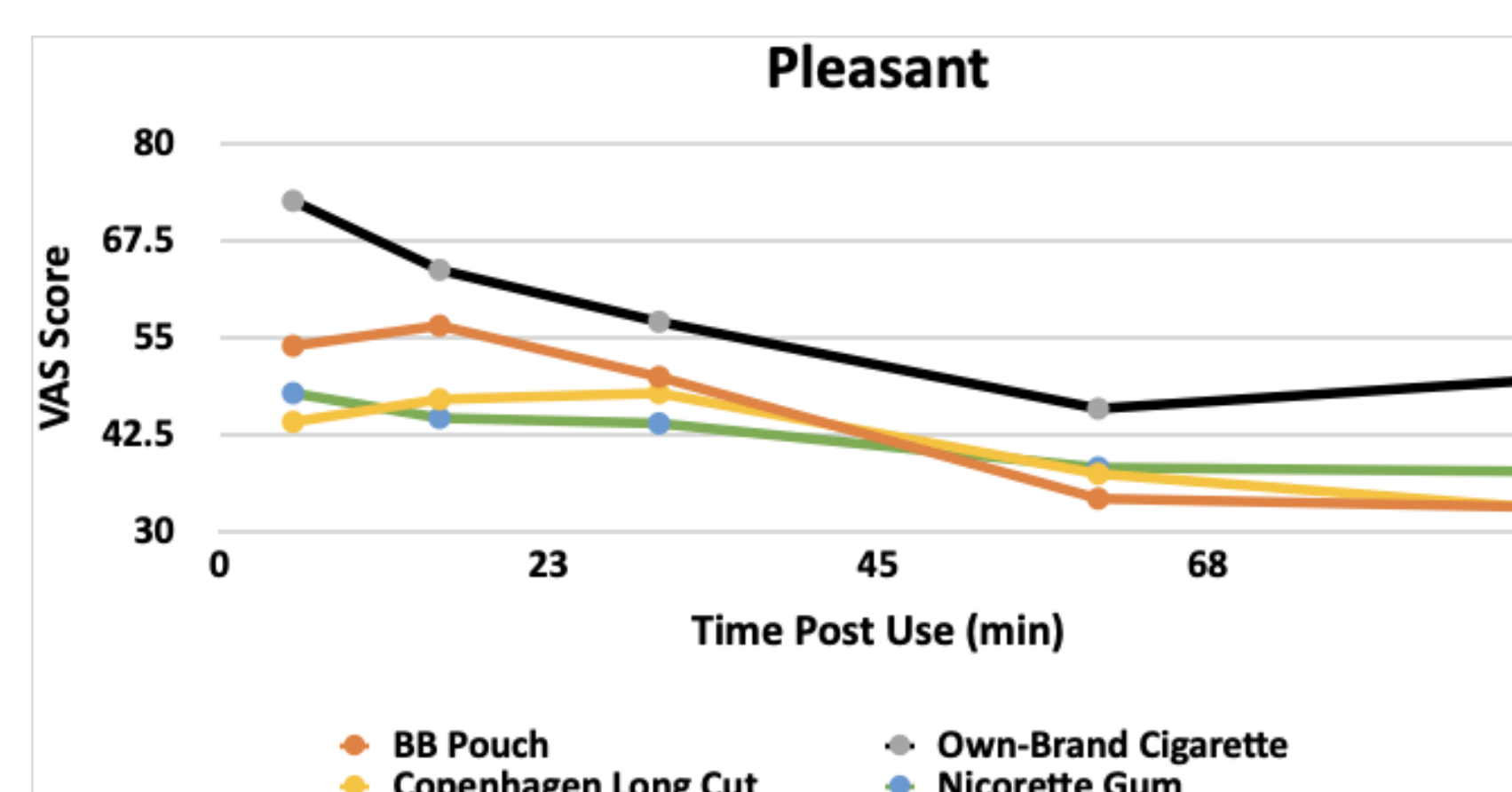


Figure 3. Urges to Smoke

