



# Abuse Liability Assessments of Modern Oral Tobacco Products in Adult Smokers

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# Modern Oral Abuse Liability Studies



**TSRC Poster 16:** Evaluation of Abuse Liability of Two Velo Nicotine Lozenge Tobacco Products Compared to Combustible Cigarettes and NRT Lozenge in Smokers

*(ClinicalTrials.gov Identifier: NCT04167384)*



**TSRC Poster 23:** Abuse Liability Evaluation of Velo Oral Nicotine Products Compared to Combustible Cigarettes and NRT Gum in Adult Smokers

*(ClinicalTrials.gov Identifier: NCT04372290)*

# Modern Oral Tobacco Products (MO)



*Nicotine lozenges*



*Nicotine pouches  
(tobacco leaf-free)*



*Nicotine tablets & gum  
(non-nicotine  
replacement therapy  
[NTP])*

# Abuse Liability of Modern Oral Tobacco Products

## Elements of Abuse Liability (AL)

### Subjective Measures



- Product Liking
- Urge to Smoke
- Product Effects

### Nicotine Uptake Measures



- Maximal Plasma Nicotine Concentration
- Time To Maximal Plasma Nicotine Concentration
- Total Nicotine Uptake

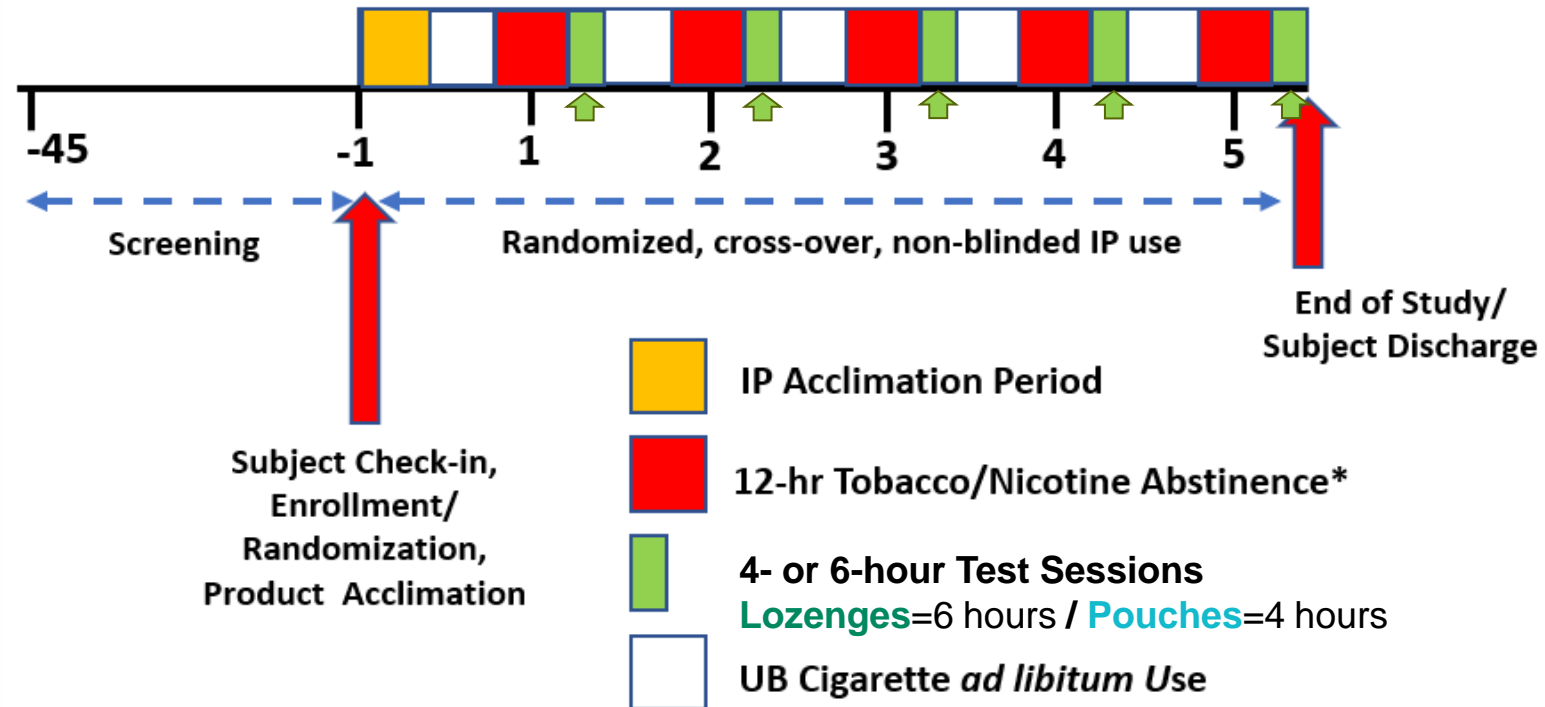
### Physiological measures



- Heart Rate
- Blood Pressure

# Study Design Overview

- 6-day confinement period
- Randomized 5-way cross-over study design each at a single site
- Oral Product familiarization on Day -1:
  - 1 lozenge or 1 pouch
  - 1 study-specific NRT comparator
- 5 Test Sessions (3 Study IP and 2 comparators) over five days
- 6-hour or 4-hour Test Sessions with PK/PD assessments (Days 1 to 5)



NRT=Nicotine replacement therapy; PD=Pharmacodynamic;  
PK=Pharmacokinetic

\* Included a minimum 4-hour caffeine restriction prior to start of Test Session that continued to end of Test Session

