

# Modern Oral Nicotine Pouches: Abuse Liability and Nicotine Pharmacokinetics Assessed in Two Randomized Crossover Clinical Studies

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# Tobacco Harm Reduction is Central to Our Company's Vision

## Our Purpose

To **reduce** the **health impact\*** of our business

A Better  
Tomorrow™

## Our Commitment

To provide **adult consumers** with a wide range of acceptable and **potentially less risky alternatives\***

\*Based on the weight of evidence and assuming a complete switch from cigarette smoking. These products are not risk free and are addictive.

# Core Principles of Tobacco Harm Reduction



“...[tobacco] harm reduction refers to minimizing harms, decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use.”<sup>1</sup>

<sup>1</sup>Institute of Medicine. 2001. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/10029>

# The Tobacco Product Risk Continuum

## Tobacco Products

Combustion

Non-Combustion

Non-  
Tobacco  
Products



\*Not to scale – for illustration purposes only

# Modern Oral Background

- Oral tobacco products range from traditional smokeless tobacco to modern oral products that contain nicotine derived from tobacco and synthetic nicotine.
- Modern oral pouched products are similar in size and shape to pouched snus but contain purified nicotine and an inert filler material, but no tobacco leaf. The nicotine, extracted and purified from tobacco leaf, is >99% pure. “
- Nicotine pouch products have substantially reduced levels of a number of harmful and potentially harmful chemicals (HPHCs), which are believed to be the primary cause of smoking-related diseases.
- These studies evaluated elements of abuse liability including subjective effects and physiological measures (pharmacodynamics [PD]) and plasma nicotine uptake (pharmacokinetics [PK]) during and following *ad libitum* use of the study investigational products (IPs) by generally healthy smokers.

# Study Investigational Products



## Study 1: Velo Pouch Products (600 mg)

### Velo Pouch Cool Mint

- 4 mg, 8 mg, and 10 mg nicotine

## Study 2: Velo Mini Pouch Products (400 mg)

### Velo Mini Pouch Cool Mint

- 4 mg & 8 mg nicotine

### Velo Mini Pouch Modern Traditions

- 4 mg & 8 mg nicotine



## Comparator Products (both studies)

**High AL:** Usual Brand combustible cigarette (UB CC)

**Low AL:** Nicorette® White Ice Mint 4 mg nicotine gum (NRT gum)

# Key Inclusion and Exclusion Criteria

## Inclusion

Generally healthy male or female, 21 to 60 years old

ECO  $\geq$  10 ppm and  $\leq$  100 ppm at Screening & Check-in

Smokes  $\geq$  10 CPD (filtered menthol or non-menthol) for at least 6 months prior to Screening

Positive urine cotinine test at Screening

Agrees to an in-clinic confinement for the study duration

Willing to use study product during the study period

Response at Screening to FTND Question 1 ("How soon after you wake up do you smoke your first cigarette?") is either "Within 5 minutes" or "6-30 minutes"

## Exclusion

Presence of any clinically significant disease, including diabetes, HIV, hepatitis B or C, or other illness or condition that would render the subject not eligible for study participation.



CPD: Cigarettes per day  
FTND: Fagerström Test for Nicotine Dependence

# Objectives and Endpoints

## Study Objectives:

Assessment of Pharmacodynamic (Subjective and Physiological) & Pharmacokinetics measures of Modern Oral nicotine pouches