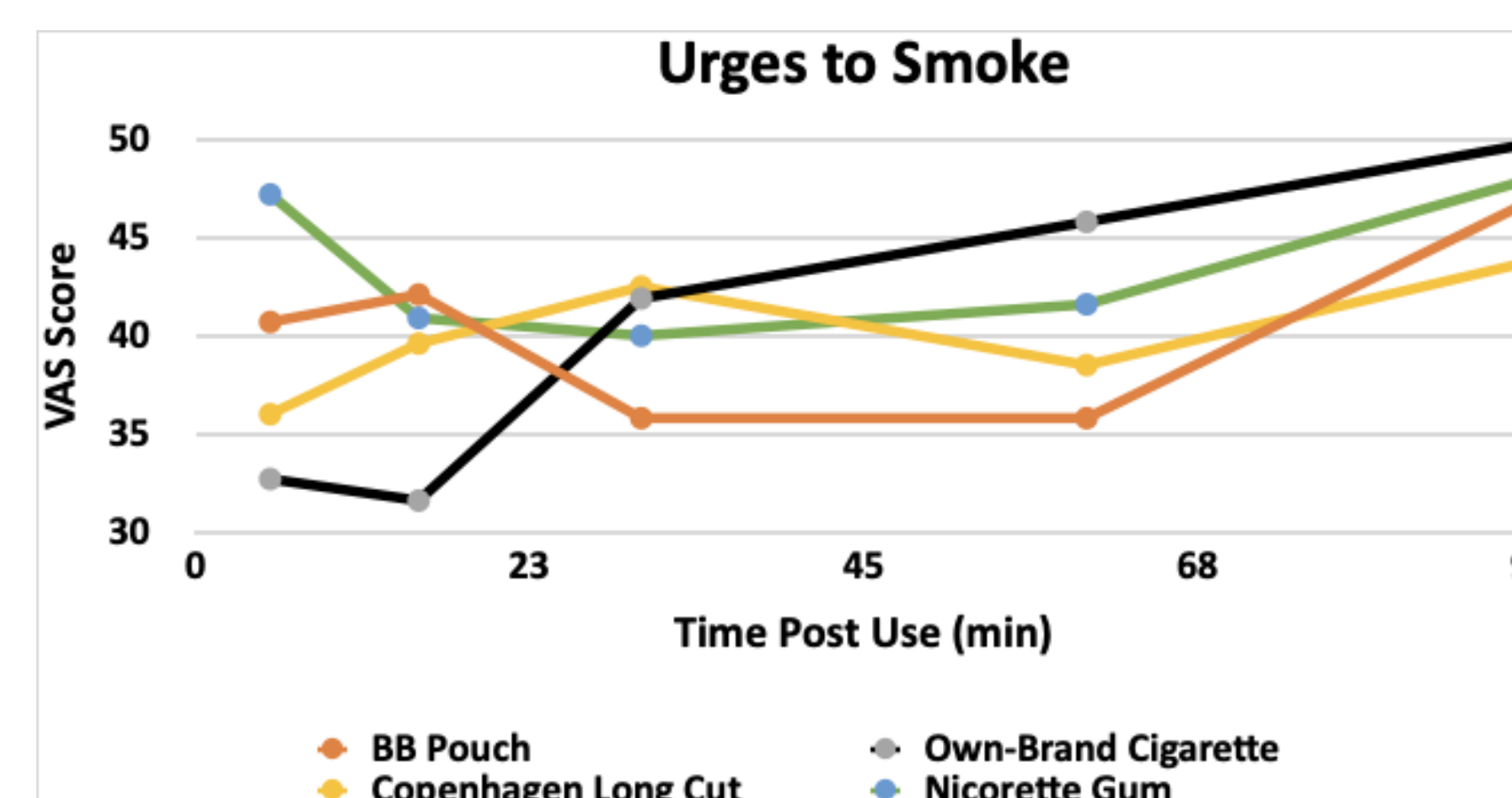


Figure 4. Is the Product Satisfying Right Now?

