

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

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ABSTRACT

Black Buffalo Inc. (BB) 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 TSNA's 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 products. The potential abuse liability of Black Buffalo Wintergreen Long Cut (BBLC) 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 oral product, 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 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. BBLC peaked at 30 minutes at a concentration of 14.3. 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 BBLC is less than and substantially slower than own-brand cigarettes and similar to CLC. The results demonstrated that BBLC has a lower abuse liability than own-brand cigarettes but equivalent to CLC.

OBJECTIVE

Determine the potential abuse liability of Black Buffalo Wintergreen Long Cut 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 TSNA's and PAHs found in traditional MST products. 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 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).



TEST PRODUCTS

ct A: Black Buffalo Smokeless Tobacco Alternative Long Cut, Wintergreen flavor
Product B: Own-brand filtered standard cigarette, regular or menthol flavor
Product C: Copenhagen Long Cut, Wintergreen flavor
Product D: Nicotine polacrilex gum, 4 mg, Nicorette White Ice Mint flavor
The subjects were provided 2 g of Long Cut product (both BB and Comparator product), smoked one cigarette and chewed on piece of gum under controlled conditions.

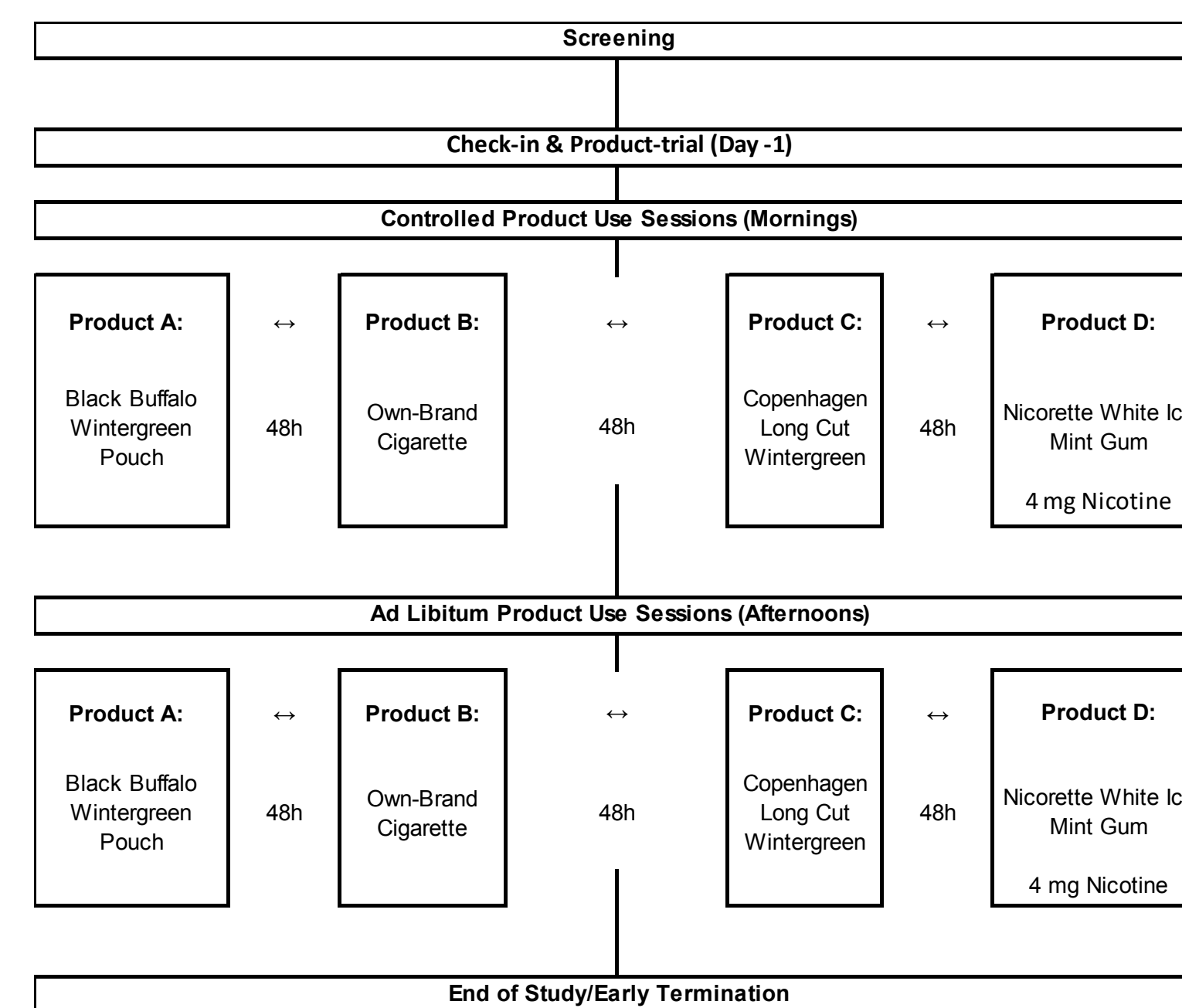
METHODS

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 Long Cut, 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 2). Each studyday 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 (using the 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 (Table 1). Product use behaviors (i.e., the number of quids, cigarettes, or pieces of gum consumed, and the duration Subjects used the products in the mouth were collected throughout each Ad Libitum Product Use Session. Subjects smoked 1 cigarette for ten 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.

