



Abuse Liability Assessments of Modern Oral Tobacco Products in Adult Smokers

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RAI Services Company



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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

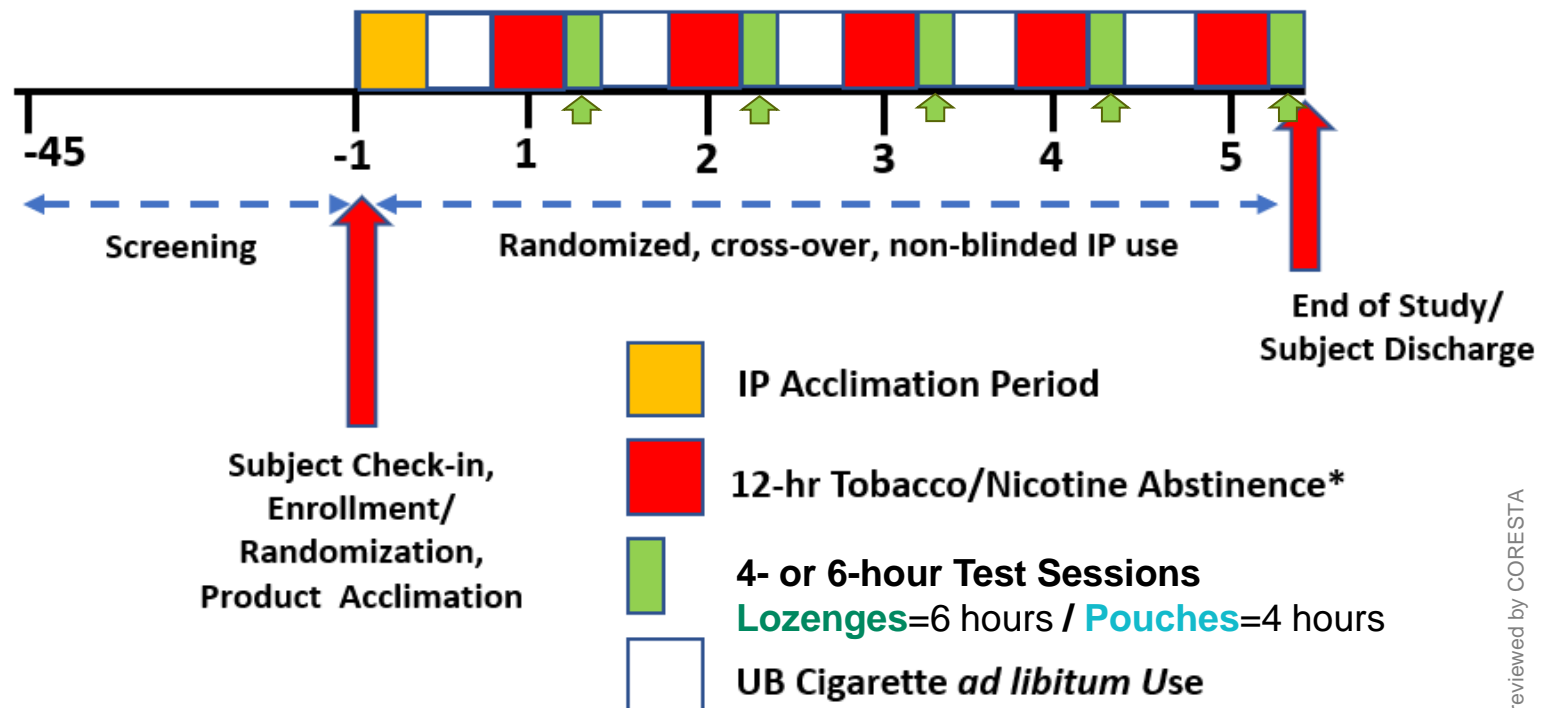
Physiological measures



- 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 Study Products

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

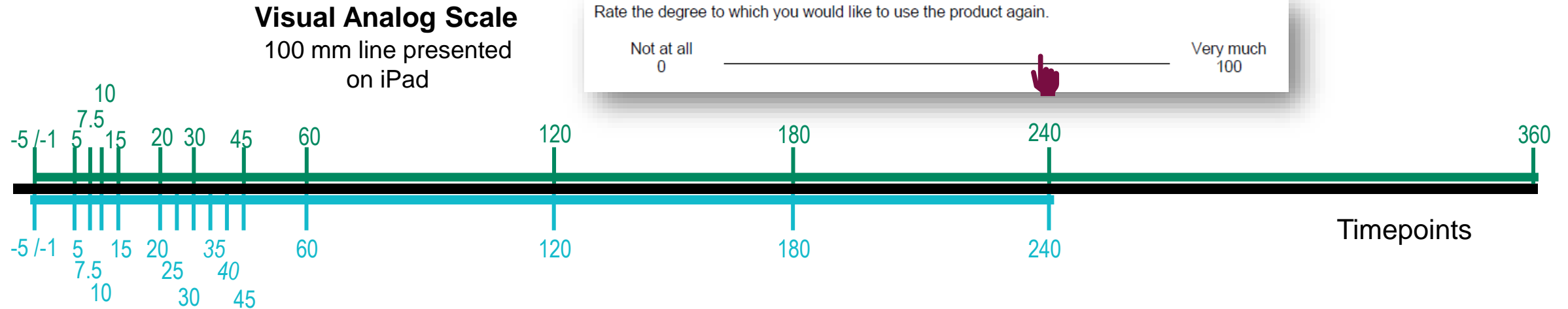


Study Eligibility

- ✓ **Generally healthy male & female smokers, 21 to 60 years old**
 - No clinically significant disease, including diabetes or clotting disorders
- ✓ **Smokes ≥ 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