## Modern Oral Tobacco Products + High and Low-Abuse Liability (AL) Comparators

### VELO NICOTINE LOZENGES STUDY

UB combustible cigarette	Up to 10 minutes
NRT lozenge (4 mg)	Until completion
1 Velo lozenge (Hard or Soft) (2 mg)	Until completion
2 Velo lozenges (Hard or Soft) (4 mg)	Until completion
4 Velo lozenges (Hard or Soft) (8 mg)	Until completion

### VELO NICOTINE POUCHES STUDY

UB combustible cigarette	Up to 10 minutes
NRT gum (2 mg)	30 minutes
1 Velo 2 mg pouch (2 mg)	30 minutes
1 Velo 4 mg pouch (4 mg)	30 minutes
2 Velo 4 mg pouches (8 mg)	30 minutes

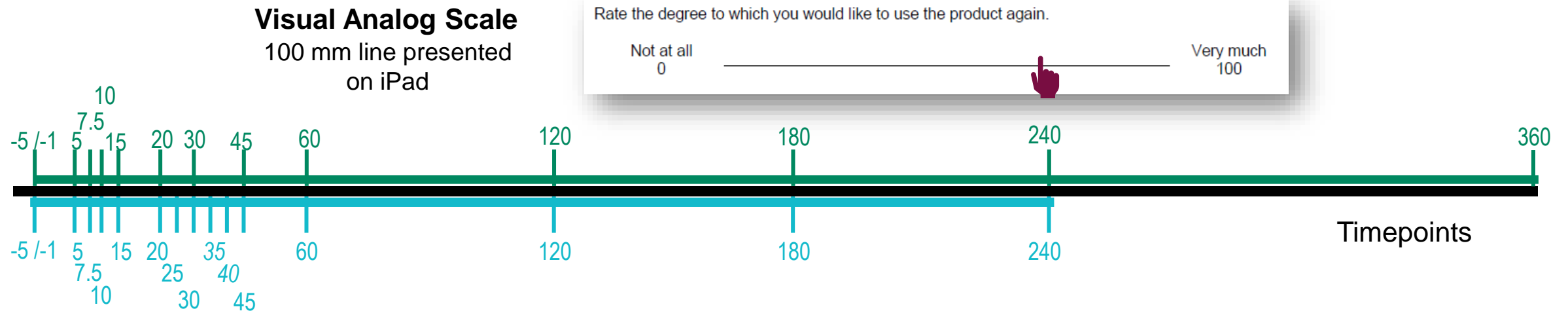


# Study Eligibility

- ✓ **Generally healthy male & female smokers, 21 to 60 years old**
  - No clinically significant disease, including diabetes or clotting disorders
- ✓ **Smokes  $\geq 10$  Cigarettes Per Day** (filtered menthol or non-menthol)
- ✓ Can **safely** participate in 5 days **of serial blood draws**
  - Meets threshold weight and blood hemoglobin levels
- ✓ Smokes **first cigarette of day** within **30 minutes** of waking up

# Timepoints and Data Collection Instruments

**Lozenge study** = 6-hour Test Session **14 timepoints** for PK blood draws, questionnaire completion, and vital sign measurements



**Pouch study** = 4-hour Test Session **16 timepoints** for PK blood draws, questionnaire completion, and vital sign measurements  
11-pt NRS

