

# EVALUATION OF THE ABUSE LIABILITY OF NIC NAC TOBACCO-FREE NICOTINE LOZENGES COMPARED WITH USUAL-BRAND CIGARETTES



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## Abstract

Nic Nac lozenges are small, tobacco-free nicotine oral products containing pharmaceutical grade excipients and natural flavors. This study evaluated the abuse liability of 6 different Nic Nac lozenges (3 mg and 6 mg) compared with usual-brand cigarettes (UBC) in adult smokers who had experience using oral tobacco (N=21). This randomized, open-label, 7-way crossover clinical study measured nicotine plasma concentrations, Urge to Smoke, Product Liking, Intent-to-Use Again, and product use behaviors under Controlled and Ad Libitum Use conditions. Following Controlled-Use, all Nic Nac lozenges had significantly longer T<sub>max</sub> compared to UBC, indicating slower nicotine delivery. Under both controlled and ad libitum use conditions, the 3 mg lozenge had a significantly lower C<sub>max</sub> than UBC, while C<sub>max</sub> values for the 6 mg lozenges were not statistically different from UBC. Differences in AUC values between the UBC and the lozenges were more variable. Following controlled-use, all lozenges suppressed Urge to Smoke similarly to UBC; under ad libitum use conditions, Urge to Smoke suppression was lower for lozenges than UBC. During Ad Libitum Use sessions, the mean number of lozenges used was consistent across products (~3 lozenges per session). The maximum number used was higher for the Wintergreen 3 mg lozenge (up to 10 lozenges) compared with a maximum use of 5 to 6 lozenges for the 6 mg products. In comparison, participants smoked a mean of 5, with a maximum of 9 UBCs. Mean duration of use per lozenge ranged from 43.0 to 48.0 minutes for the 6 mg lozenges and was 51.5 minutes for the 3 mg lozenge. Taken together, these findings indicate that Nic Nac 3 mg and 6 mg nicotine lozenges provide nicotine delivery and subjective effects sufficient to reduce urge to smoke, but without evidence of greater abuse liability than UBC.

## Background



Nic Nac lozenges, are small, tobacco-free oral products containing a measured dose of nicotine, pharmaceutical and food grade excipients, and flavors in a dissolvable tablet. The lozenges are offered in 9 flavor variants, consisting of 8 flavored products and one unflavored product, Classic. Each flavor is available in two nicotine strengths: 3 mg and 6 mg nicotine per lozenge.