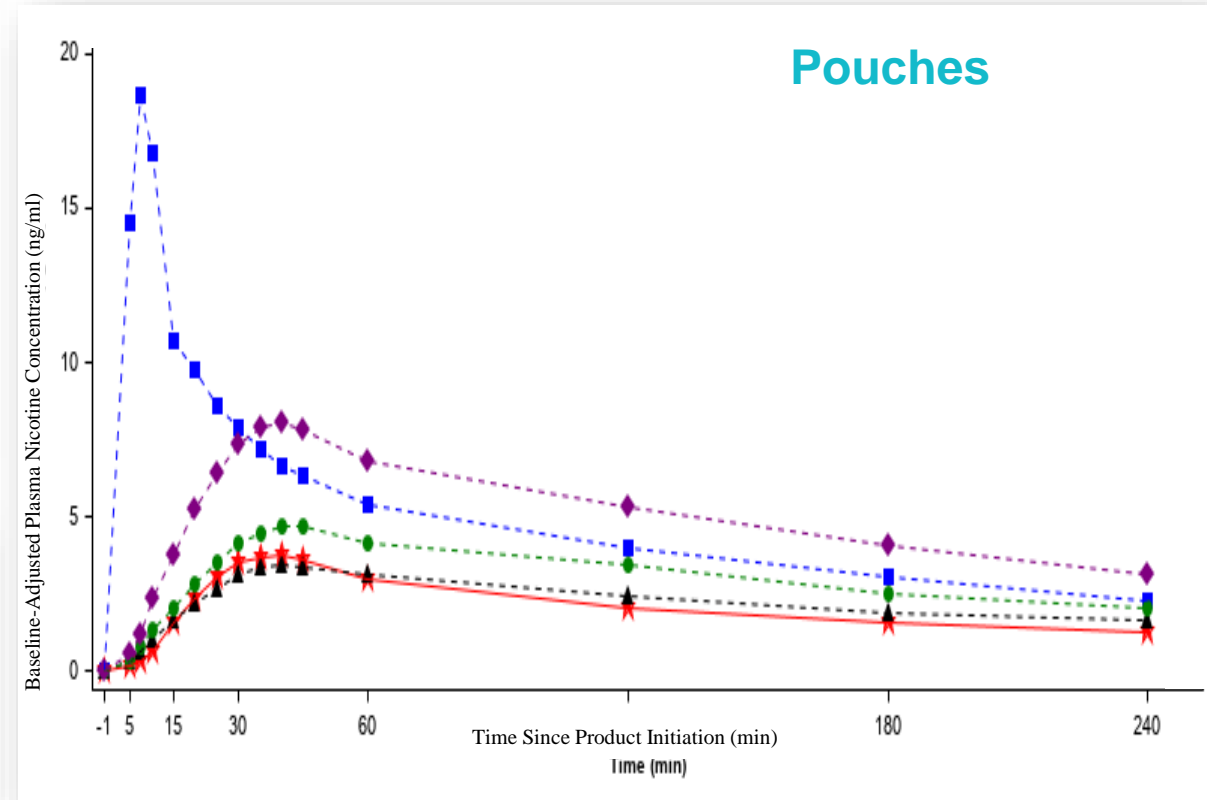
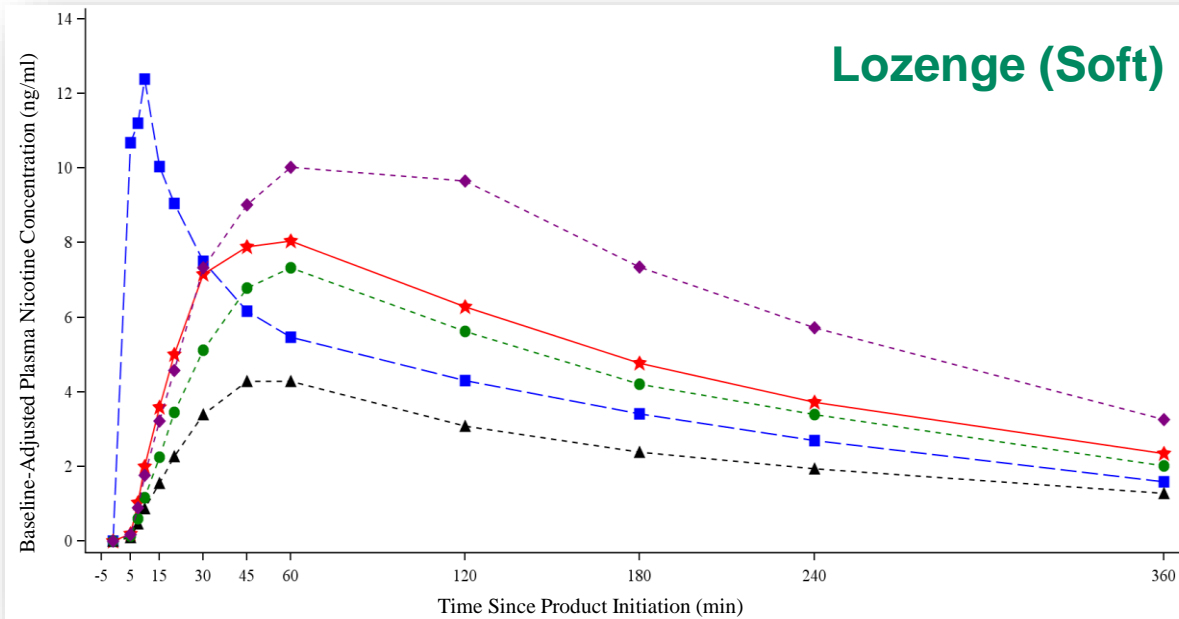
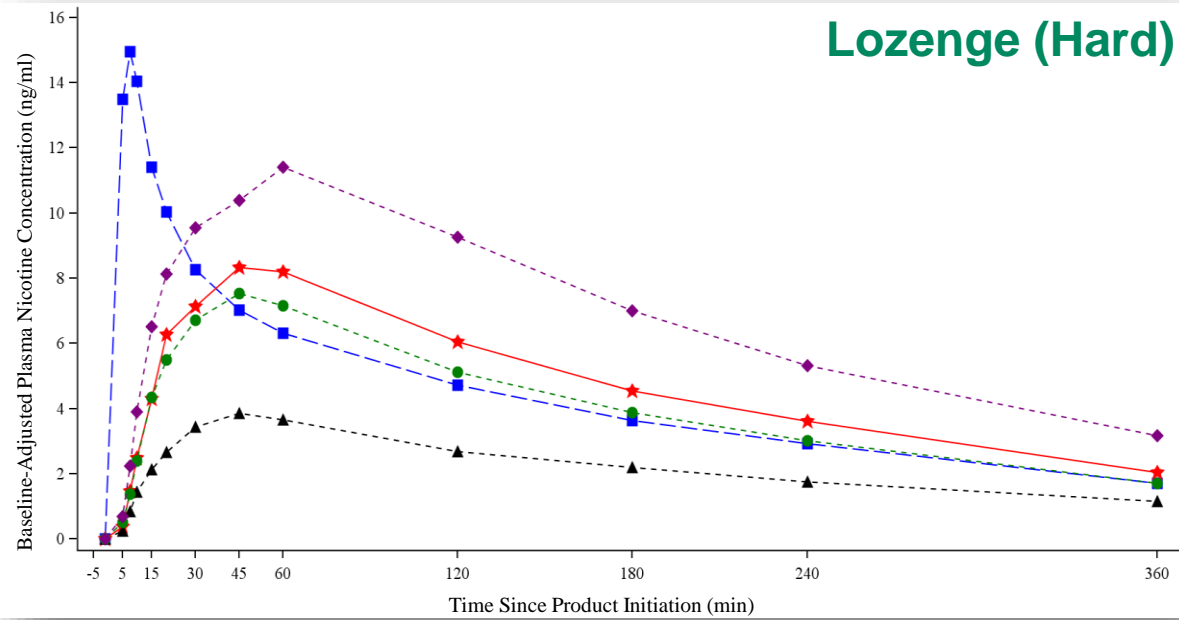
Pouch study = 4-hour Test Session **16 timepoints** for PK blood draws, questionnaire completion, and vital sign measurements
11-pt NRS