Study Design



RESULTS

CONTROLLED USE

A total of 30 subjects were randomized and 25 completed the study. The subjects smoked approximately one pack of cigarettes a day and had been smoking for approximately 20 years. After use, the subjects were asked a number of subjective questions.

- All of the oral products were considered less pleasant than own-brand cigarettes (Figure 1). There were no differences among the oral products. The time to the median effect was 5 minutes for own-brand cigarettes, 15 minutes for BB Wintergreen Long Cut, 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 2; Table1) 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 3). Nicotine plasma levels were measured after controlled use of the products. Table 2 shows the amount of nicotine in each product and the effective nicotine dose for each product. Figure 4 shows the baseline adjusted plasma nicotine concentrations of each product. Table 3 lists the nicotine pharmacokinetic values.

4-HOUR AD LIBITUM USE

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

- Used 2.7 portions of Black Buffalo Wintergreen Long Cut for an average time of 83 minutes
 - Used 2.2 Copenhagen Wintergreen Long Cut portions for an average time of 89 minutes
 - Smoked a mean of 5.9 own-brand cigarettes for an average time of 39 minutes
 - Chewed 3.1 pieces of Nicorette gum for an average time of 61 minutes
- Subjects were asked if they would use the product again indicating that the product was pleasant and satisfying. Own-brand cigarettes were rated the highest with a score of 85 followed by Nicorette gum (64), Copenhagen Long Cut (51), and BB Long Cut (49).

ADVERSE EXPERIENCES

There was a single adverse experience with Black Buffalo Wintergreen Long Cut Product – a swollen lip. Copenhagen Long Cut had four adverse experiences including headache, nasal discomfort, increased blood glucose, and hiccup.

Figure 1. Is the Product Pleasant Right Now?

