# Comparison of nicotine pharmacokinetic and subjective profiles of three Modern Oral Nicotine Products and a snus product

**2024 American College of Clinical Pharmacology Annual Meeting**
**8th–10th September**

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**Figure 1**: A tobacco-free Modern Oral Nicotine Product (not to scale). This consists of a pouch containing a tobacco-free substrate, nicotine, flavour ingredients and humectants.

## 1. INTRODUCTION

Tobacco-free Modern Oral Nicotine Products (MONPs) form an expanding category of products which offer potentially reduced harm nicotine delivery (i.e., reduced levels of tobacco-associated toxicants). MONPs are pouches containing a plant-based fibre substrate along with nicotine, flavour ingredients and humectants, and they do not contain tobacco, unlike traditional oral tobacco products, nor involve combustion in their use, unlike cigarettes. In order to provide an acceptable alternative for current adult users of tobacco products, it is important to offer a range of nicotine strengths to suit different consumer preferences. This study aimed to assess the nicotine pharmacokinetic (blood plasma nicotine) and subjective effects of three MONP, Zone X #5 slim (14mg nicotine/pouch), Zone X #5 (16mg) and Zone X #6 (20mg) and compare these to a tobacco snus product (Skruf Slim Fresh #5 (16.6mg)) in adult snus or nicotine pouch users. The study also assessed adverse event and tolerability profiles of the products.

## 2. METHODS

**Study design**

This was a randomised, open-label, cross-over, confinement study in adult snus and MONP consumers, to evaluate nicotine pharmacokinetics (PK), subjective effects and short-term tolerability, following use of three MONP and a comparator snus. Figure 2 outlines the study design.

The study was approved by the Swedish Ethical Review Authority (SERA), carried out in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference of Harmonisation (ICH)/ Good Clinical Practice (GCP), European Union Clinical Trials Directive and applicable local regulatory requirements.

Twenty-seven adult snus and nicotine pouch users participated in the study, which was carried out at a single clinical site.

Clinical Trial identifier: NCT05452278 (clinicaltrials.gov).

**Study products**

Three MONP with different nicotine contents (all Cold Blast mint flavour profile): Zone X #5 slim - 14mg nicotine per pouch; Zone X #5 regular - 16mg nicotine per pouch; Zone X #6 regular - 20mg nicotine per pouch.

Snus comparator: Skruf Fresh slim - 16.6mg nicotine per pouch.

None of the study products are sold in the US.

Products were provided along with instructions for use: a pouch was to be placed between the upper lip and gum for 20min; pouches were not to be chewed or swallowed (normal swallowing of saliva was allowed).

**Study procedure**

The study followed a similar procedure to that in Chapman *et al*. (2022).

*Nicotine PK assessment*: Blood samples (approx. 4ml/sample) were collected using an indwelling venous catheter at timepoints up to 480min post-start of product use. Pre-product use samples were taken within 5min prior to the start of product use. Nicotine concentrations in the blood plasma was analysed by Lablytica AB using a validated LC-MS/MS method.

*Subjective assessment*: Subjects were asked to self-assess their experience in relation to using the products (urge to smoke (also recorded pre-dose) and satisfaction, psychological reward, aversion and relief following use) using a Product Evaluation Scale (PES) at timepoints up to 480min post-start of product use. Participant ratings were recorded using a 100mm visual analogue scale (VAS) with the anchor points printed on paper. For urge to smoke: 0mm = no urge and 100mm = extreme urge. Product satisfaction/ reward/ aversion/ relief were measured on a 7-point Likert scale (1 = not at all and 7 = extremely). The outcomes were entered into an electronic format by the study personnel.

*Short-term tolerability*: AEs (including serious AEs (SAEs)) were recorded from the start of the first product used until the follow-up phone call. Severity/ intensity was graded by the Investigator as mild, moderate or severe and assessed as unlikely, possibly or probably related to the study product. Clinically significant changes in laboratory assessments (clinical chemistry, haematology, urinalysis, pregnancy, SARS-COV-2 detection), vital signs and electrocardiograms (ECGs) were also assessed throughout.