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

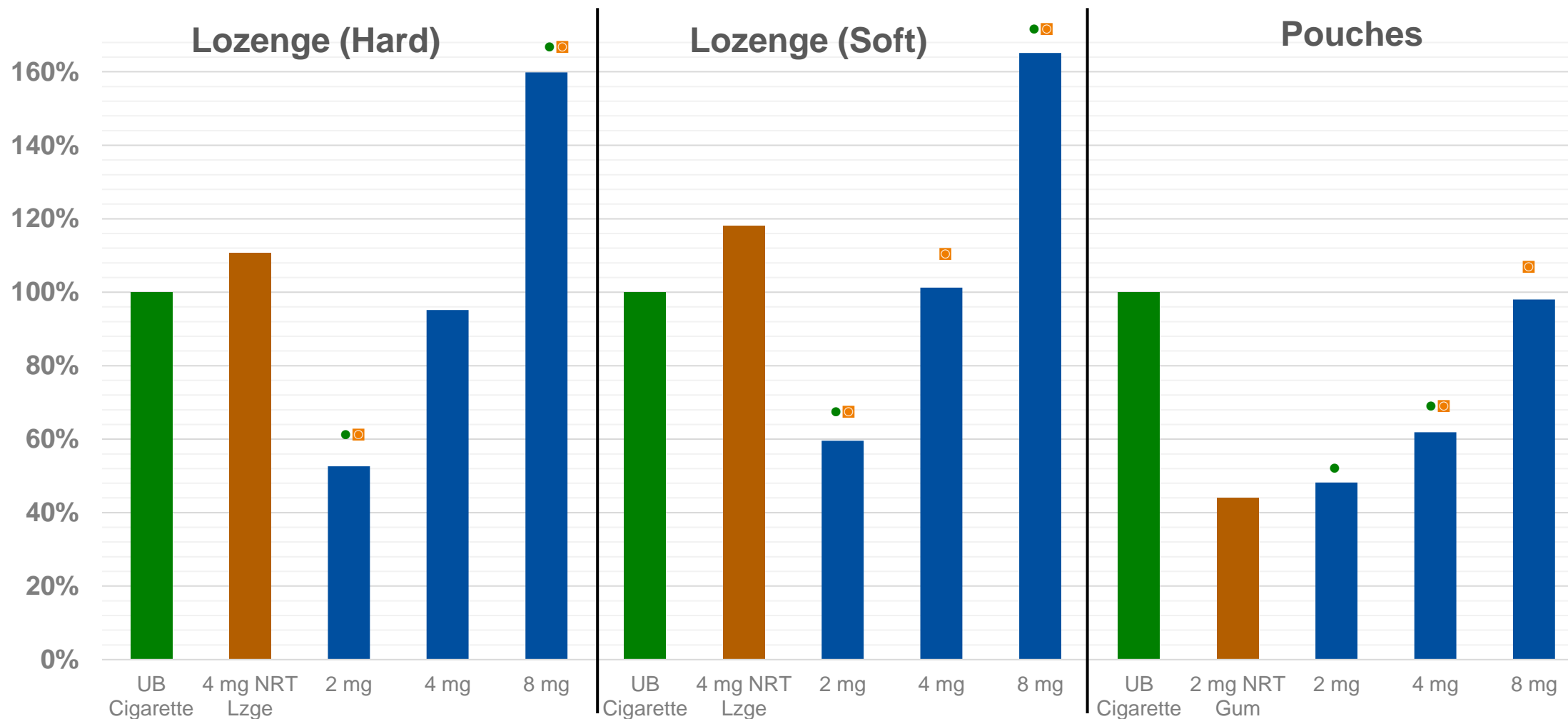
Nicotine Uptake Over Time