### Endpoints

#### Subjective Measures

Product Liking (PL)  
AUEC,  $E_{\max}$

Product Effects (PE)  
AUEC,  $E_{\max}$

Urge to Smoke (UTS)  
AUEC,  $E_{\min}$

Overall Product Liking (OPL)  
 $E_{\text{overall PL}}$

Overall Intent to use Again (OIUA)  
 $E_{\text{overall IUA}}$

#### Pharmacokinetics

Max. plasma nicotine  
concentration  
 $C_{\max}$

Time to reach  $C_{\max}$   
 $T_{\max}$

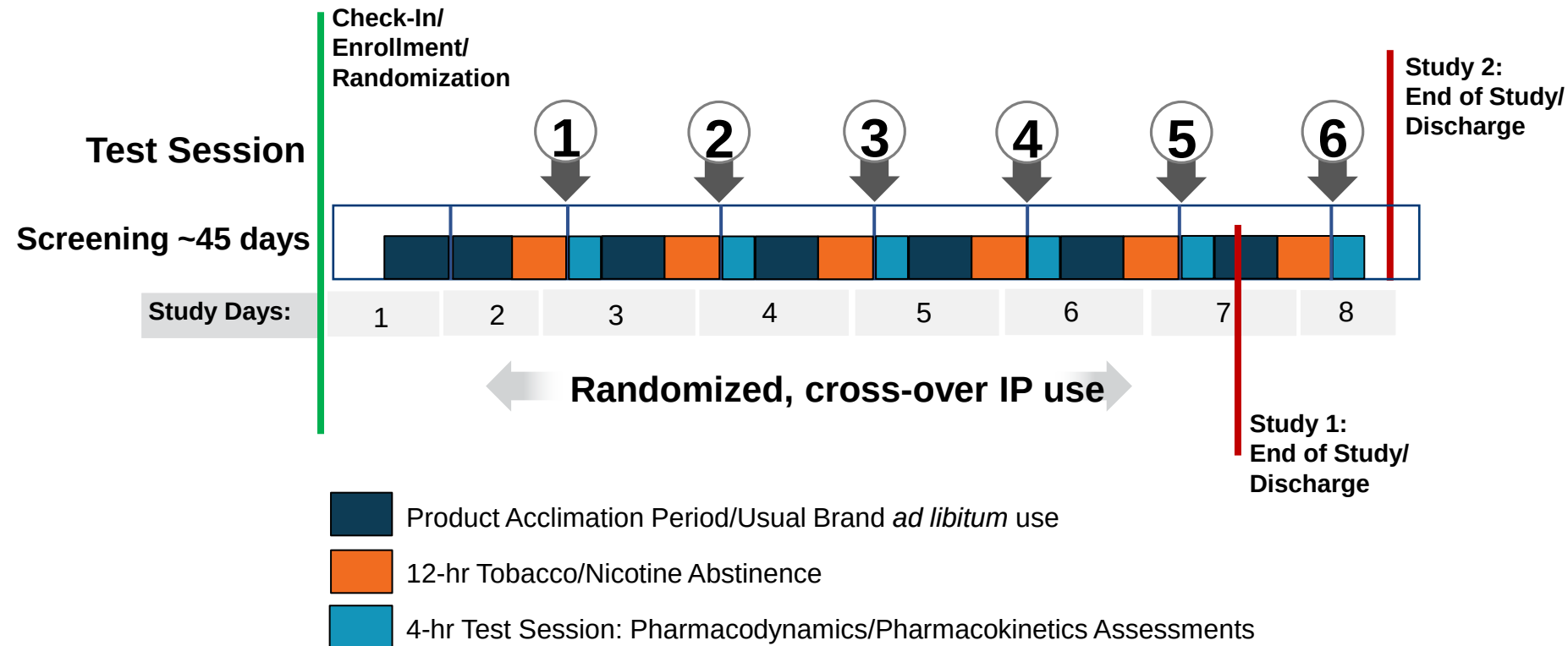
Total Nicotine Uptake  
AUC

#### Physiological Measures

Blood Pressure

Heart Rate

# Combined Study Design Overview



|                            | TIMEPOINTS (mins)* |      |   |   |    |    |    |    |    |    |    |    |     |     |
|----------------------------|--------------------|------|---|---|----|----|----|----|----|----|----|----|-----|-----|
| ASSESSMENTS                | -5**               | 0*** | 5 | 8 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 60 | 120 | 240 |
| Subjective & Physiological |                    |      | X |   | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   |
| Pharmacokinetic            | X                  |      | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   |

\*Relative to start of product use

\*\*Baseline assessment

\*\*\*Start of product use

# Participant Demographics

| Characteristic            | Study 1 Velo Pouch (n = 41) | Study 2 Velo Mini Pouch (n = 43) |
|---------------------------|-----------------------------|----------------------------------|
| Age (years)               | 42.4 ± 10.3                 | 40.6 ± 8.1                       |
| Weight (kg)               | 82.8 ± 21.1                 | 94.3 ± 22.7                      |
| Height (cm)               | 171 ± 8.1                   | 174 ± 10.6                       |
| BMI (kg/m <sup>3</sup> )  | 28.3 ± 6.6                  | 31.0 ± 6.7                       |
| <b>Gender</b>             |                             |                                  |
| Male                      | 26 (63.4%)                  | 33 (78.7%)                       |
| Female                    | 15 (36.6%)                  | 10 (23.3%)                       |
| <b>Ethnicity</b>          |                             |                                  |
| Hispanic/Latino           | 14 (34.1%)                  | 0                                |
| Not Hispanic/Latino       | 27 (65.9%)                  | 43 (100%)                        |
| <b>Race</b>               |                             |                                  |
| White                     | 32 (78.0%)                  | 28 (65.1%)                       |
| Black/African American    | 8 (19.5%)                   | 14 (32.6%)                       |
| Multiple/Other            | 1 (2.4%)                    | 1 (2.3%)                         |
| <b>Smoking Status</b>     |                             |                                  |
| Number of years smoked    | 20.9 ± 12.5                 | 23.9 ± 8.4                       |
| Cigarettes smoked per day | 15.8 ± 5.5                  | 18.0 ± 6.9                       |
| FTND score                | 6.3 ± 1.6                   | 5.9 ± 1.4                        |
| Smokers who also used ST  | 9 (22.0%)                   | 19 (44.2%)                       |

BMI: Body Mass Index FTND: Fagerström Test for Nicotine Dependence, n: number of participants, ST: smokeless tobacco; Data: mean ± SD