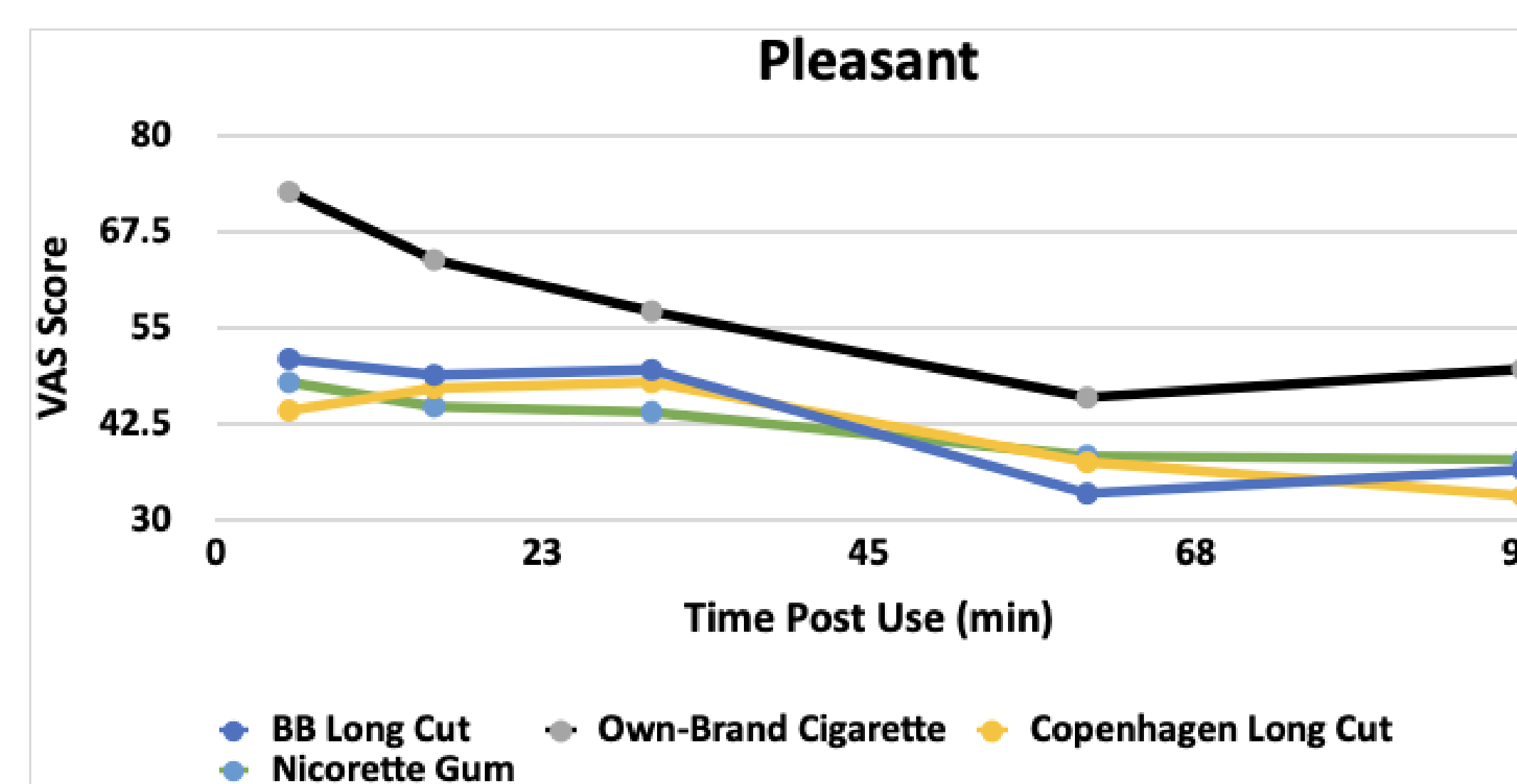


Table 1. Primary Endpoints of Urges to Smoke and Pleasant VAS

Measure Parameter Statistic	Black Buffalo Long Cut (N=27)	Own-Brand Cigarette (N=28)	Copenhagen Long Cut (N=26)	Nicorette Gum (N=27)
Urges to Smoke VAS				
Emax(controlled)				
Median	19.0	15.0	28.0	23.0
TEmin (minutes)				
Median	15.0	5.0	15.0	15.0
Pleasant VAS				
Emax(controlled)				
Median	60.0	92.0	54.0	52.0
TEmax (minutes)				
Median	15.00	5.00	30.00	15.00