**Purpose of Study:** To determine the abuse liability of 6 Nic Nac lozenges compared with subjects' UBC.

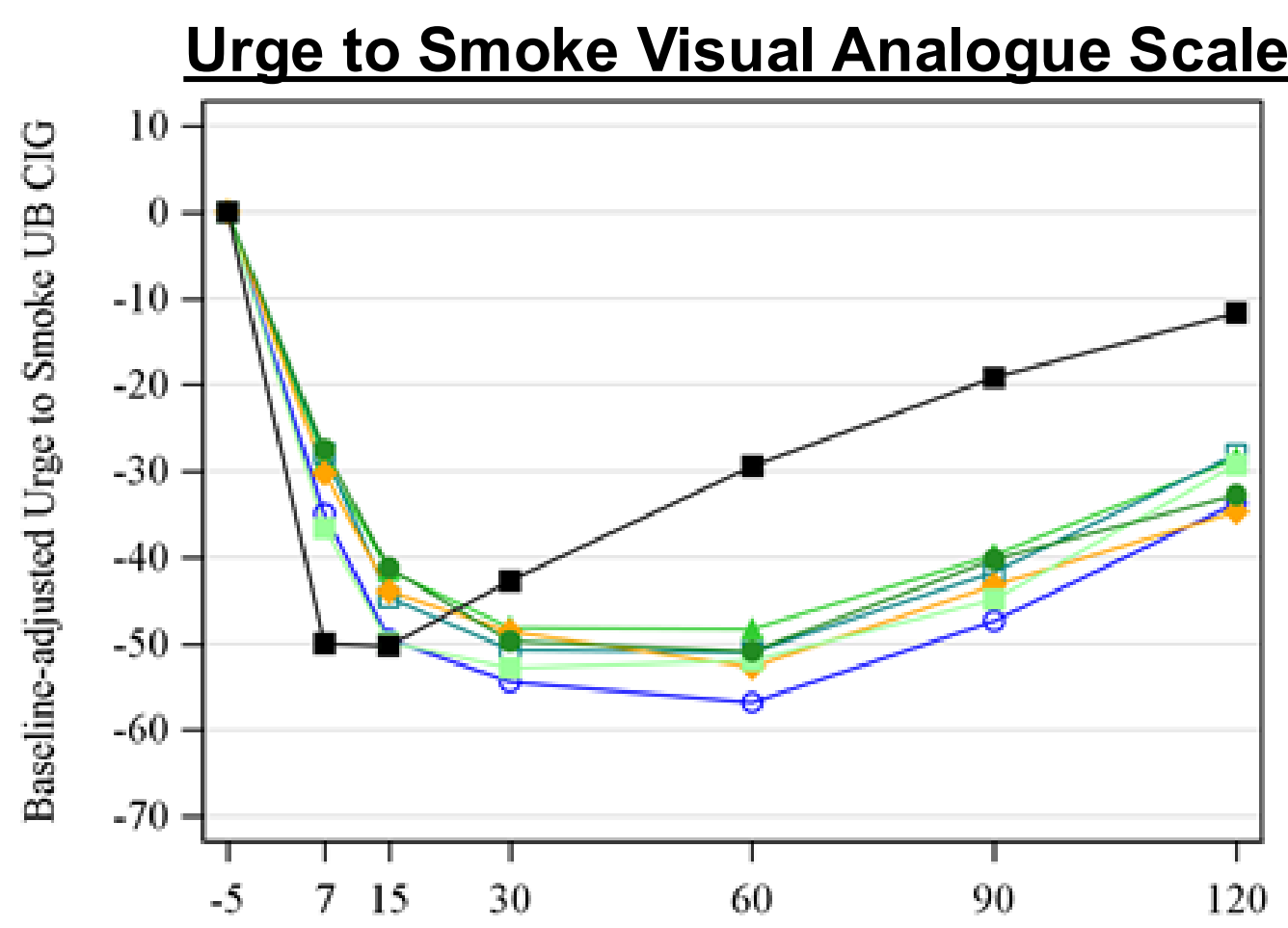
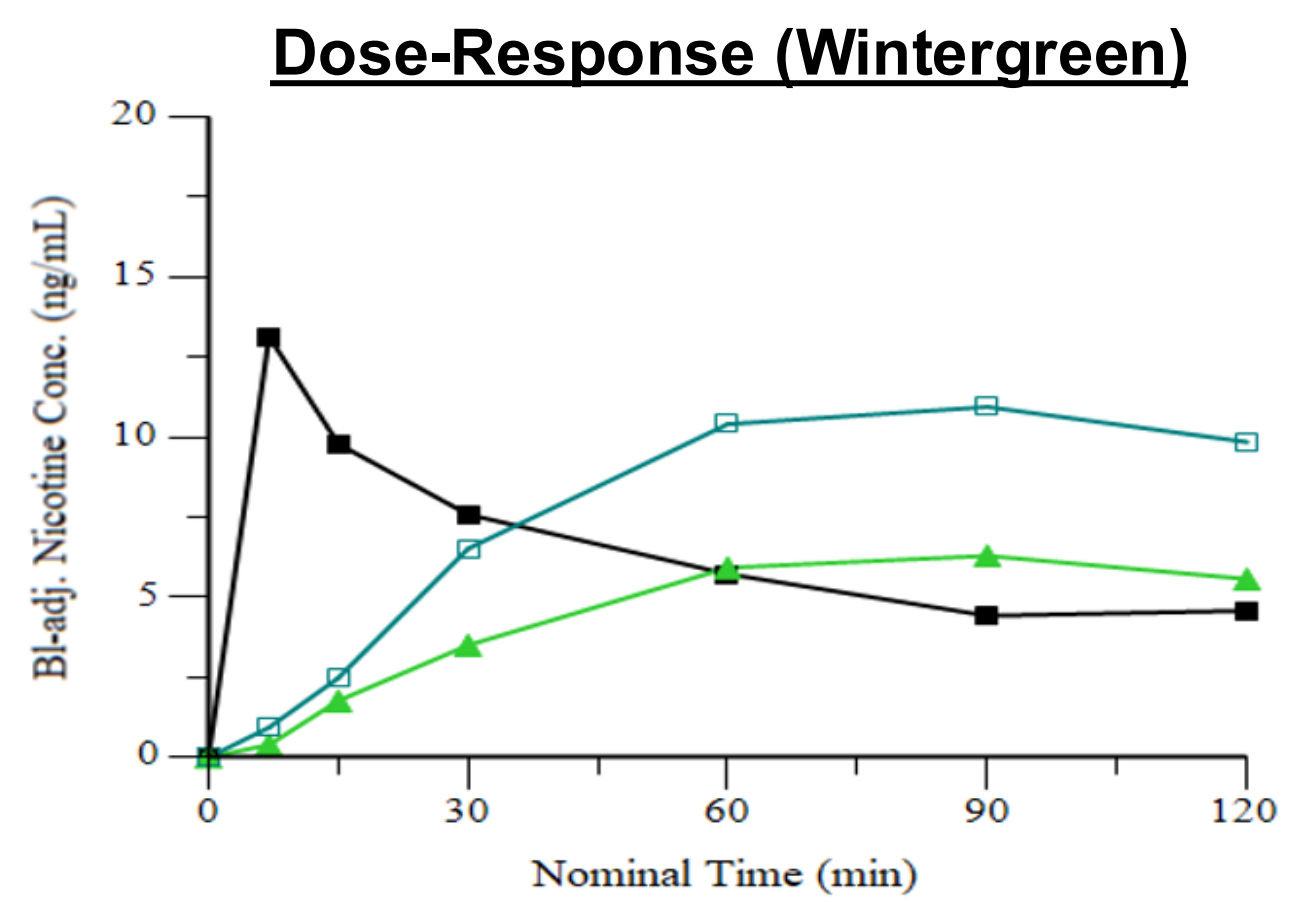
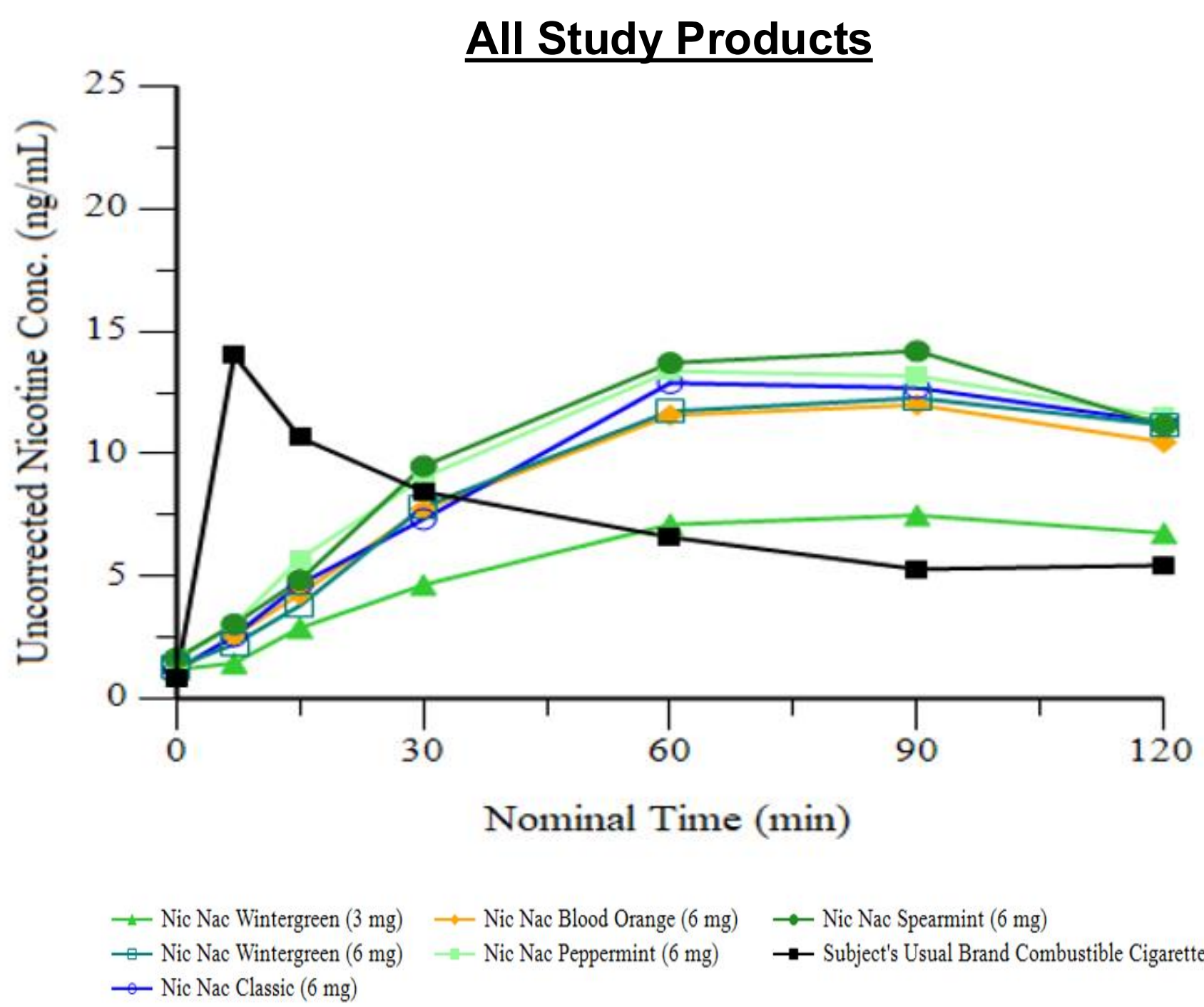
## Methods