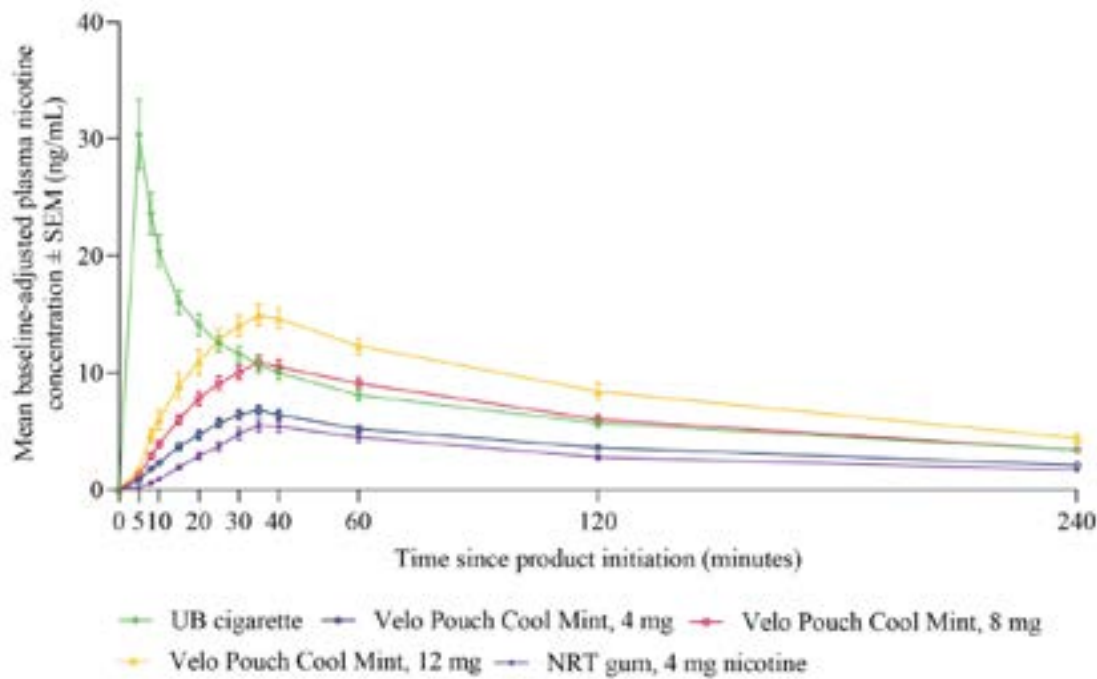


# Pharmacokinetic Results

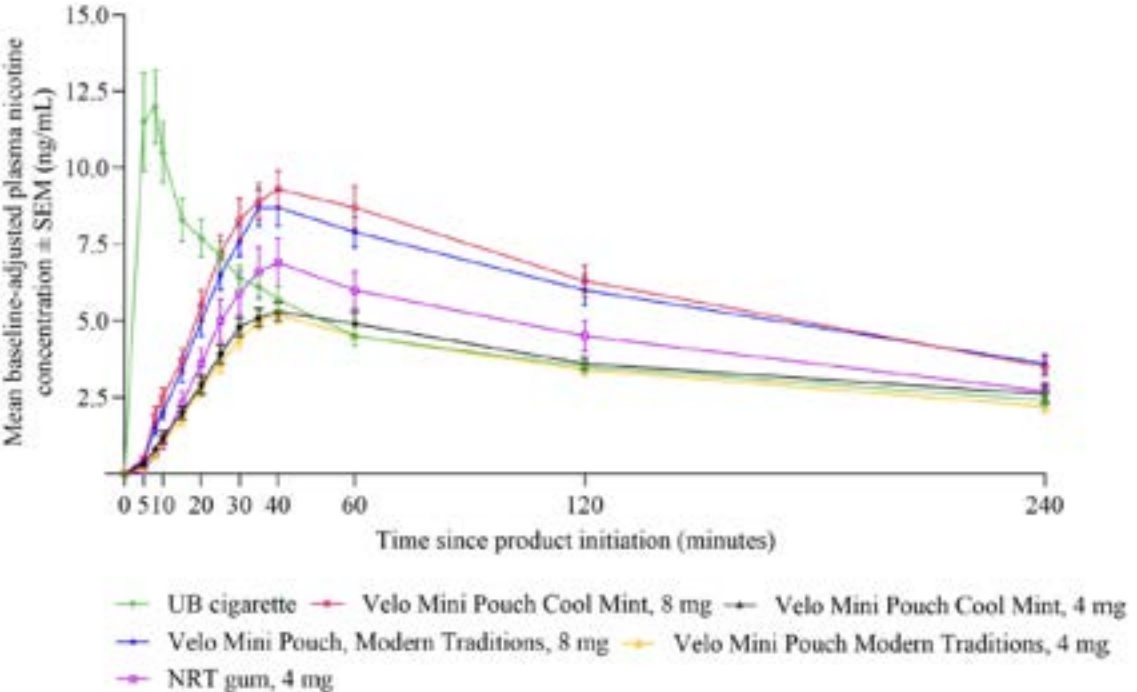


# Baseline Adjusted Plasma Nicotine Concentration verses Time

## Study 1: Velo Pouch (600 mg)



## Study 2: Velo Mini Pouch (400 mg)



UB: Usual Brand  
NRT: Nicotine Replacement Therapy

# Plasma Nicotine Pharmacokinetic Results

| Study 1: Velo Pouch AL                   |                             |                             |                              |                   |                    | Study 2: Velo Mini Pouch AL |                             |                                        |                                        |                   |                    |
|------------------------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|--------------------|-----------------------------|-----------------------------|----------------------------------------|----------------------------------------|-------------------|--------------------|
|                                          | Cool Mint<br>(4 mg)<br>n=40 | Cool Mint<br>(8 mg)<br>n=41 | Cool Mint<br>(12 mg)<br>n=40 | UB<br>cig<br>n=40 | NRT<br>gum<br>n=40 | Cool Mint<br>(4 mg)<br>n=42 | Cool Mint<br>(8 mg)<br>n=42 | Modern<br>Traditions<br>(4 mg)<br>n=42 | Modern<br>Traditions<br>(8 mg)<br>n=42 | UB<br>cig<br>n=42 | NRT<br>gum<br>n=42 |
| AUC <sub>0-15</sub><br>(ng x<br>min/mL)  | 20.3 <sup>a,b</sup>         | 35.1 <sup>a,b</sup>         | 46.8 <sup>a,b</sup>          | 268.6             | 8.2                | 9.2 <sup>a</sup>            | 20.2 <sup>a,b</sup>         | 8.4 <sup>a</sup>                       | 16.8 <sup>a,b</sup>                    | 97.8              | 7.4                |
| AUC <sub>0-240</sub><br>(ng x<br>min/mL) | 805.6 <sup>a,b</sup>        | 1305.7 <sup>a,b</sup>       | 1763.1 <sup>b</sup>          | 1680.5            | 648.2              | 791.8                       | 1304.0 <sup>a,b</sup>       | 714.3 <sup>a</sup>                     | 1221.5 <sup>a,b</sup>                  | 881.1             | 804.4              |
| C <sub>max</sub><br>(ng/mL)              | 6.6 <sup>a,b</sup>          | 10.5 <sup>a,b</sup>         | 14.8 <sup>a,b</sup>          | 27.5              | 5.2                | 5.9 <sup>a</sup>            | 9.4 <sup>b</sup>            | 5.2 <sup>a</sup>                       | 9.0 <sup>b</sup>                       | 10.8              | 5.9                |
| T <sub>max</sub> (min)                   | 35.0 <sup>a</sup>           | 35.0 <sup>a</sup>           | 35.1 <sup>a</sup>            | 5.1               | 35.0               | 40.0 <sup>a</sup>           | 40.0 <sup>a</sup>           | 39.0 <sup>a</sup>                      | 39.0 <sup>a</sup>                      | 7.0               | 39.5               |

Least-squares mean data; T<sub>max</sub> mean data; Significantly different (p<0.05) from UB cig (a) or NRT gum (b). C<sub>max</sub> maximum baseline-adjusted plasma nicotine concentration, T<sub>max</sub> time to reach C<sub>max</sub>