Figure 2. Urges to Smoke

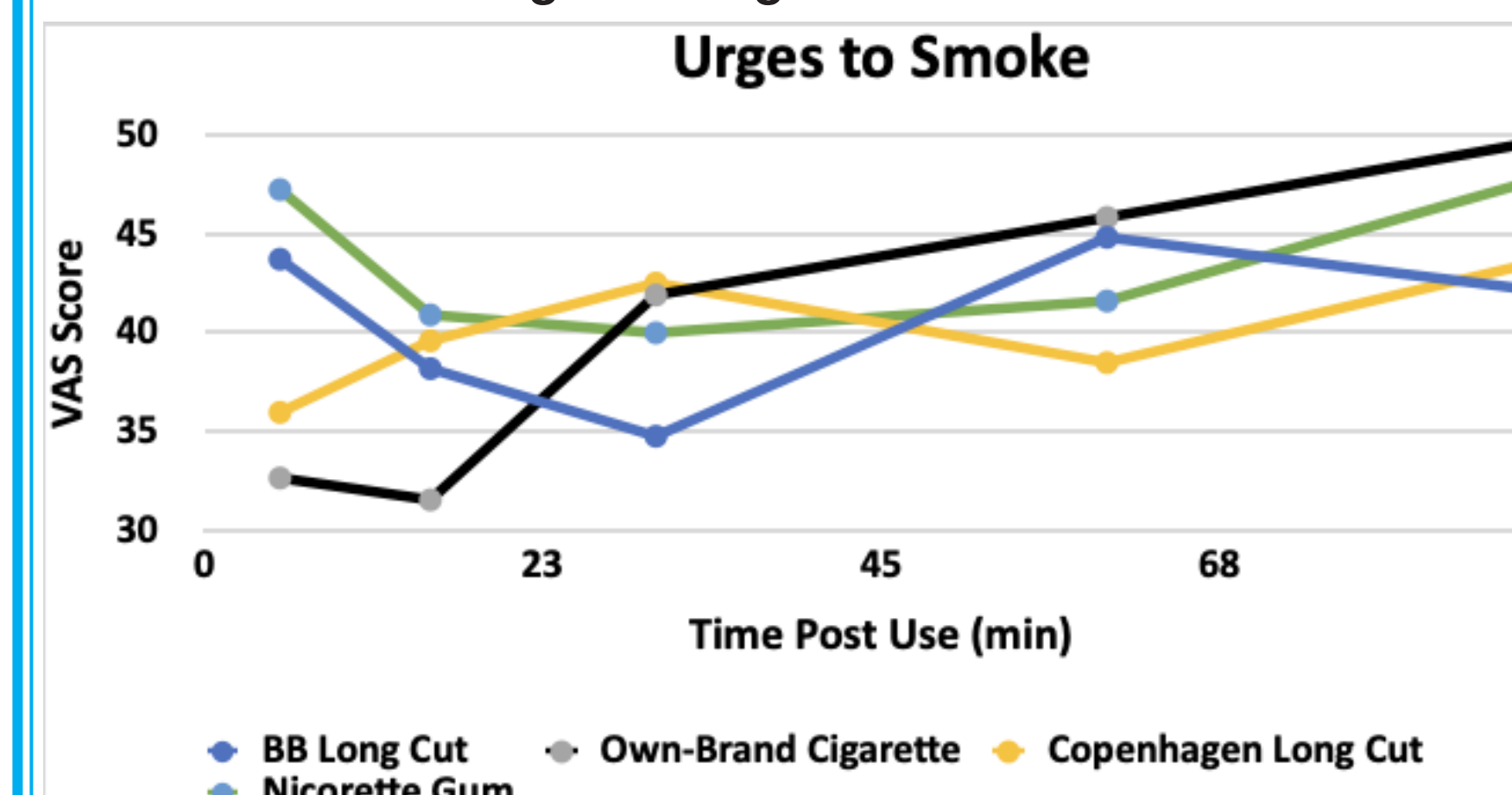


Figure 3. Is the Product Satisfying Right Now?