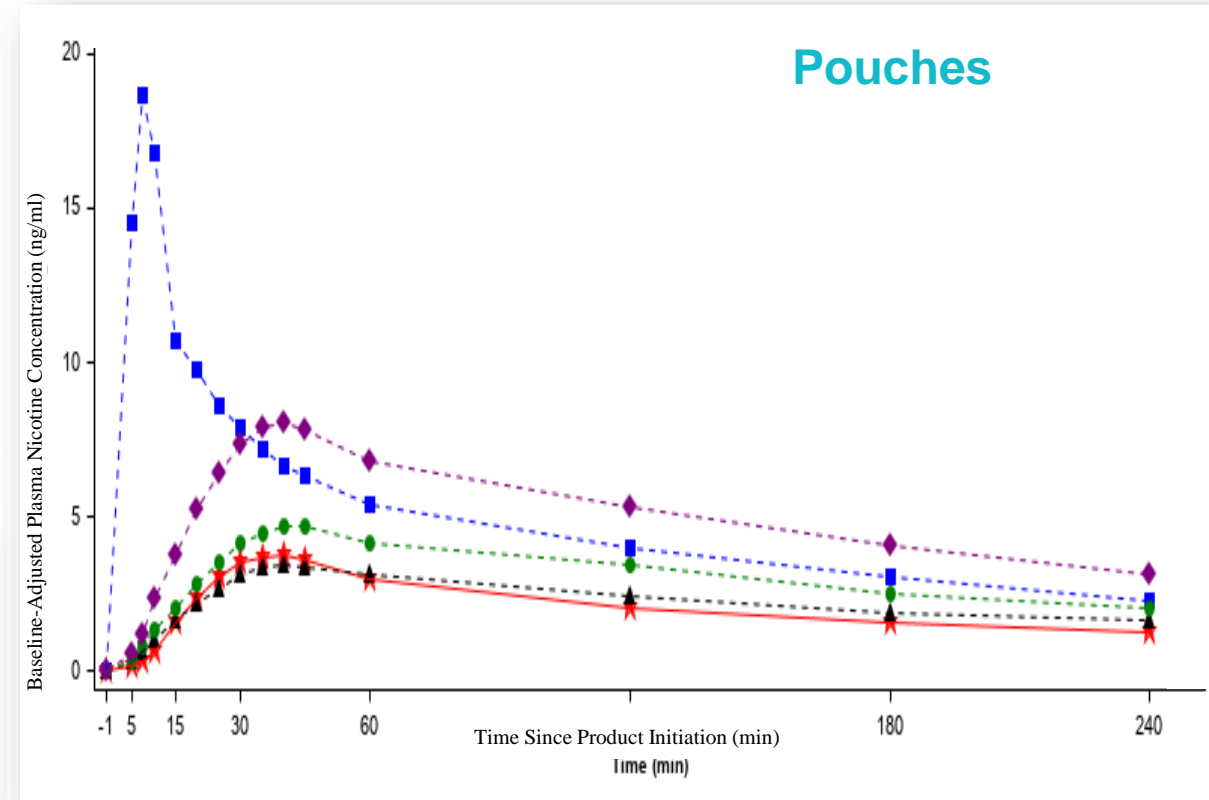
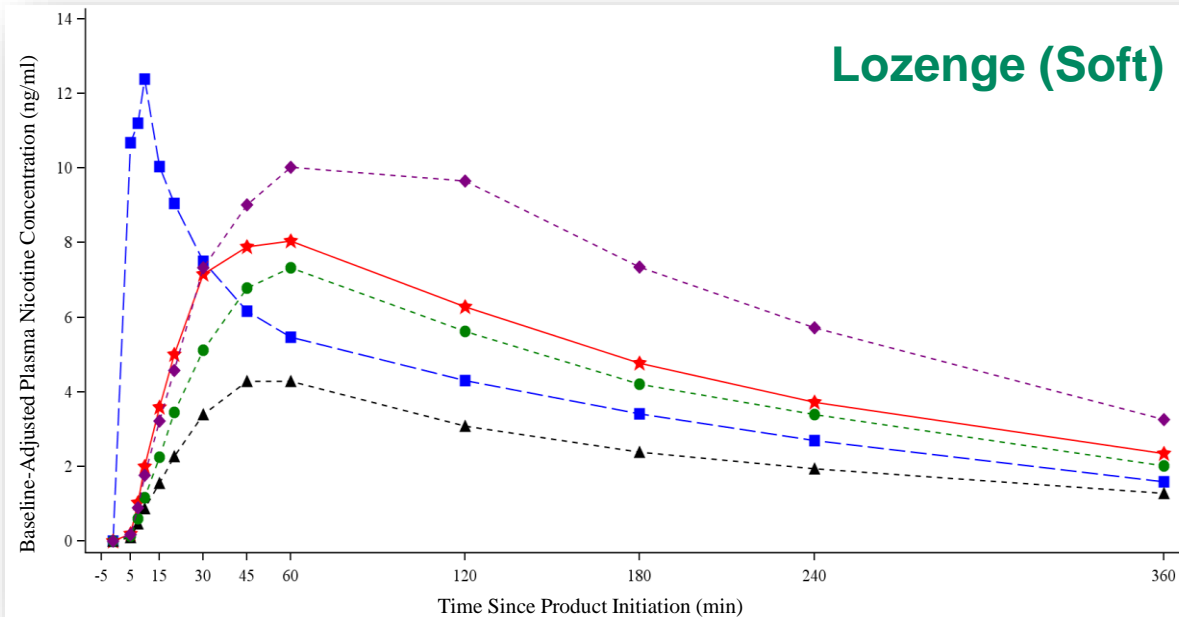
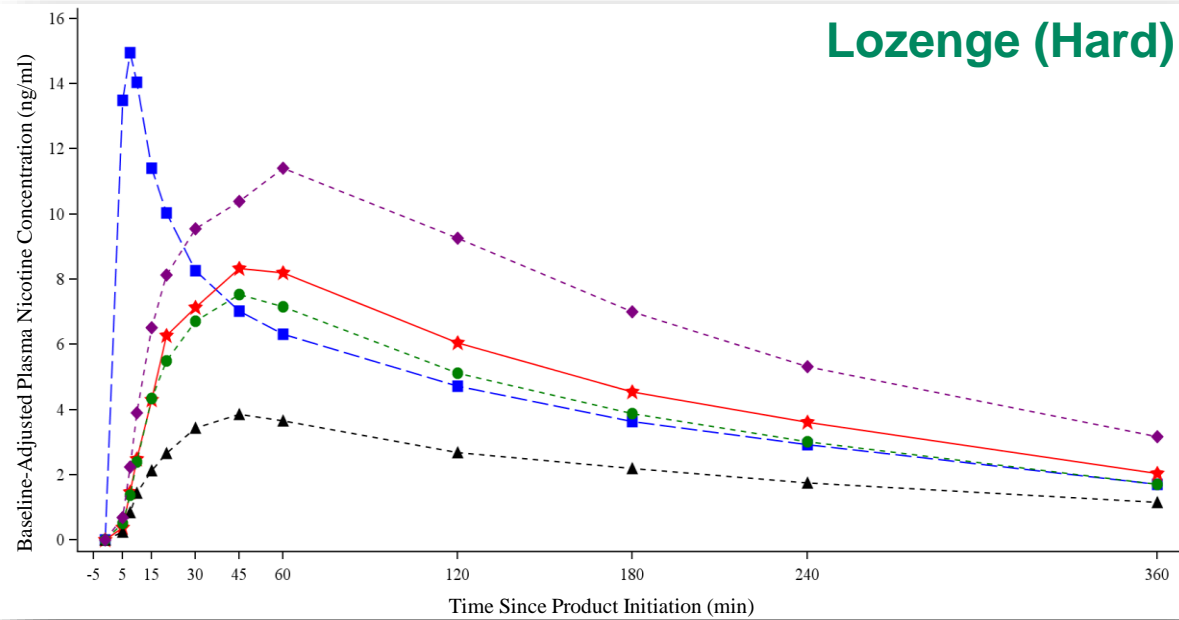
**Numeric Rating Scale**  
11-point scale presented on paper