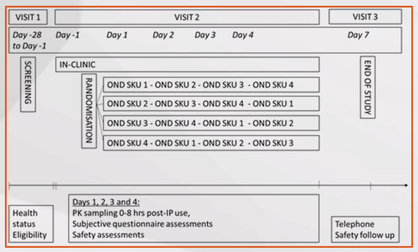



**Figure 2**: Study design overview: the four study products were randomised to 27 adult snus and nicotine pouch users for assessments across 4 days. IP = investigational product; OND = oral nicotine delivery (product) (MONP or snus); PK = pharmacokinetic; SKU = stock-keeping unit (product variant).

## 3. RESULTS

### 3.1 Nicotine pharmacokinetics

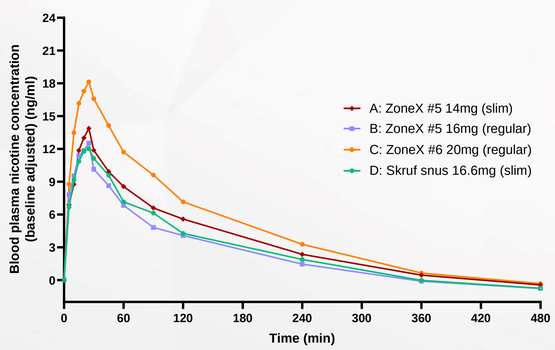



**Figure 3**: Nicotine pharmacokinetic profiles (baseline adjusted blood plasma nicotine concentrations) of the study products following the start of a 20 minute (min) controlled use period, assessed at timepoints between 0 and 480min. Values in milligrams (mg) refer to pouch nicotine content. Number of subjects per product is detailed in **Table 1**.

| Assessment (unit) | | ZoneX #5 14mg (slim) | ZoneX #5 16mg | ZoneX #6 20mg | Skruf snus 16.6mg (slim) |
|---|---|---|---|---|---|
| | n subjects | 27 | 26 | 26 | 27 |
| $C_{max}$ (ng/ml) | Mean | 14.98 | 13.43 | 19.35 | 13.85 |
| | (SD) | (4.956) | (4.967) | (6.576) | (3.853) |
| $T_{max}$ (min) | Mean | 21.66 | 22.68 | 24.24 | 27.78 |
| | (SD) | (5.89) | (9.18) | (14.76) | (19.32) |
| $AUC_{0\text{-last}}$ (h*ng/ml) | Mean | 36.48 | 31.72 | 48.44 | 32.11 |
| | (SD) | (12.72) | (9.500) | (19.68) | (9.458) |

**Table 1**: Baseline adjusted nicotine pharmacokinetic parameter outcomes for the four study products. Values in milligrams (mg) refer to pouch nicotine content. $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve from time 0 to the time of the last sampling timepoint; $C_{max}$: Maximum observed plasma concentration; h: hours; SD: standard deviation; $T_{max}$: Time to $C_{max}$.

- Use of the ZoneX #6 20mg pouch resulted in significantly higher levels of blood plasma nicotine (assessed using comparison of $C_{max}$, $AUC_{0\text{-last}}$) compared to the other three study products, which did not demonstrate significantly different blood plasma nicotine profiles to one another
- The average $C_{max}$ for ZoneX #5 slim (14mg) was slightly higher than ZoneX #5 Regular (16mg), however, this observation was not statistically significant

### 3.2 Subjective effects

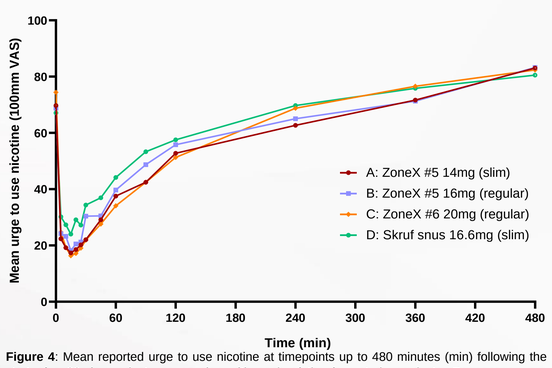
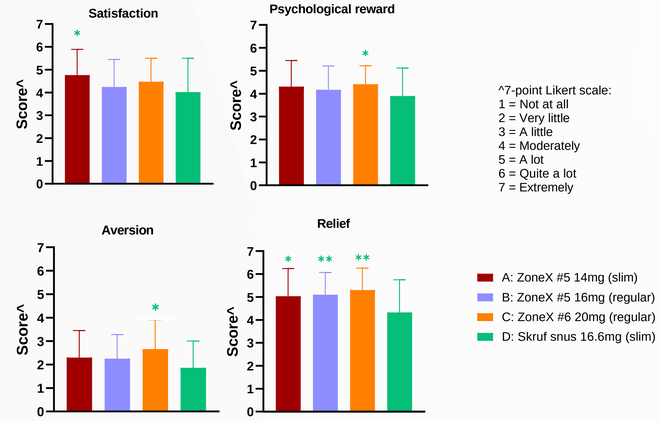