# Pharmacodynamic Results



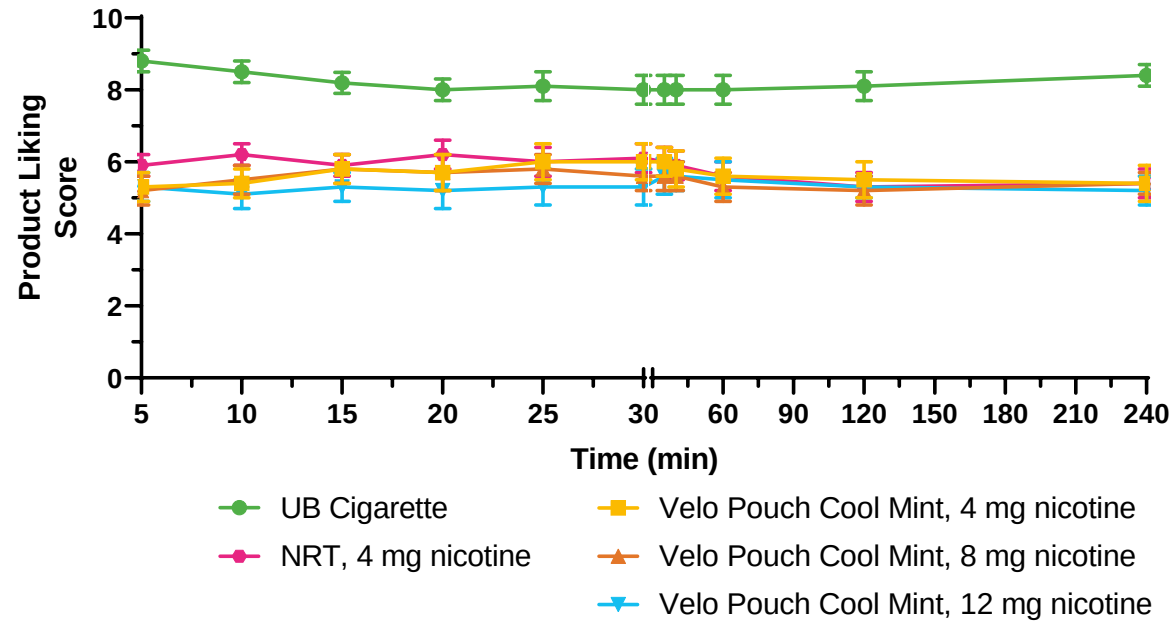
# Product Liking

Product Liking Questionnaire

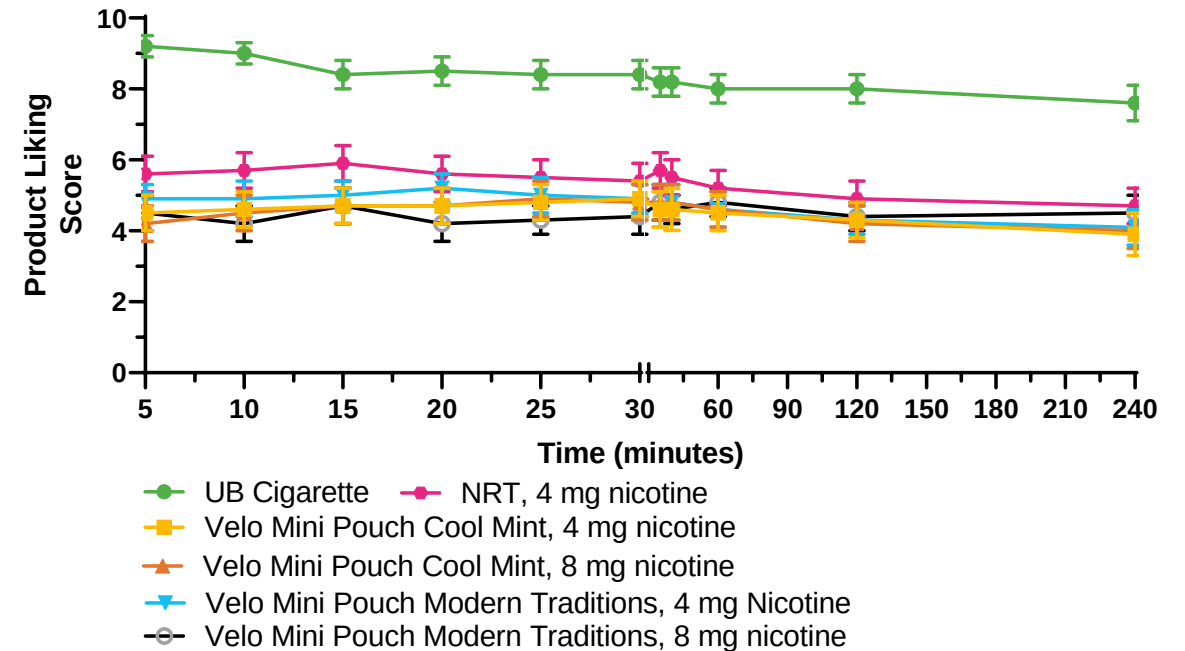
At this moment, how much do you like the product?

|                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       |
| Strongly dislike         |                          |                          |                          |                          | Neither like nor dislike |                          |                          |                          |                          | Strongly like            |