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 checked="" 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



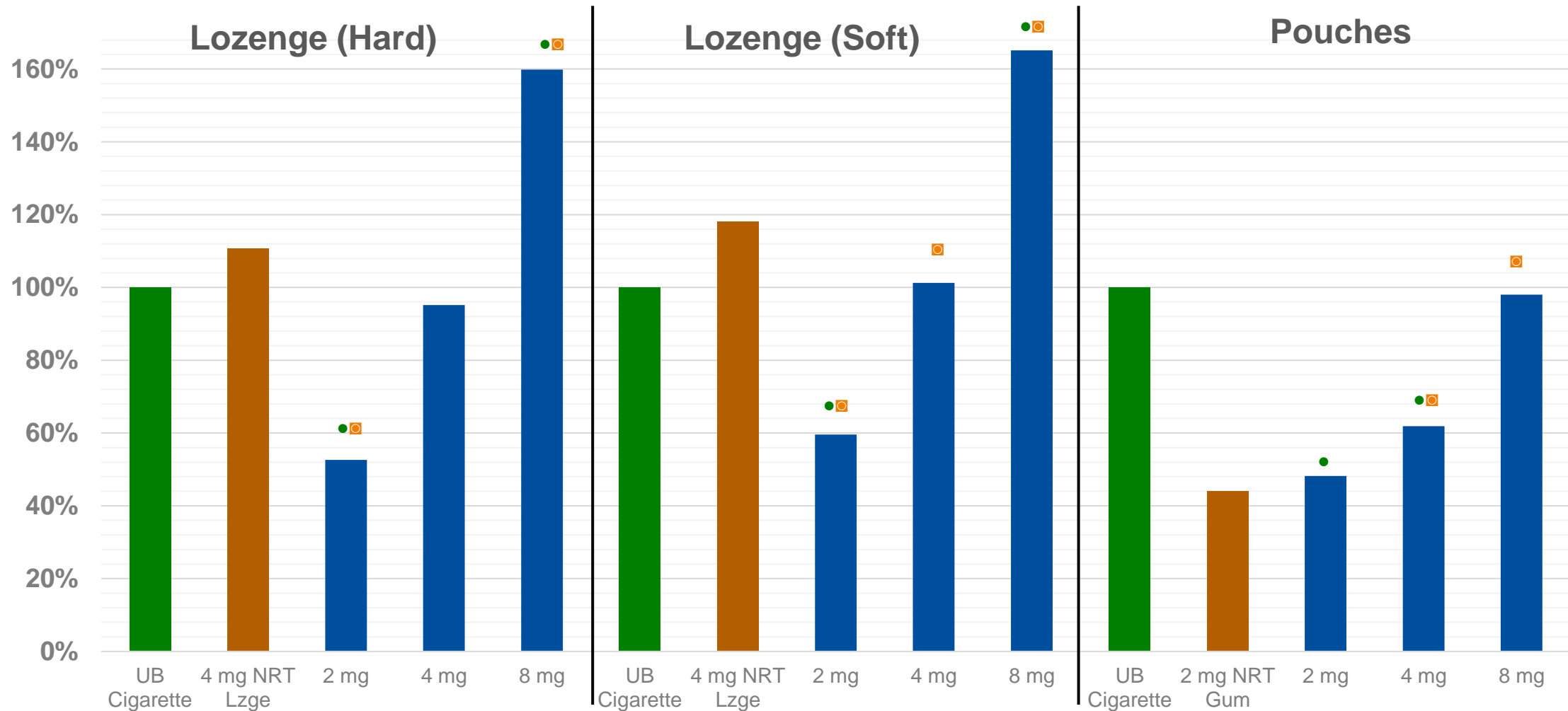
# Nicotine Uptake Over Time



- UB Cigarette
- ★— NRT
- ▲- 2 mg (1 lozenge or 1 pouch)
- 4 mg (2 lozenge or 1 pouch)
- ◆- 8 mg (4 lozenge or 2 pouch)