- Overview:** In-patient partially-randomized, open-label, 7-way crossover
- Study Site:** LA Clinical Trials, Burbank, CA
- Participants:** 21 adult smokers who smoke ≥10 cigarettes daily for at least 6 months prior to screening, and self-reported lifetime use of at least 30 nicotine pouches, with use of at least one pouch in the last 30 days
- Primary Objectives:**
- To determine nicotine absorption kinetics when subjects smoke their UBC or use the study nicotine lozenges
  - To characterize subjective effects after use of their UBC or use of the study nicotine lozenges
  - To characterize the usage patterns of the study nicotine lozenges compared to subject's UBC

- Secondary Objectives:**
- To evaluate overall safety in subjects using the study nicotine pouches.
  - To characterize change in a biomarker of exposure (eCO) from the start to the end of the ad libitum period for each arm the study nicotine lozenges compared with a combustible cigarette

## Results

### Controlled Use

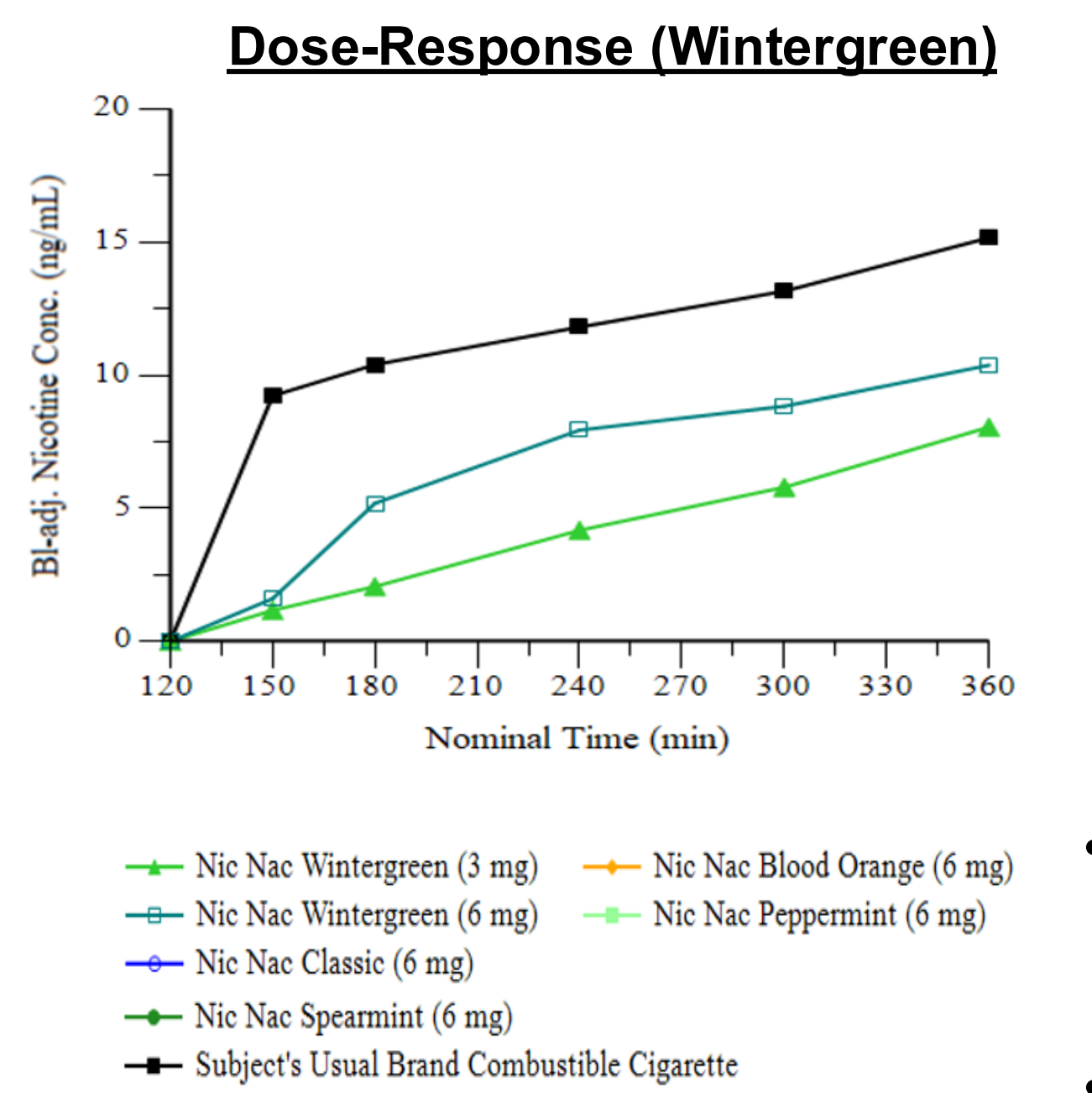
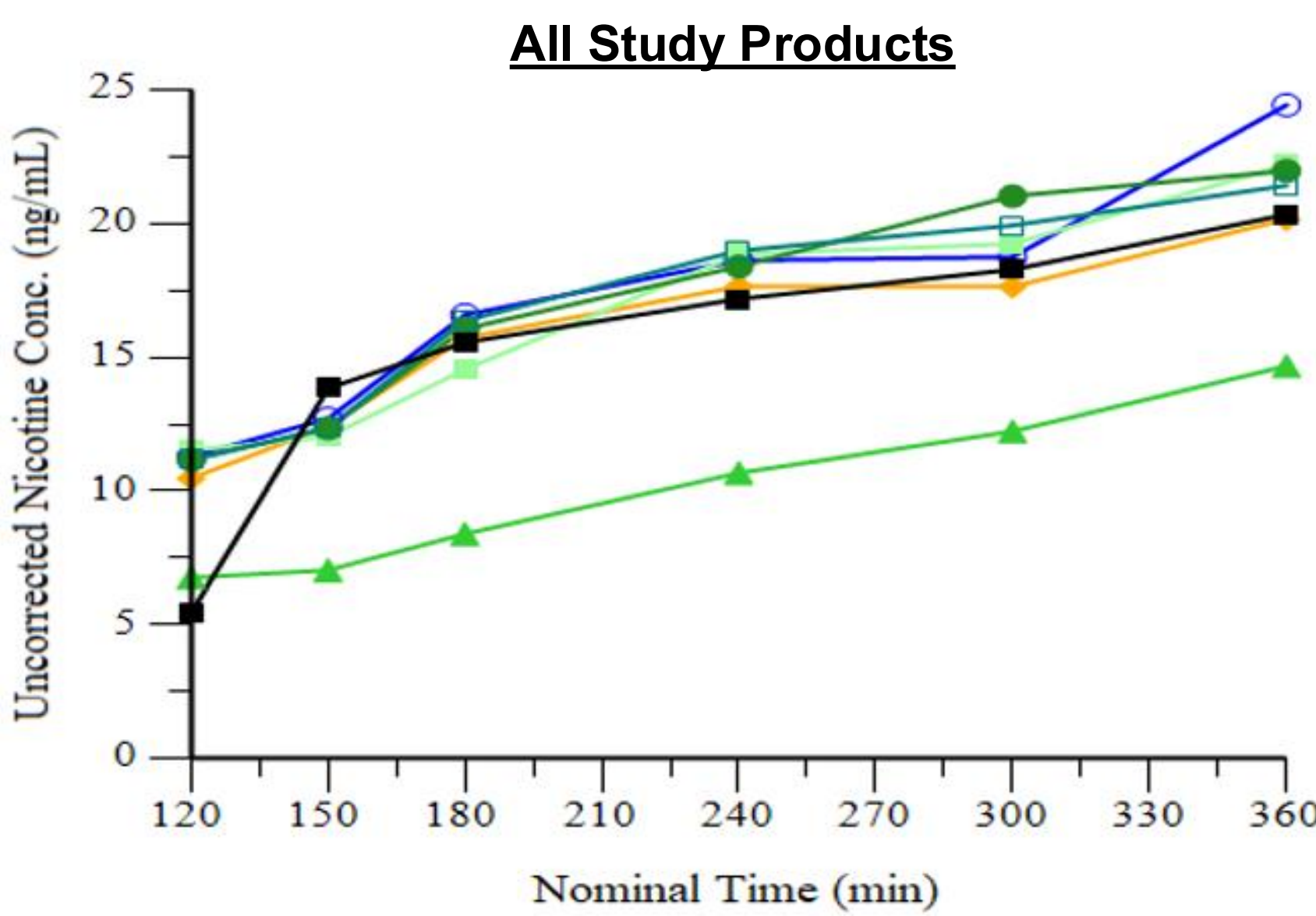