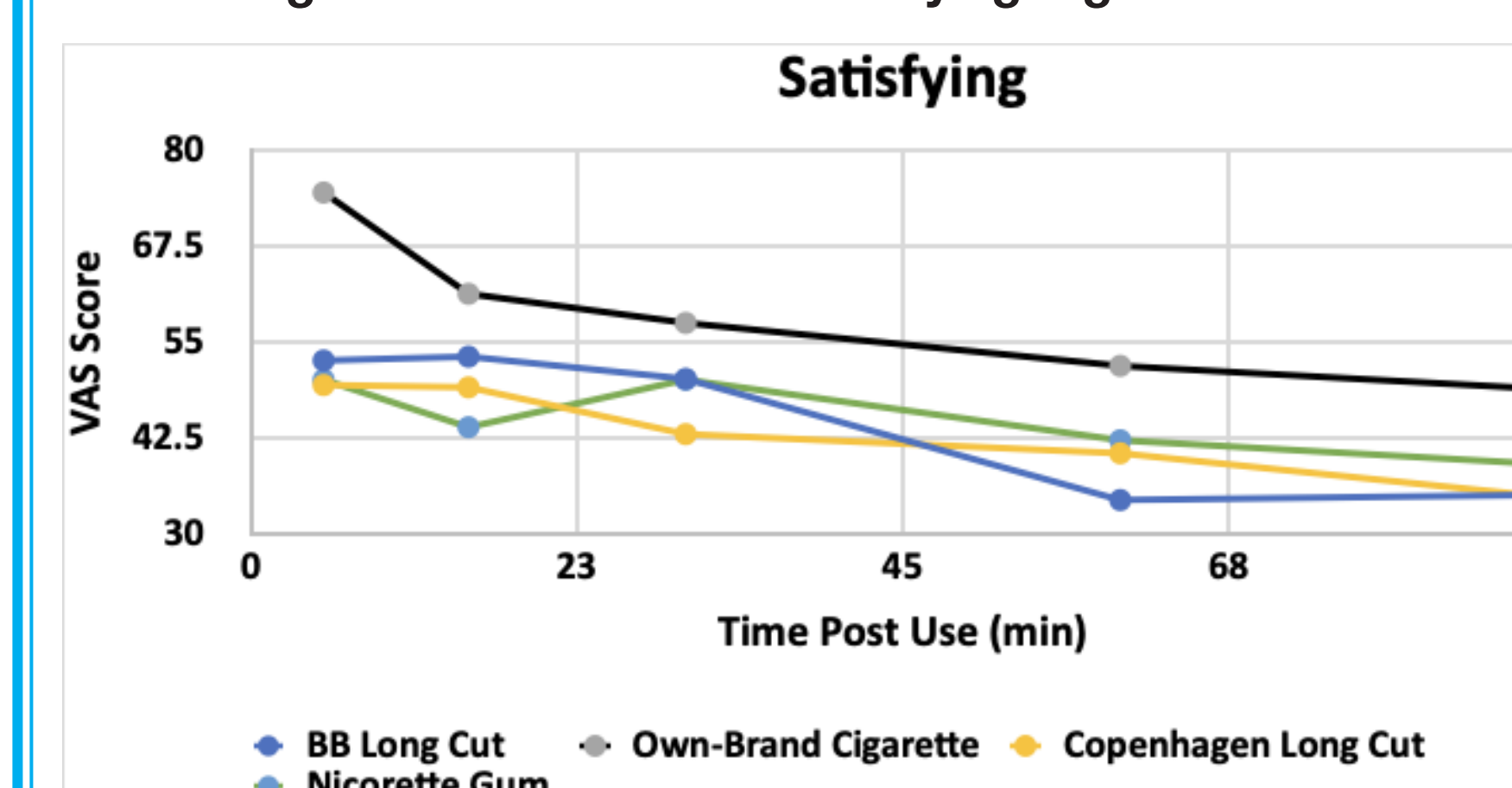


Table 2. Product Nicotine Dose

Product	Total Nicotine (mg/g product Mean (SD))	Product Dose**	Nicotine Dose (mg)*
Black Buffalo Wintergreen Long Cut	7.25 (0.15)	2 g	14.5
Copenhagen Long Cut Wintergreen	9.58 (0.12)	2 g	19.16
Nicorette Gum	4 (-)	1 piece	4