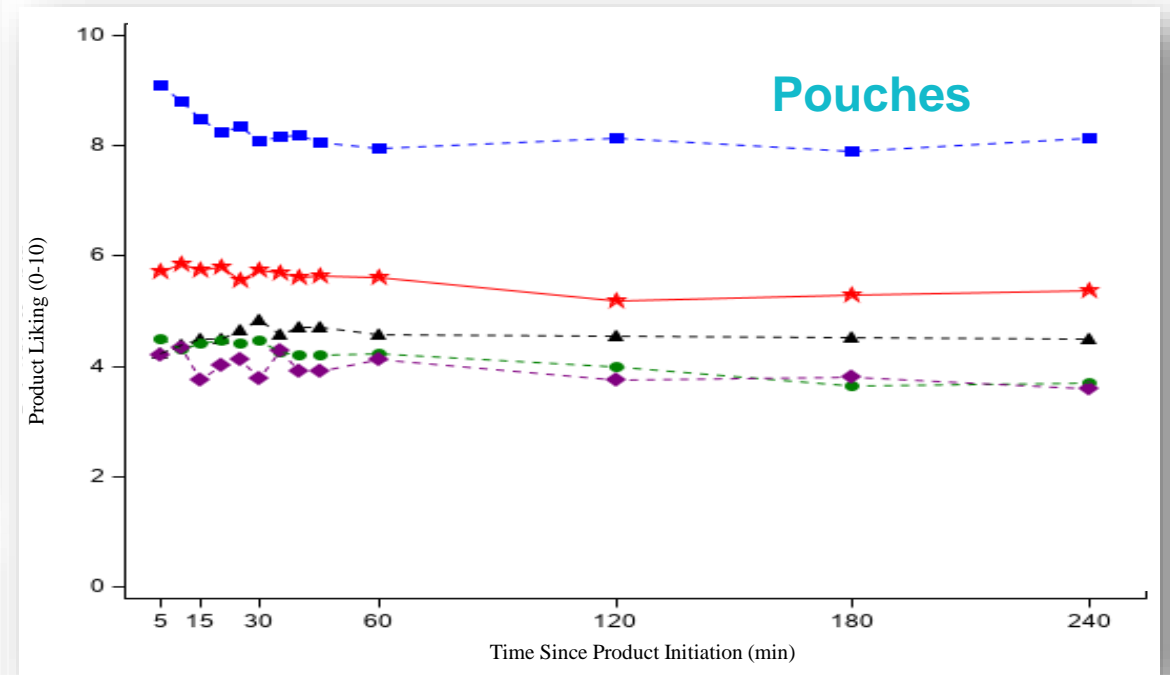
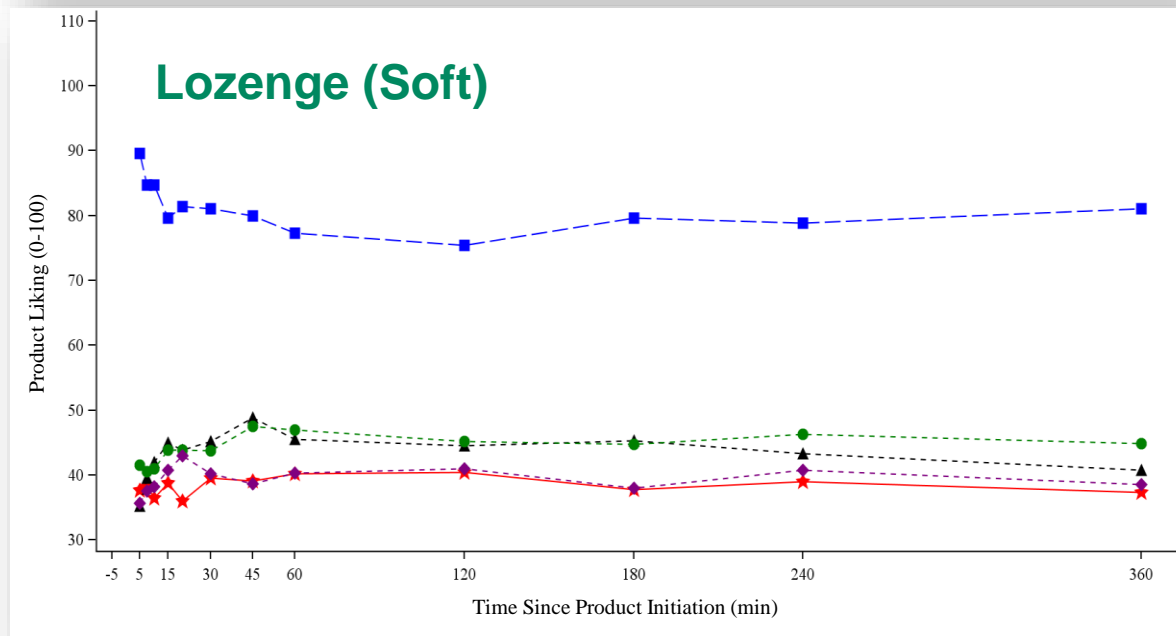
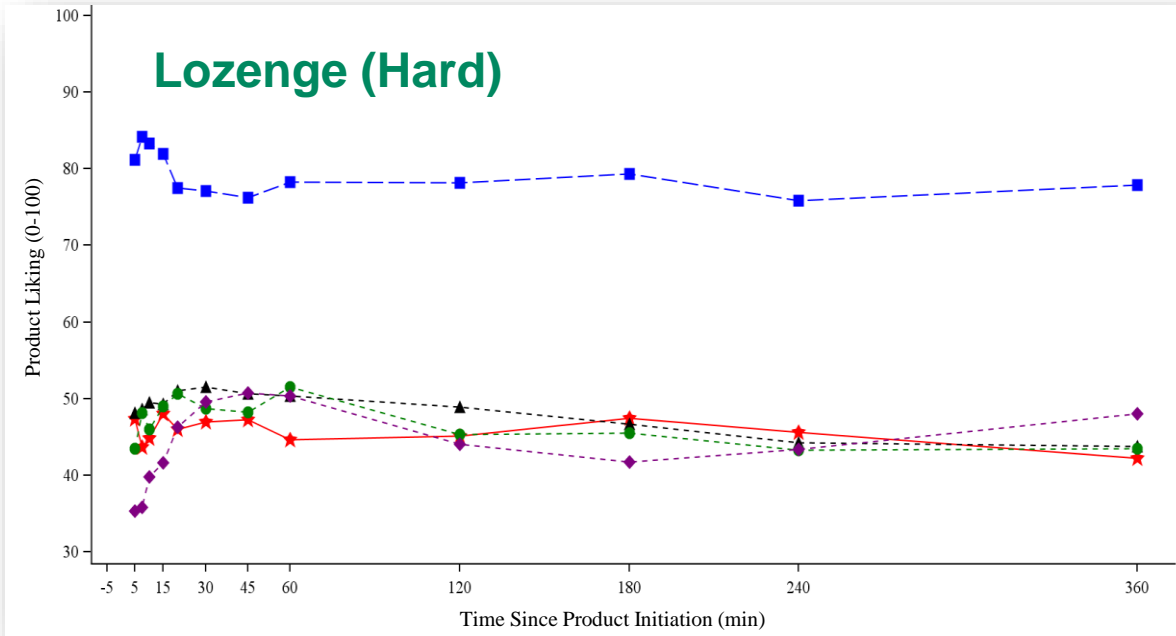
# Overall Nicotine Uptake ( $AUC_{nic\ 0-240/360}$ ) Varies by Product