| Study Product             | Nicotine C <sub>max</sub> (ng/ml) | Nicotine T <sub>max</sub> (min) | Nicotine AUC (min*ng/mL) | Urge to Smoke E <sub>max</sub> (mm) |
|---------------------------|-----------------------------------|---------------------------------|--------------------------|-------------------------------------|
| Usual-Brand Cigarette     | 13.73                             | 7.000                           | 748.2                    | -58.0                               |
| Nic Nac Wintergreen 3 mg  | 7.480*                            | 90.00*                          | 549.9                    | -56.5                               |
| Nic Nac Wintergreen 6 mg  | 12.40                             | 90.00*                          | 968.1                    | -62.5                               |
| Nic Nac Classic 6 mg      | 12.83                             | 75.00*                          | 1033*                    | -59.0                               |
| Nic Nac Blood Orange 6 mg | 12.16                             | 90.00*                          | 972.7                    | -60.5                               |
| Nic Nac Peppermint 6 mg   | 13.69                             | 60.00*                          | 1073*                    | -65.5                               |
| Nic Nac Spearmint 6 mg    | 13.80                             | 90.00*                          | 1099*                    | -53.5                               |

\* denotes statistically significant difference from Usual-Brand Cigarette (p<0.05)

- Nic Nac Wintergreen 3 mg nicotine lozenge produced significantly lower C<sub>max</sub> compared with UBCs; Nic Nac 6 mg lozenges C<sub>max</sub> did not differ from UBC.
- AUC was significantly higher for the Classic 6 mg, Peppermint 6 mg, and Spearmint 6 mg Nic Nac nicotine lozenges compared with UBC, while total exposures for the Wintergreen 3 mg, Wintergreen 6 mg, and Blood Orange 6 mg lozenges did not differ from UBC.
- Time to C<sub>max</sub> (T<sub>max</sub>) values were significantly longer for all Nic Nac nicotine lozenges compared with UBC.
- Nic Nac nicotine lozenges reduced the Urge to Smoke similar to UBCs, but the reduction induced by the lozenges was sustained for longer.