## Study 1: Velo Pouch (600 mg)



## Study 2: Velo Mini Pouch (400 mg)



# Product Liking

| Study 1: Velo Pouch AL   |                             |                             |                              |                   |                    | Study 2: Velo Mini Pouch AL |                             |                                        |                                        |                   |                    |
|--------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|--------------------|-----------------------------|-----------------------------|----------------------------------------|----------------------------------------|-------------------|--------------------|
|                          | Cool Mint<br>(4 mg)<br>n=40 | Cool Mint<br>(8 mg)<br>n=41 | Cool Mint<br>(12 mg)<br>n=40 | UB<br>cig<br>n=40 | NRT<br>gum<br>n=40 | Cool Mint<br>(4 mg)<br>n=42 | Cool Mint<br>(8 mg)<br>n=42 | Modern<br>Traditions<br>(4 mg)<br>n=42 | Modern<br>Traditions<br>(8 mg)<br>n=42 | UB<br>cig<br>n=42 | NRT<br>gum<br>n=42 |
| AUEC <sub>PL 5-240</sub> | 1297.0 <sup>a</sup>         | 1259.7 <sup>a</sup>         | 1250.9 <sup>a</sup>          | 1919.7            | 1306.9             | 1026.5 <sup>a</sup>         | 1031.9 <sup>a</sup>         | 1049.4 <sup>a</sup>                    | 1071.6 <sup>a</sup>                    | 1885.2            | 118.0              |
| E <sub>max PL</sub>      | 6.7 <sup>a</sup>            | 6.7 <sup>a</sup>            | 6.7 <sup>a</sup>             | 9.3               | 7.1                | 5.8 <sup>a</sup>            | 5.7 <sup>a</sup>            | 6.4 <sup>a</sup>                       | 6.2 <sup>b</sup>                       | 9.4               | 6.5                |

Least-squares mean data; Significantly different ( $p < 0.0042$  [Study 1];  $p < 0.0031$  [Study 2]) from UB cig (a). AUEC<sub>PL 5-240</sub> PL for 5-240 minutes after product use; E<sub>max PL</sub> the maximum PL effect after product use

# Urge to Smoke

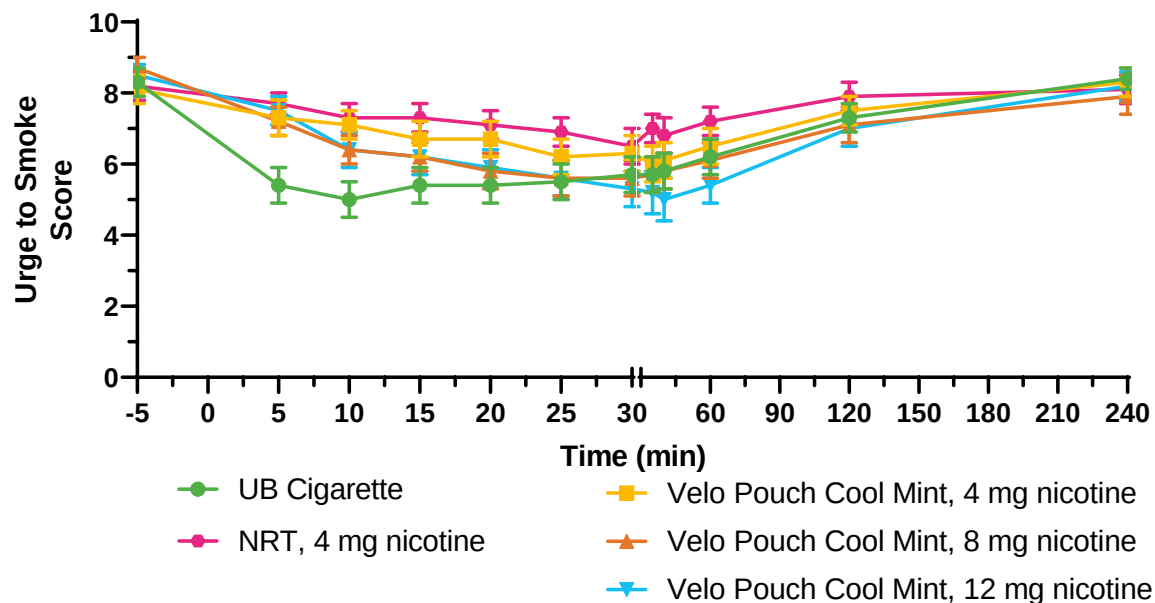
Urge to Smoke Questionnaire

How strong is your current urge to smoke your usual brand cigarette?

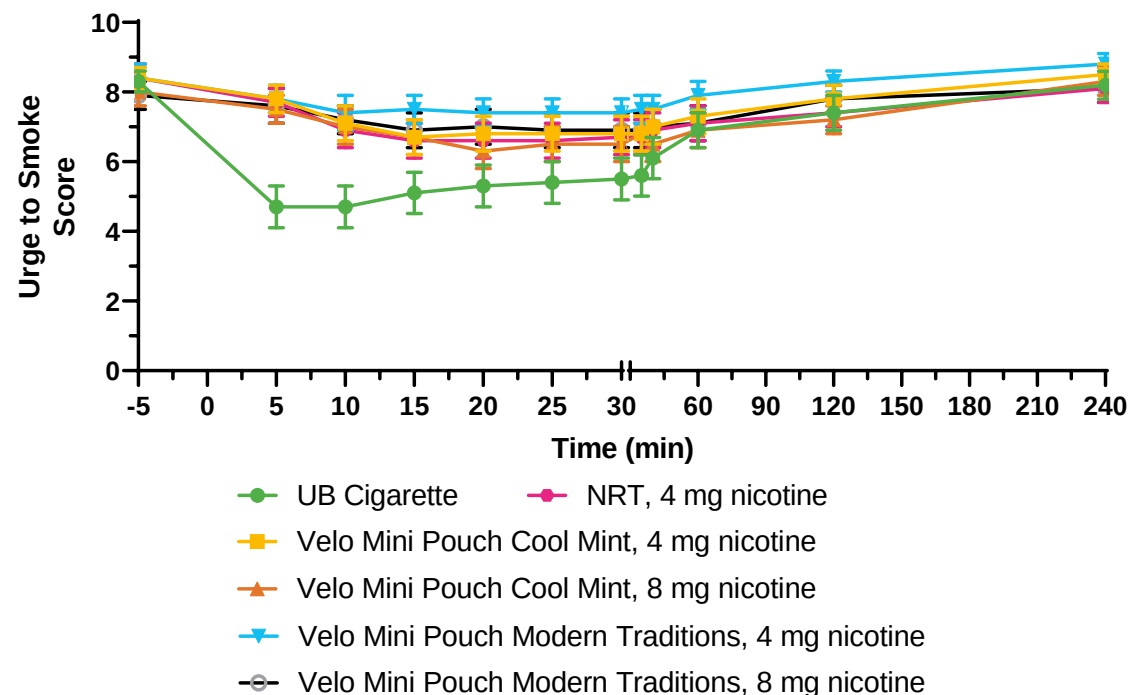
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No urge Extremely strong urge