	ng*min/ml				
	UB CC	NRT	2 mg	4 mg	8 mg
Lozenge (Hard)	1427	1579	750.7	1358	2281
Lozenge (Soft)	1384	1633	824.3	1401	2285
Pouches	1022	450	493	633	1002



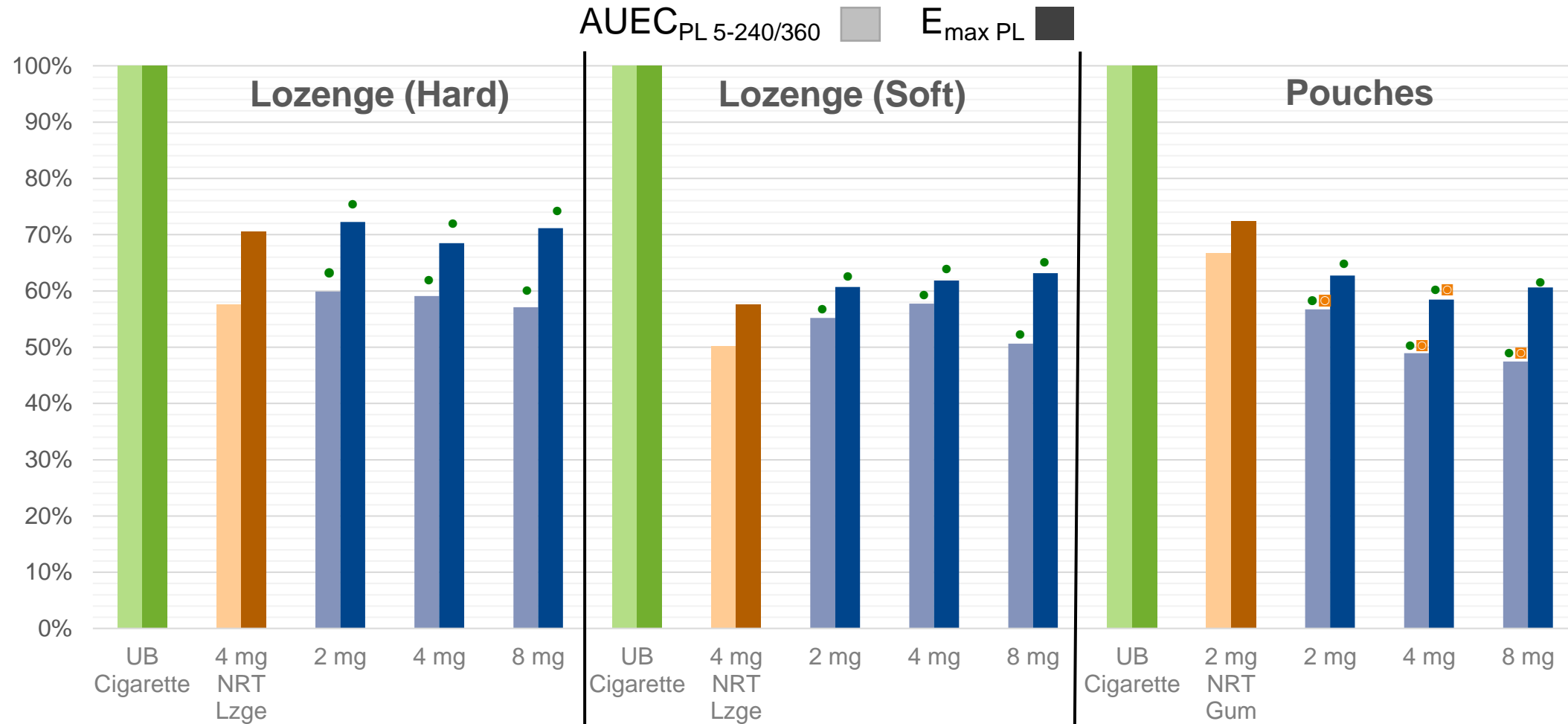
● Statistically significantly different from High-AL comparator; ◻ Statistically significantly different from Low-AL comparator.  
 $p \leq 0.05$  is considered significant for secondary endpoints. Statistical comparisons are based on geometric LS means

# Product Liking Over Time



- UB Cigarette
- ★--- NRT
- ▲--- 2 mg (1 lozenge or 1 pouch)
- 4 mg (2 lozenge or 1 pouch)
- ◆--- 8 mg (4 lozenge or 2 pouch)