Figure 4. Baseline Adjusted Plasma Nicotine Levels

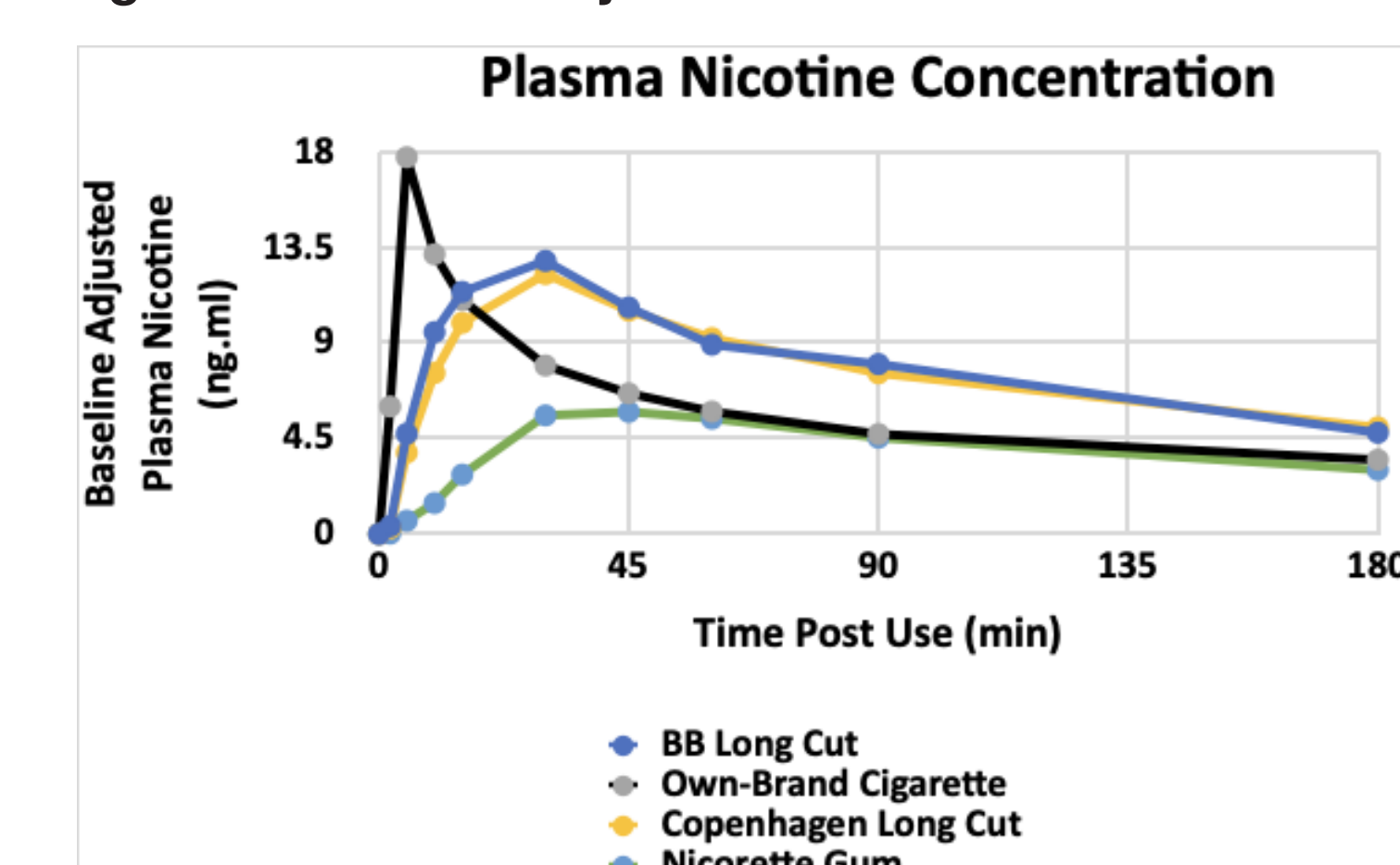


Table 3. Baseline-Adjusted Derived Parameters for Plasma Nicotine

Parameter Statistic	Black Buffalo Long Cut (N=26-27)	Own-Brand Cigarette (N=27-28)	Copenhagen Long Cut (N=24-26)	Nicorette Gum 4 mg (N=27)
Cmax (ng/mL)				
Mean (SD)	14.260 (5.897)	19.592 (6.086)	13.226 (5.519)	6.607 (3.118)
Tmax (minutes)				
Median	29.88	5.47	30.30	45.00

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

Parameter Statistic	Black Buffalo Long Cut (N=27)	Own-Brand Cigarette (N=28)	Copenhagen Long Cut (N=26)	Nicorette Gum 4 mg (N=27)
Number of Products Used				
Mean (SD)	2.7 (1.15)	5.9 (2.19)	2.2 (1.01)	3.1 (1.79)
Total Weight of Portions (grams)				
Mean (SD)	8.977 (6.7411)	-	8.597 (9.4656)	-
Average Time in Mouth (minutes)				
Mean (SD)	82.8 (42.4)	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 Long Cut (N=27)	Own-Brand Cigarette (N=28)	Copenhagen Long Cut (N=26)	Nicorette Gum 4 mg (N=27)
Mean (SD)	48.5 (27.12)	85.1 (21.81)	55.7 (28.78)	63.5 (28.45)
Median	50.0	99.0	50.5	61.5

CONCLUSIONS

The Black Buffalo Wintergreen Long Cut Product:

- Was not considered as satisfying or pleasant as own-brand cigarettes
- Suppressed the urge to smoke equivalent to cigarettes and Copenhagen Wintergreen Long Cut but slightly better than Nicorette gum
- Suppression of the 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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