## Study 1: Velo Pouch (600 mg)



## Study 2: Velo Mini Pouch (400 mg)



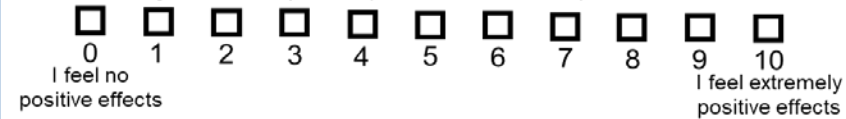
# Urge to Smoke

| Study 1: Velo Pouch AL    |                             |                             |                              |                   |                    | Study 2: Velo Mini Pouch AL |                             |                                        |                                        |                   |                    |
|---------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|--------------------|-----------------------------|-----------------------------|----------------------------------------|----------------------------------------|-------------------|--------------------|
|                           | Cool Mint<br>(4 mg)<br>n=40 | Cool Mint<br>(8 mg)<br>n=41 | Cool Mint<br>(12 mg)<br>n=40 | UB<br>cig<br>n=40 | NRT<br>gum<br>n=40 | Cool Mint<br>(4 mg)<br>n=42 | Cool Mint<br>(8 mg)<br>n=42 | Modern<br>Traditions<br>(4 mg)<br>n=42 | Modern<br>Traditions<br>(8 mg)<br>n=42 | UB<br>cig<br>n=42 | NRT<br>gum<br>n=42 |
| AUEC <sub>UTS 0-15</sub>  | 91.5 <sup>a</sup>           | 81.7 <sup>a</sup>           | 84.6 <sup>a</sup>            | 67.2              | 94.8               | 104.4 <sup>a</sup>          | 104.2 <sup>a</sup>          | 109.5 <sup>a</sup>                     | 108.3 <sup>a</sup>                     | 66.7              | 103.0              |
| AUEC <sub>UTS 5-240</sub> | 1779.7                      | 1624.0 <sup>b</sup>         | 1616.0 <sup>b</sup>          | 1667.6            | 1843.3             | 1818.0 <sup>a</sup>         | 1769.2                      | 1935.2 <sup>a,b</sup>                  | 1848.1 <sup>a</sup>                    | 1692.2            | 1759.7             |
| E <sub>min UTS</sub>      | 5.7 <sup>a</sup>            | 4.9 <sup>a,b</sup>          | 4.7 <sup>b</sup>             | 3.8               | 6.1                | 6.1 <sup>a</sup>            | 5.7 <sup>a</sup>            | 6.5 <sup>a</sup>                       | 6.2 <sup>a</sup>                       | 3.1               | 5.9                |

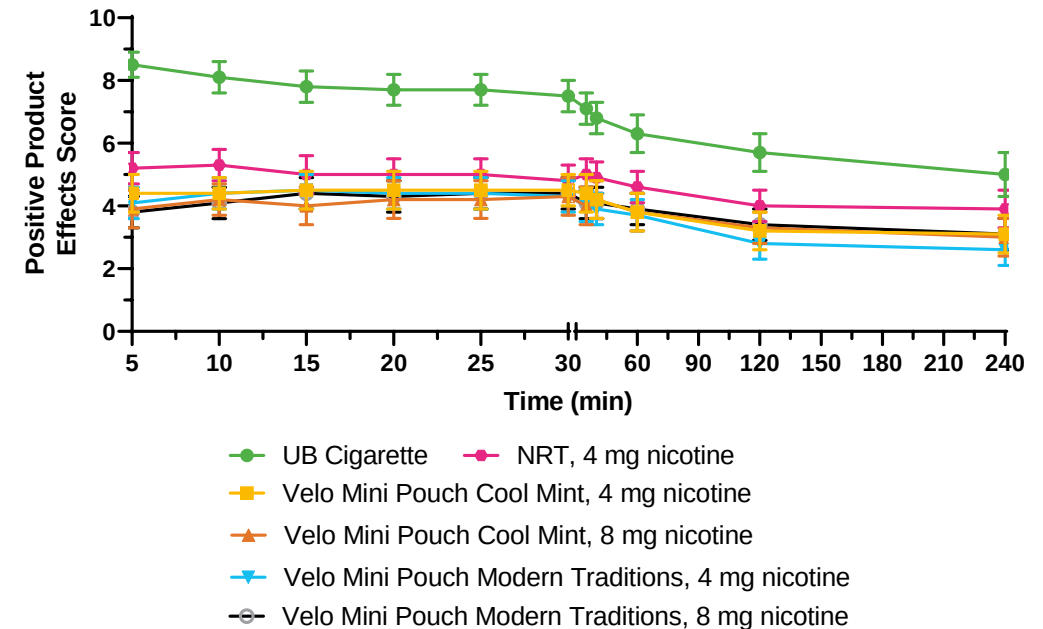
Least-squares mean data; Significantly different ( $p < 0.0042$  [Study 1];  $p < 0.0031$  [Study 2]) from UB cig (a) or NRT gum (b). UTS: Urge to Smoke; AUEC<sub>UTS 0-15</sub> UTS at 15 min after product use; AUEC<sub>UTS 5-240</sub> UTS at 240 min after product use; E<sub>min UTS</sub> minimum UTS score