# Product Liking Parameters are Similar to NRT

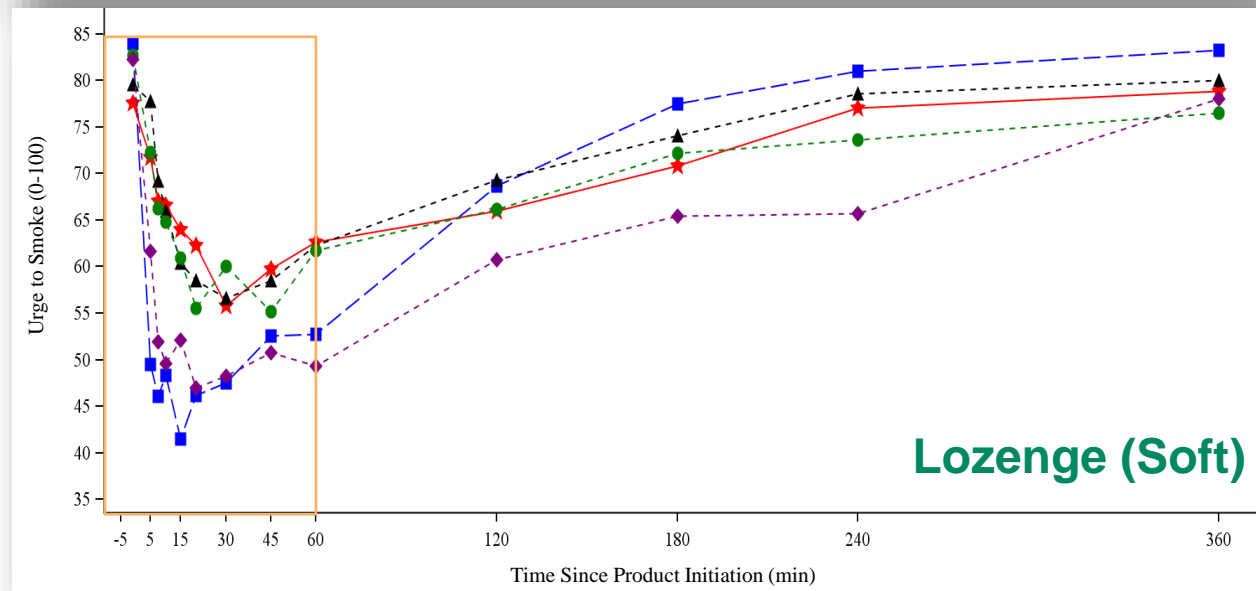
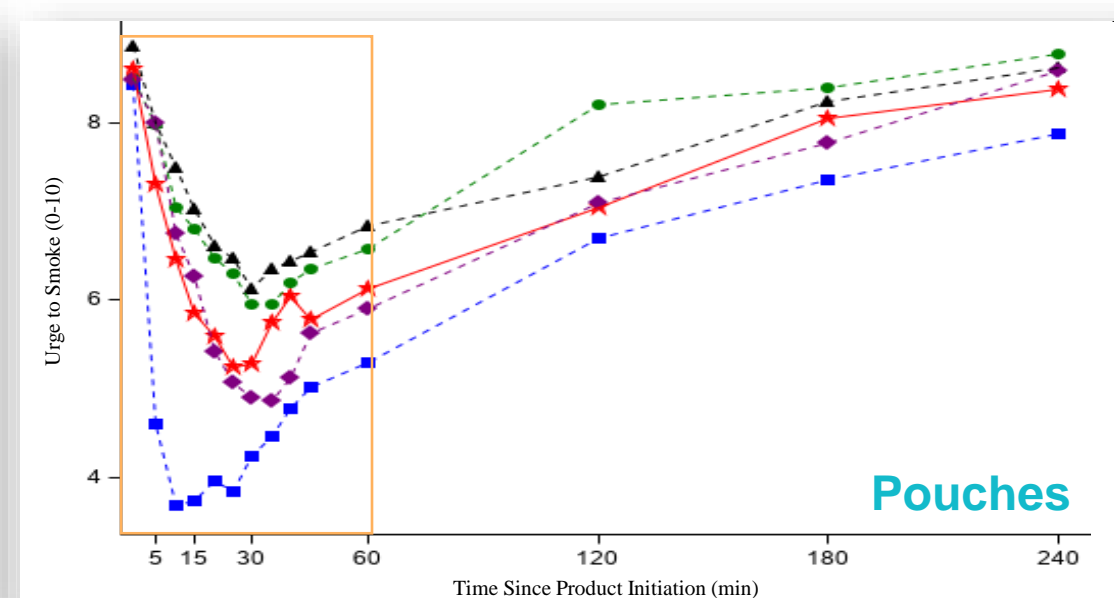
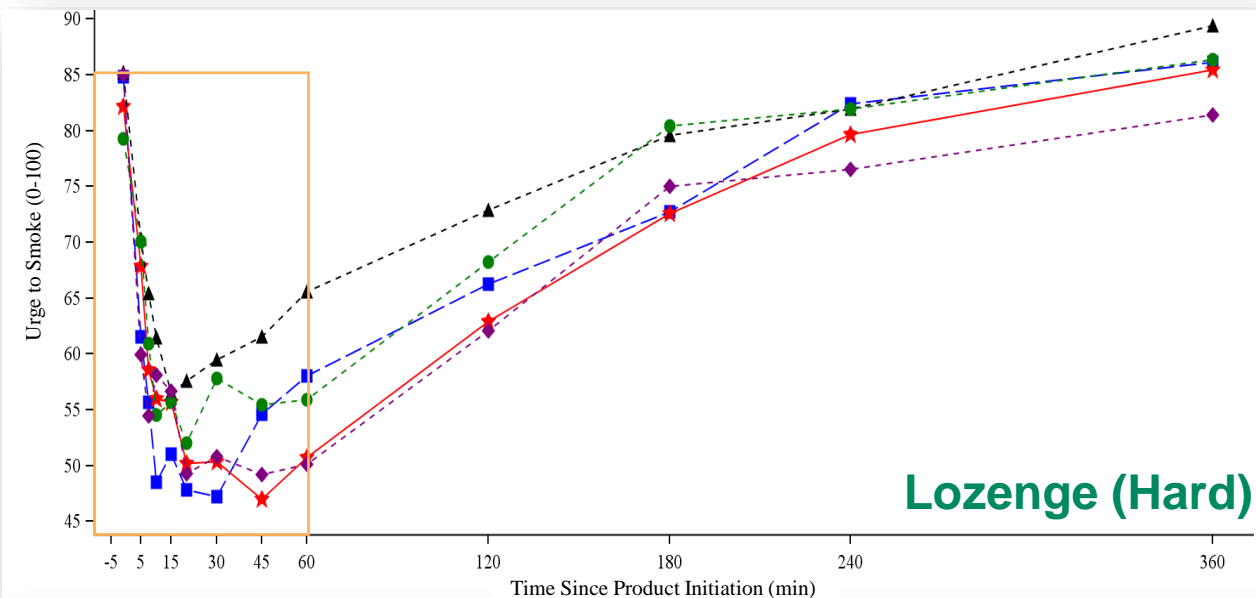