### Ad Libitum Use



| Study Product             | Peak Nicotine (ng/ml) | Nicotine AUC (min*ng/mL) | Product Used | Per Product Use Duration (min) | Total Use Duration (min) |
|---------------------------|-----------------------|--------------------------|--------------|--------------------------------|--------------------------|
| Usual-Brand Cigarette     | 18.42                 | 2680                     | 5.1          | 7.15                           | 36.4                     |
| Nic Nac Wintergreen 3 mg  | 8.280*                | 964.2*                   | 3.6          | 35.99                          | 105.8                    |
| Nic Nac Wintergreen 6 mg  | 13.15                 | 1587*                    | 3.3          | 29.82                          | 93.8                     |
| Nic Nac Classic 6 mg      | 14.22                 | 1614                     | 3.1          | 32.06                          | 93.6                     |
| Nic Nac Blood Orange 6 mg | 12.19                 | 1506*                    | 3.2          | 29.40                          | 87.2                     |
| Nic Nac Peppermint 6 mg   | 12.52                 | 1556                     | 3.2          | 32.74                          | 94.5                     |
| Nic Nac Spearmint 6 mg    | 13.52                 | 1732                     | 3.2          | 29.27                          | 89.3                     |

\* denotes statistically significant difference from Usual-Brand Cigarette (p<0.05)  
Note: No statistical comparisons of product use were conducted.

| Subjective Effects        |                                     |                     |                          |               |      |      |      |
|---------------------------|-------------------------------------|---------------------|--------------------------|---------------|------|------|------|
| Study Product             | Urge to Smoke E <sub>max</sub> (mm) | Product Liking (mm) | Intent to Use Again (mm) | PES Subscales |      |      |      |
|                           |                                     |                     |                          | S             | PR   | A    | R    |
| Usual-Brand Cigarette     | -43.5                               | 89.5                | 93.5                     | 6.38          | 4.80 | 1.38 | 5.60 |
| Nic Nac Wintergreen 3 mg  | -33.0                               | 66.5                | 56.0                     | 4.63          | 3.80 | 1.00 | 4.10 |
| Nic Nac Wintergreen 6 mg  | -30.5                               | 65.0                | 57.0                     | 4.00          | 4.10 | 1.63 | 4.60 |
| Nic Nac Classic 6 mg      | -35.5                               | 65.0                | 50.0                     | 4.25          | 4.10 | 1.50 | 4.80 |
| Nic Nac Blood Orange 6 mg | -27.5                               | 68.0                | 61.0                     | 5.25          | 3.60 | 1.00 | 4.90 |
| Nic Nac Peppermint 6 mg   | -35.0                               | 62.5                | 61.0                     | 4.75          | 3.90 | 1.25 | 4.90 |
| Nic Nac Spearmint 6 mg    | -25.5                               | 50.0                | 56.5                     | 4.13          | 3.80 | 1.00 | 4.40 |

Note: PES=Product Evaluation Scale; A=aversion; PR=psychological reward; R=relief; S=satisfaction.  
No statistical comparisons were conducted for Subjective Effects outcomes.

- Nic Nac Wintergreen 3 mg nicotine lozenge produced significantly lower C<sub>max</sub> compared with UBCs, while the same metric for the 6 mg nicotine lozenges did not differ from UBC.
- The Wintergreen 3 mg, Wintergreen 6 mg, and Blood Orange 6 mg nicotine lozenges produced significantly lower AUCs compared with UBCs. Total exposures for Classic 6 mg, Peppermint 6 mg, and Spearmint 6 mg lozenges did not differ from UBC.
- Nic Nac nicotine lozenges received lower ratings for Product Liking and Intent to Use Product Again compared with UBC. Based on E<sub>max</sub>, all Nic Nac nicotine lozenges eased the Urge to Smoke less than UBC did..
- Subjects used each of the Nic Nac 6 mg nicotine lozenges to a comparable degree (mean and maximum number of lozenges and mean duration of use per unit). Subjects used a higher maximum number of the Nic Nac 3 mg nicotine lozenges for a modestly longer period of time per unit.
- eCO did not increase following use of Nic Nac nicotine lozenges, but it did increase following use of subjects' UBCs

## Conclusions

Results suggest that Nic Nac 3 mg and 6 mg nicotine lozenges have abuse liability that does not exceed that of subjects' usual brands of combustible cigarettes (UBCs), as supported by a slower nicotine absorption profile (longer T<sub>max</sub>), generally comparable or lower peak and total nicotine exposure depending on formulation, and lower Product Liking and Intent to Use Again. The lozenges also provided sustained relief of Urge to Smoke without the increase in eCO associated with combustible cigarette use.

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