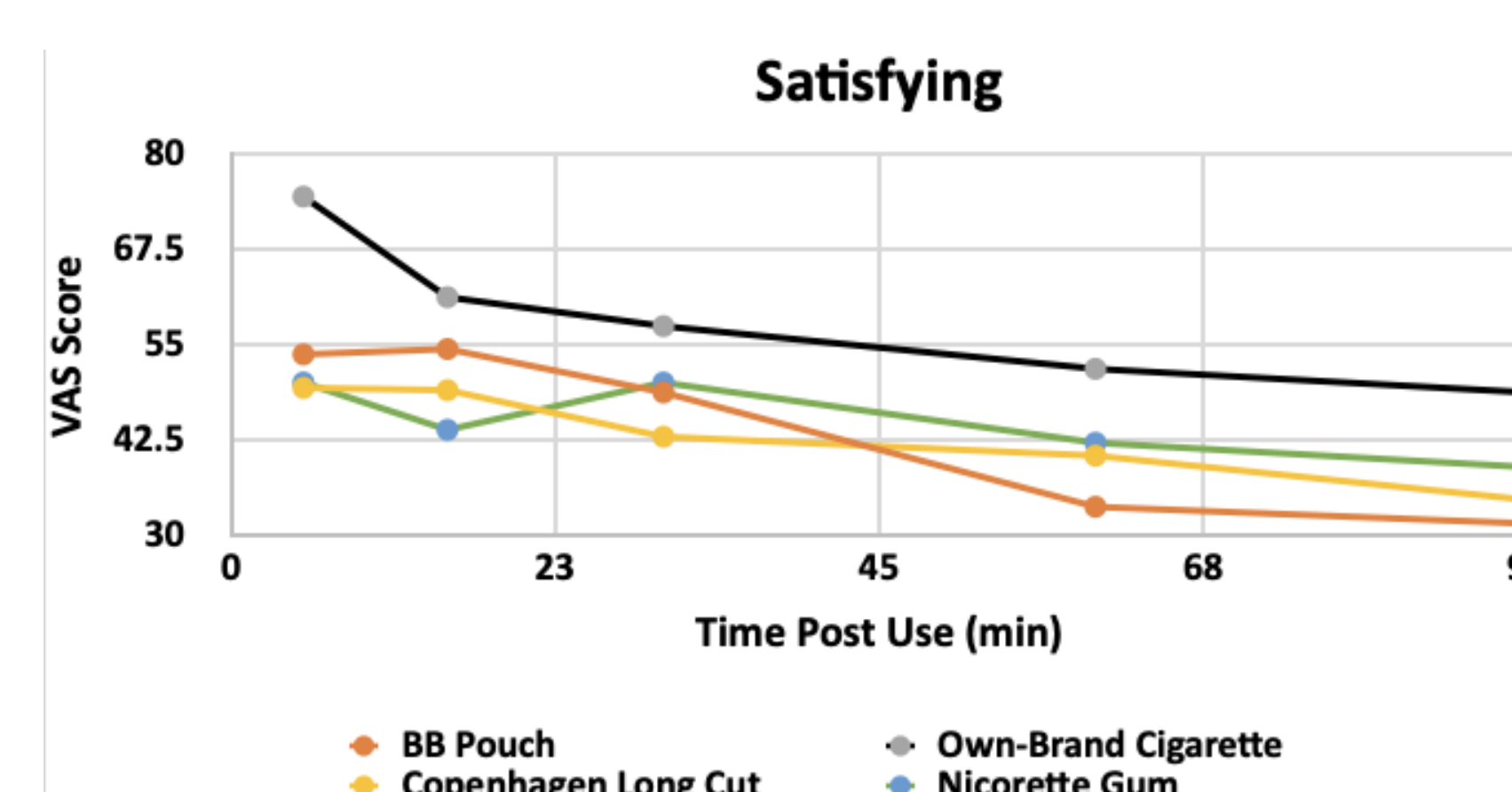


Table 2. Product Nicotine Dose

Product	mg/g product or pouch Mean (SD)	Product Dose**	Nicotine Dose (mg)*
Black Buffalo Wintergreen Pouches	9.28 (0.74)	1 pouch	9.28
Copenhagen Long Cut Wintergreen	9.58 (0.12)	2 g	19.16
Nicorette Gum	4 (-)	1 piece	4
Product	mg/g product or pouch Mean (SD)	Product Dose**	Nicotine Dose (mg)*