● Statistically significantly different from High-AL comparator; ■ Statistically significantly different from Low-AL comparator.

$p \leq 0.0042$  (adjusted for multiple comparisons) was considered significant for primary endpoints

Underlying values and statistical comparisons are based on LS Means

# Reductions in Urge To Smoke are Similar to NRT



- UB Cigarette
- ★— NRT
- ▲— 2 mg (1 lozenge or 1 pouch)
- 4 mg (2 lozenge or 1 pouch)
- ◆— 8 mg (4 lozenge or 2 pouch)

# Additional results

- **Positive Effects (AUEC &  $E_{\max \text{ pos}}$ )**

**Lozenges:** lower than CC, similar to NRT, and independent of nicotine level

**Pouches:** lower than NRT and CC and independent of nicotine level

- **Negative Effects (AUEC &  $E_{\max \text{ neg}}$ )**

**Lozenges:** higher negative scores than CC, similar to NRT, and *increased with increasing nicotine level / lozenge #*

**Lozenges:** The highest nicotine level (4 lozenges) elicited the highest negative  $E_{\max}$  scores

**Pouches:** Higher negative scores than both CC and NRT, and increased with *increasing nicotine level / pouch #*

**Pouches:** The highest nicotine level (2 pouches) elicited the highest negative  $E_{\max}$  scores

## **Adverse Events (AEs)**

- All products were well-tolerated with AEs similar to those seen with FDA-approved commercially-available NRTs.
- Total number of AEs increased with increasing nicotine level
- Most common AEs: Nausea, Hiccups, Throat Irritation

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The PK parameters for the commercially-available modern oral tobacco products (MO) used in these studies are more similar to NRT than CC.

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Increasing nicotine uptake with simultaneous use of multiple products negatively affected subjective measures such as product liking and positive effects and increased negative effects and incidence of adverse events

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Collectively, these data suggest lower AL for MO as compared to CC and similar or lower AL as compared to current commercially available oral NRTs.

# Acknowledgements

## RAIS STUDY STAFF

### **Clinical Project Leads**

- Kristen Prevette
- Tony Guzman

### **Outsourcing Bioanalytical Lead**

- Eckhardt Schmidt

### **Statistician**

- Chao Wei

### **Data Manager**

- Satender Sajwan

### **Regulatory**

- Jeff Coffield

## EXTERNAL STUDY PARTNERS

### **CROs**

- United BioSource (UBC)
- NCGS

### **Sites**

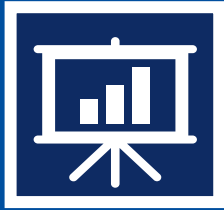
- High Point Clinical Trial Center (HPCTC), Highpoint, NC
- Alliance for Multispecialty Research (AMR), Knoxville, TN

### **Bioanalytical Services**

- Celerion



# Additional RAIS and RJRT Presentations at 2021 TSRC



**POSTER 5:** Assessment of in Vitro Toxicities Demonstrated by Total Particulate Matter (TPM) Generated from Current Market and Research Reference Standard Cigarettes Using the Bhas-42 Promotor Cell Transformation Assay

**POSTER 6:** Analysis of (S)- and (R)-Nicotine in Commercial Nicotine Samples and E-liquids and (R)-Nicotine Pharmacology

**POSTER 7:** ENDS Topography Across Multiple Platforms in an Ambulatory Setting

**POSTER 11:** Biomarkers of Potential Harm in Smoking Abstinence and in the Use of Vuse Electronic Nicotine Delivery Systems (ENDS)

**POSTER 17:** Pharmacokinetic Evaluation of E-liquid Flavors in Three Vuse Electronic Nicotine Delivery Systems (ENDS)

**POSTER 20:** NRF2 Response to Whole Smoke And Aerosol of Two Different Tobacco Product Types in a 3D Human Airway Model

**POSTER 22:** Characterization of Free Radicals in Cigarette Smoke and E-cigarette Aerosols by Spin-trapping EPR Spectroscopy



**PRESENTATION 27:** Ambulatory Use of Electronic Nicotine Delivery Systems – Redefining Topography Endpoints

**PRESENTATION 71:** Abuse Liability Assessment of Vuse Alto Electronic Nicotine Delivery System (ENDS) as Compared to Combustible Cigarettes and Nicotine Replacement Therapy (NRT) in Adult Smokers

**PRESENTATION 77:** Correlation of NNK Levels in Tobacco and Moist Snuff with the Levels of Pseudooxynicotine and Nicotine-1'-n-Oxide

# Questions?