**Figure 4**: Mean reported urge to use nicotine at timepoints up to 480 minutes (min) following the start of a 20min product use session with each of the four study products. Responses were recorded according to a 100mm visual analogue scale (VAS). Values in milligrams (mg) refer to pouch nicotine content.

- For all four study products, the maximum reduction in urge to use nicotine compared to baseline (pre-administration) ($E_{max}$) was recorded 15 minutes post-administration (Figure 4)
- Although ZoneX #6 (20mg) had higher nicotine delivery compared to the other products, the $E_{max}$ values for all products were not significantly different from one another (Figure 3)
- The only significant difference observed for the $AUC_{0\text{-last}}$ was between ZoneX #5 Slim (14mg) and the Skruf snus product
- Overall, the ZoneX products appeared to perform consistently higher on the PES compared to the Skruf product (Figure 5)
- Significantly greater responses were observed for all ZoneX products for the subcategory 'Relief', and overall ZoneX #6 (20mg) resulted in the most significant increases, compared to the snus product (Figure 5)




^7-point Likert scale:
1 = Not at all
2 = Very little
3 = A little
4 = Moderately
5 = A lot
6 = Quite a lot
7 = Extremely

**Figure 5**: Average product evaluation scale (PES) scores (7-point Likert scale, detailed in the legend) in each of four categories, satisfaction, psychological reward, aversion and relief, for each of the four study products, 8 hours following the start of a 20min controlled product use session. Values in milligrams (mg) refer to pouch nicotine content. Statistical comparisons to Skruf Slim Fresh #5 were carried out using Wilcoxon signed rank tests; *p<0.05, **p<0.01.

### 3.3 Product adverse event and short-term tolerability profiles

- Single use of any of the four study products for the 20min controlled use and *ad lib* use periods, was well tolerated in the study population as assessed by AEs, clinical laboratory parameters, vital signs, and ECGs
- In total, there were 24 AEs reported by 10 of the 27 subjects who completed the study. All AEs reported were mild to moderate in intensity, and most were assessed as unlikely to be due to the use of the study product/s.
- Three AEs (headache and flatulence (x2 events)) were assessed as at least possibly related to the use of the study product/s, with the most reported AE during product use being a headache (reported by 5 subjects on 6 occasions)
- Overall, there were no safety concerns based on the evaluations undertaken

## 4. CONCLUSIONS

- Overall, the three tobacco-free MONP products delivered comparable levels and rates of nicotine delivery to adult snus/nicotine pouch users. As expected, the higher strength ZoneX #6 20mg product use resulted in significantly higher blood plasma nicotine delivery than the other study products. Delivery of nicotine is also slower than that observed for cigarettes (Chapman et al., 2022), indicating a potential for lower abuse liability
- The PK outcomes were reflected by decreases in urges to use nicotine following the start of product use, indicating satisfactory blood nicotine delivery
- The MONPs performed well compared to the snus product in terms of product satisfaction, psychological reward, aversion and relief, and therefore may be an acceptable alternative to tobacco snus for adult users
- The MONPs demonstrated good short-term tolerability profiles, with only mild to moderate adverse events observed
- In summary, the MONPs tested in this study demonstrated tobacco harm reduction potential through offering adult snus/nicotine pouch users, and adult smokers, a satisfactory alternative form of nicotine delivery

**REFERENCES**

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