Figure 3. Baseline Adjusted Plasma Nicotine Levels

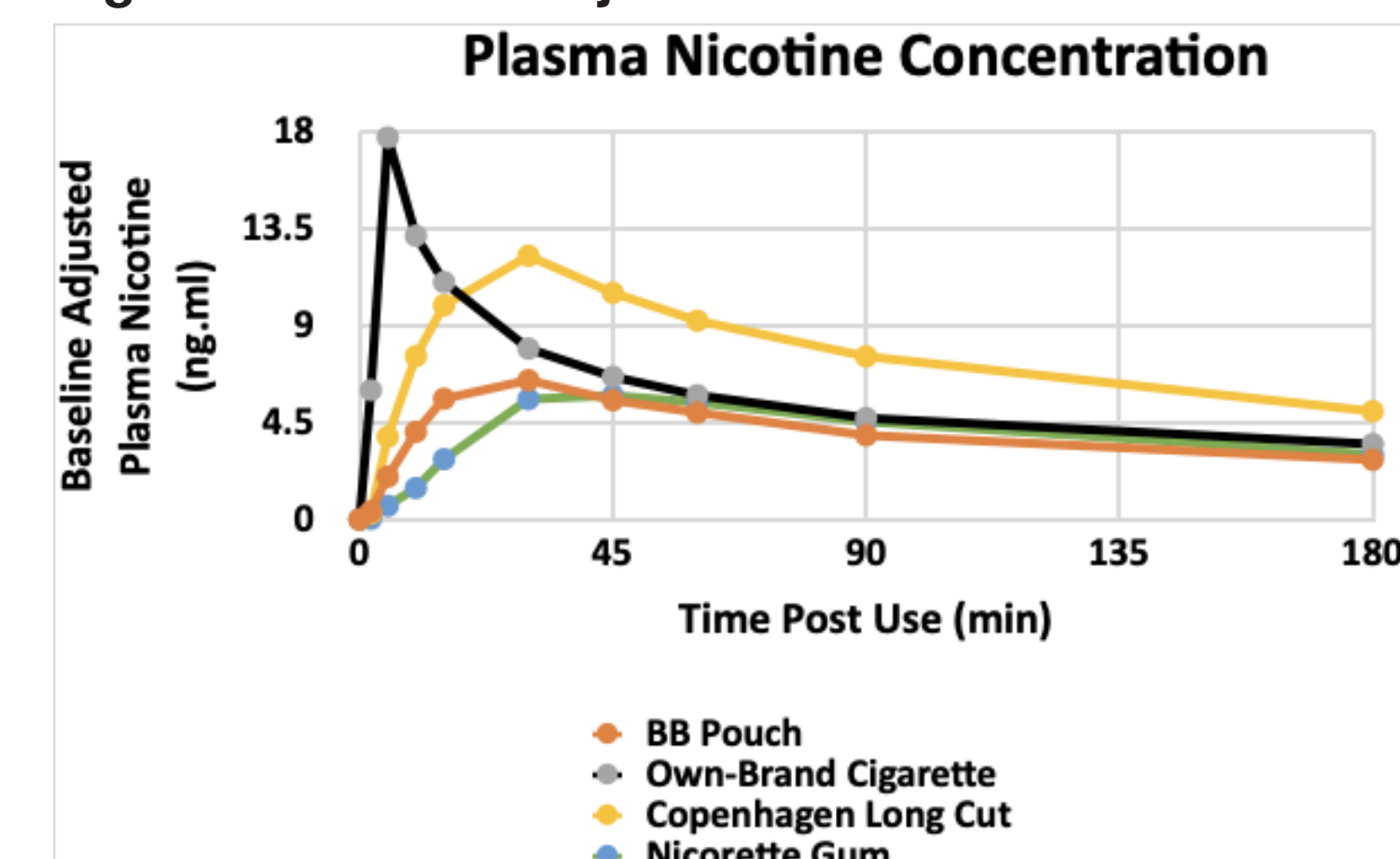


Table 3. Baseline-Adjusted Derived Parameters for Plasma Nicotine

Parameter Statistic	Black Buffalo Pouch (N=28)	Own-Brand Cigarette (N=27)	Copenhagen Long Cut (N=24)	Nicorette Gum 4 mg (N=27)
C _{max} (ng/mL)				
Mean (SD)	7.069 (3.181)	19.592 (16.086)	13.226 (5.519)	6.607 (3.118)
T _{max} (minutes)				
Median	30.06	5.47	30.30	45.00
AUC ₀₋₉₀ (ng*min/mL)				
Mean (SD)	723.902 (251.342)	1077.539 (402.294)	1389.918 (513.750)	765.114 (331.536)

Table 4. Summary of Product Use Behavior During the Ad Libitum Use Sessions (PD Population)

Parameter Statistic	Black Buffalo Pouch (N=28)	Own-Brand Cigarette (N=26)	Copenhagen Long Cut (N=26)	Nicorette Gum 4 mg (N=27)
Number of Products Used				
Mean (SD)	5.3 (4.47)	5.9 (2.19)	2.2 (1.01)	3.1 (1.79)
Total Weight of Portions (grams)				
Mean (SD)	-	-	8.597 (9.4656)	-
Average Time in Mouth (minutes)				
Mean (SD)	50.6 (33.6)	39.1 (13.2)	89.2 (52.0)	60.9 (37.9)

Table 5. Use the Product Again VAS – Ad Libitum Use

Measure Parameter Statistic	Black Buffalo Pouch (N=28)	Own-Brand Cigarette (N=26)	Copenhagen Long Cut (N=26)	Nicorette Gum 4 mg (N=27)
Mean (SD)	66.8 (25.44)	85.1 (21.8)	55.7 (28.78)	63.5 (28.45)
Median	72.0	99.0	50.5	61.5

CONCLUSIONS

The Black Buffalo Wintergreen Pouch Product:

- ✓ Was not as satisfying or pleasant as own-brand cigarettes
- ✓ Suppressed the urge to smoke equivalent to cigarettes and Copenhagen Wintergreen Long Cut and slightly better than Nicorette gum
- ✓ Suppression of urge to smoke took longer with the oral products compared to cigarettes
- ✓ Nicotine absorption is less than and substantially slower than cigarettes and is similar to Copenhagen Wintergreen Long Cut
- ✓ Lower abuse liability compared with cigarettes and similar abuse liability compared with Copenhagen Wintergreen Long Cut and Nicorette gum

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