Rate the degree to which you feel positive effects of the product at this moment



### Study 2: Velo Mini Pouch (400 mg)



# Positive Product Effects

| Study 1: Velo Pouch AL      |                             |                             |                              |                   |                    | Study 2: Velo Mini Pouch AL |                             |                                        |                                        |                   |                    |
|-----------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|--------------------|-----------------------------|-----------------------------|----------------------------------------|----------------------------------------|-------------------|--------------------|
|                             | Cool Mint<br>(4 mg)<br>n=40 | Cool Mint<br>(8 mg)<br>n=41 | Cool Mint<br>(12 mg)<br>n=40 | UB<br>cig<br>n=40 | NRT<br>gum<br>n=40 | Cool Mint<br>(4 mg)<br>n=42 | Cool Mint<br>(8 mg)<br>n=42 | Modern<br>Traditions<br>(4 mg)<br>n=42 | Modern<br>Traditions<br>(8 mg)<br>n=42 | UB<br>cig<br>n=42 | NRT<br>gum<br>n=42 |
| AUEC <sub>PEpos 5-240</sub> | 1048.0 <sup>a</sup>         | 960.1 <sup>a</sup>          | 1009.9 <sup>a</sup>          | 1420.0            | 865.7              | 852.8 <sup>a</sup>          | 836.9 <sup>a</sup>          | 778.5 <sup>a,b</sup>                   | 857.2 <sup>a</sup>                     | 1403.0            | 1002.6             |
| E <sub>max PEpos</sub>      | 6.5 <sup>a</sup>            | 6.5 <sup>a</sup>            | 6.6 <sup>a</sup>             | 9.0               | 6.2                | 5.6 <sup>a</sup>            | 5.3 <sup>a</sup>            | 5.3 <sup>a</sup>                       | 5.4 <sup>a</sup>                       | 8.9               | 5.9                |

Least-squares mean data; Significantly different ( $p < 0.0042$  [Study 1];  $p < 0.0031$  [Study 2]) from UB cig (a) or NRT gum (b). PE: Product Effects, AUEC<sub>PEpos 5-240</sub> PE Positive from 5-240 min after product use; E<sub>max PEpos</sub> maximum PE positive score

# Negative Product Effects

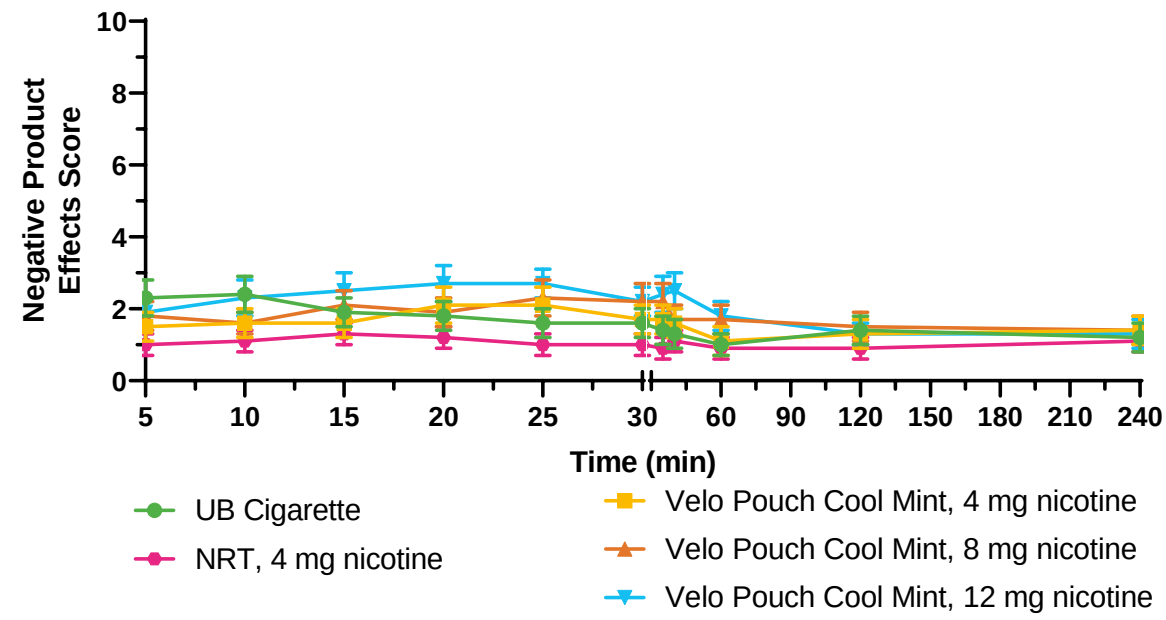
Negative Product Effect Questionnaire

Rate the degree to which you feel negative effects of the product at this moment

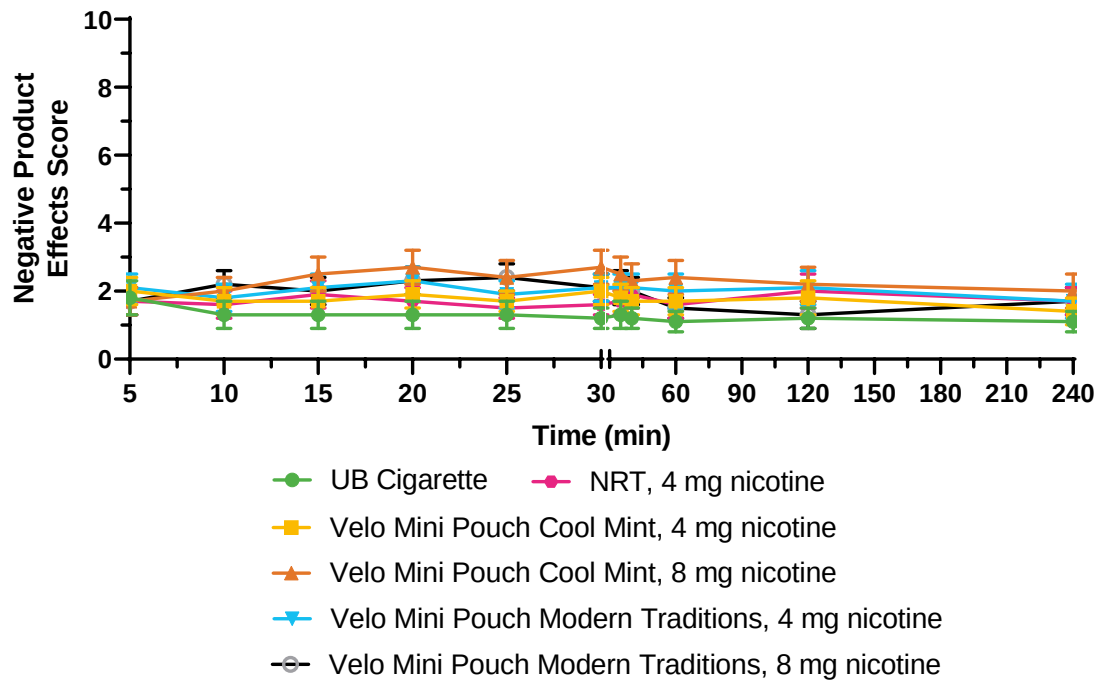
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

I feel no negative effects I feel extremely negative effects

Study 1: Velo Pouch (600 mg)



Study 2: Velo Mini Pouch (400 mg)



# Negative Product Effect

| Study 1: Velo Pouch AL      |                             |                             |                              |                   |                    | Study 2: Velo Mini Pouch AL |                             |                                        |                                        |                   |                    |
|-----------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|--------------------|-----------------------------|-----------------------------|----------------------------------------|----------------------------------------|-------------------|--------------------|
|                             | Cool Mint<br>(4 mg)<br>n=40 | Cool Mint<br>(8 mg)<br>n=41 | Cool Mint<br>(12 mg)<br>n=40 | UB<br>cig<br>n=40 | NRT<br>gum<br>n=40 | Cool Mint<br>(4 mg)<br>n=42 | Cool Mint<br>(8 mg)<br>n=42 | Modern<br>Traditions<br>(4 mg)<br>n=42 | Modern<br>Traditions<br>(8 mg)<br>n=42 | UB<br>cig<br>n=42 | NRT<br>gum<br>n=42 |
| AUEC <sub>PEneg 5-240</sub> | 334.0                       | 387.0                       | 398.2                        | 334.7             | 259.8              | 401.4                       | 517.1 <sup>b</sup>          | 449.7                                  | 372.6                                  | 301.0             | 424.2              |
| E <sub>max PEneg</sub>      | 2.9                         | 3.2                         | 3.9 <sup>b</sup>             | 3.5               | 2.2                | 2.9                         | 3.3                         | 3.2                                    | 3.2                                    | 2.6               | 2.6                |

Least-squares mean data; Significantly different ( $p < 0.0042$  [Study 1];  $p < 0.0031$  [Study 2]) NRT gum (b). PE: Product Effects, AUEC<sub>PEneg 5-240</sub> PE Negative from 5-240 min after product use; E<sub>max PEneg</sub> maximum PE negative score



Overall Product Liking Questionnaire

Overall, how much did you like the product?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Strongly dislike Neither like nor dislike Strongly like

Overall Intent to Use Again Questionnaire

Rate the degree to which you would like to use the product again

|                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       |

Not at all Very much

Least-squares mean data; Significantly different ( $p < 0.0042$  [Study 1];  $p < 0.0031$  [Study 2]) from UB cig (a) or NRT gum (b). IUA: Intent to use again, PL: Product liking

# Summary and Conclusions

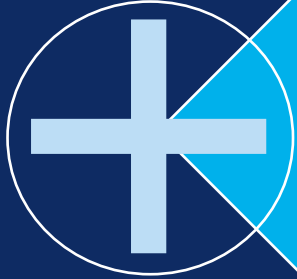


# Summary

- Nicotine uptake parameters of Velo Pouches and Mini Pouches increased with higher levels of nicotine and were generally similar across product flavors at the same nicotine level.
- Compared to UB Cigarettes, Velo Pouches and Mini Pouches had:
  - significantly lower scores of PL endpoints and Positive PE
  - generally similar Negative PE scores
  - significantly higher UTS during the first 15 minutes of product use
- Compared to NRT gum, Velo Pouches and Mini Pouches had:
  - similar scores for PL endpoints and Positive PE
  - generally similar negative PE scores
  - generally lower UTS parameters
- UTS with use of Velo Pouches slightly decreased with increasing nicotine levels of the product.
- Velo Pouches and Mini Pouches were well-tolerated; no SAEs or deaths reported; no unexpected AEs and AEs were similar to those observed with commercially-available FDA-approved NRT gum.



# Conclusions



**Velo Pouches and Mini Pouches demonstrate an abuse liability profile that is lower than usual-brand cigarettes, and similar to that of a commercially-available NRT gum.**



**Similar to NRT gum, Velo Pouches and Mini Pouches demonstrate low risk of abuse compared with usual brand cigarettes and may provide levels of nicotine that enable some adult cigarette smokers to transition away from smoking to use of the Velo pouches.**

# Acknowledgements

- Study Planning, Conduct, Interpretation
  - Kanobe MN, Powell CY, Patrudu M, Baxter SA, Tapia MA, Darnell J, Prevette K, Gibson AG, Ayoku SA, Campbell L, Coffield JW, Keyser BM, Ganesh BS, Gale N and Jordan KG (2025) Randomized crossover clinical studies to assess abuse liability and nicotine pharmacokinetics of Velo Oral Nicotine pouches. Front. Pharmacol. 16:1547073.doi: 10.3389/fphar.2025.1547073
  - Clinicaltrials.gov
    - Study 1: NCT05129657
    - Study 2: NCT05294487
  - Advarra Institutional Review Board
  - Conducted under GCP in accordance with ICH E6(R2)
  - Contract Research Organization
    - ICON Early Phase Services
  - Bioanalytical Laboratory
    - Celerion Global Bioanalytical Services
  - Study Sites
    - ICON Early Phase Services
    - Carolina Phase I
  - Alliance for Multispecialty Research (AMR)
    - AMR Lexington, KY
    - AMR Knoxville, TN
- Study 1
- Study 2