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

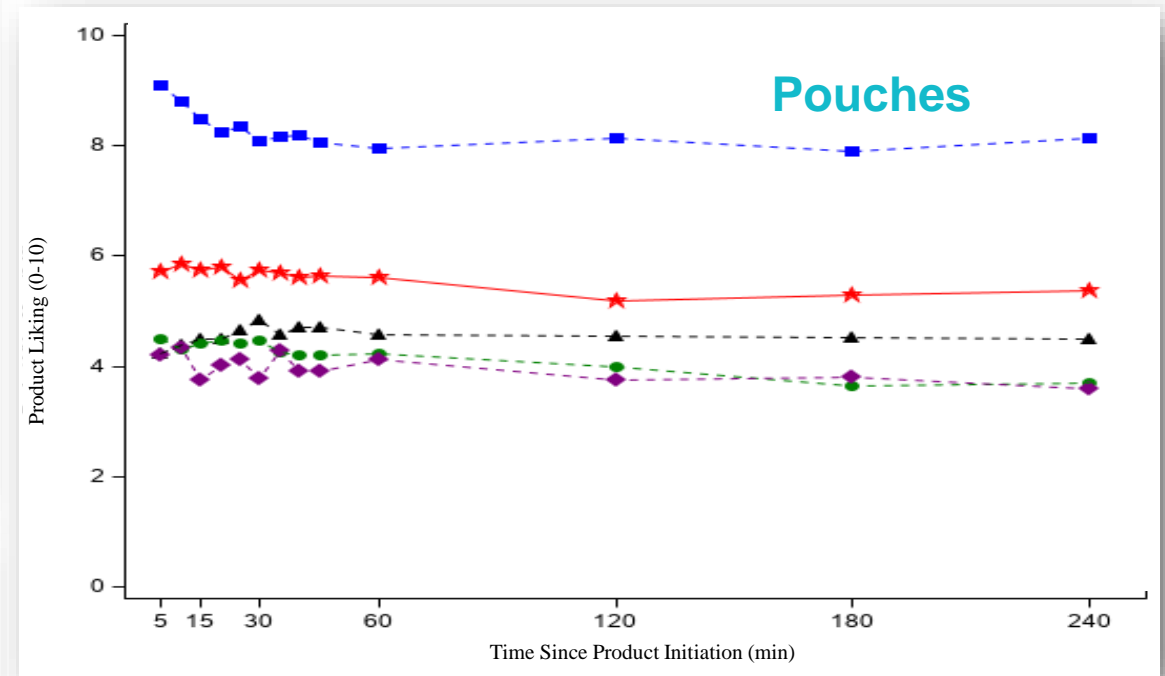
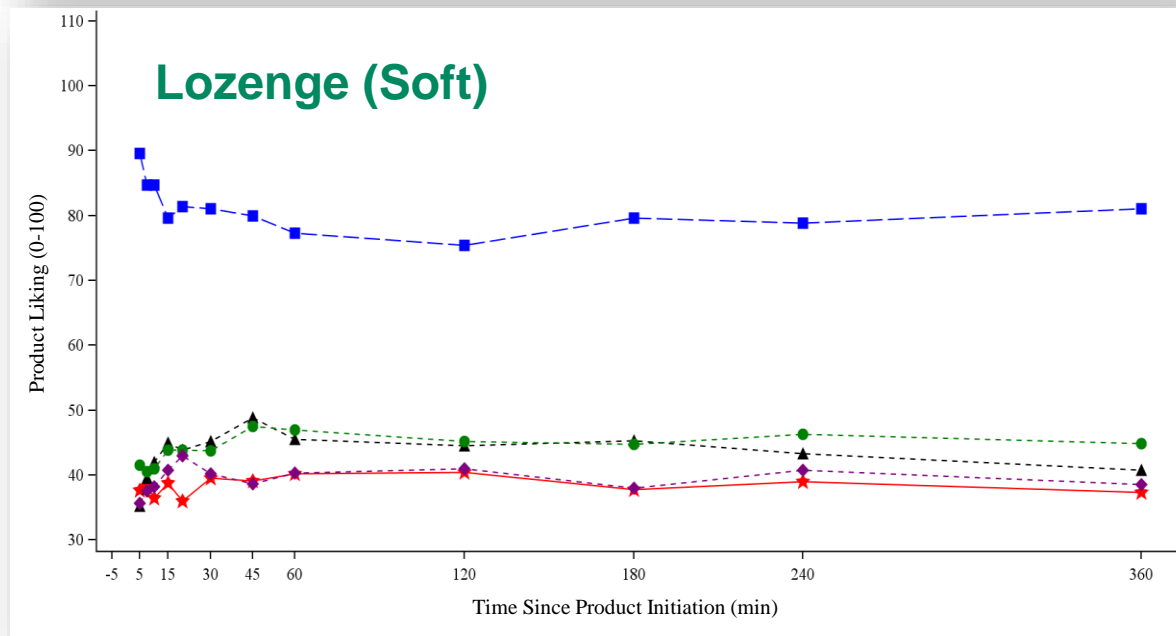
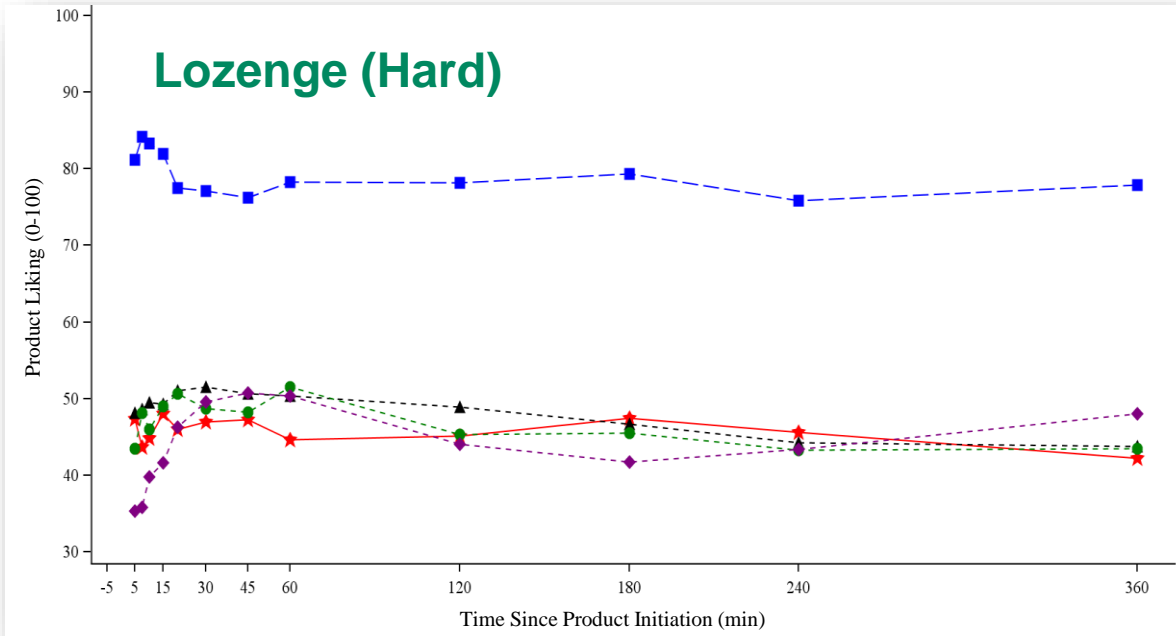
Overall Nicotine Uptake ($AUC_{nic\ 0-240/360}$) Varies by Product

	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



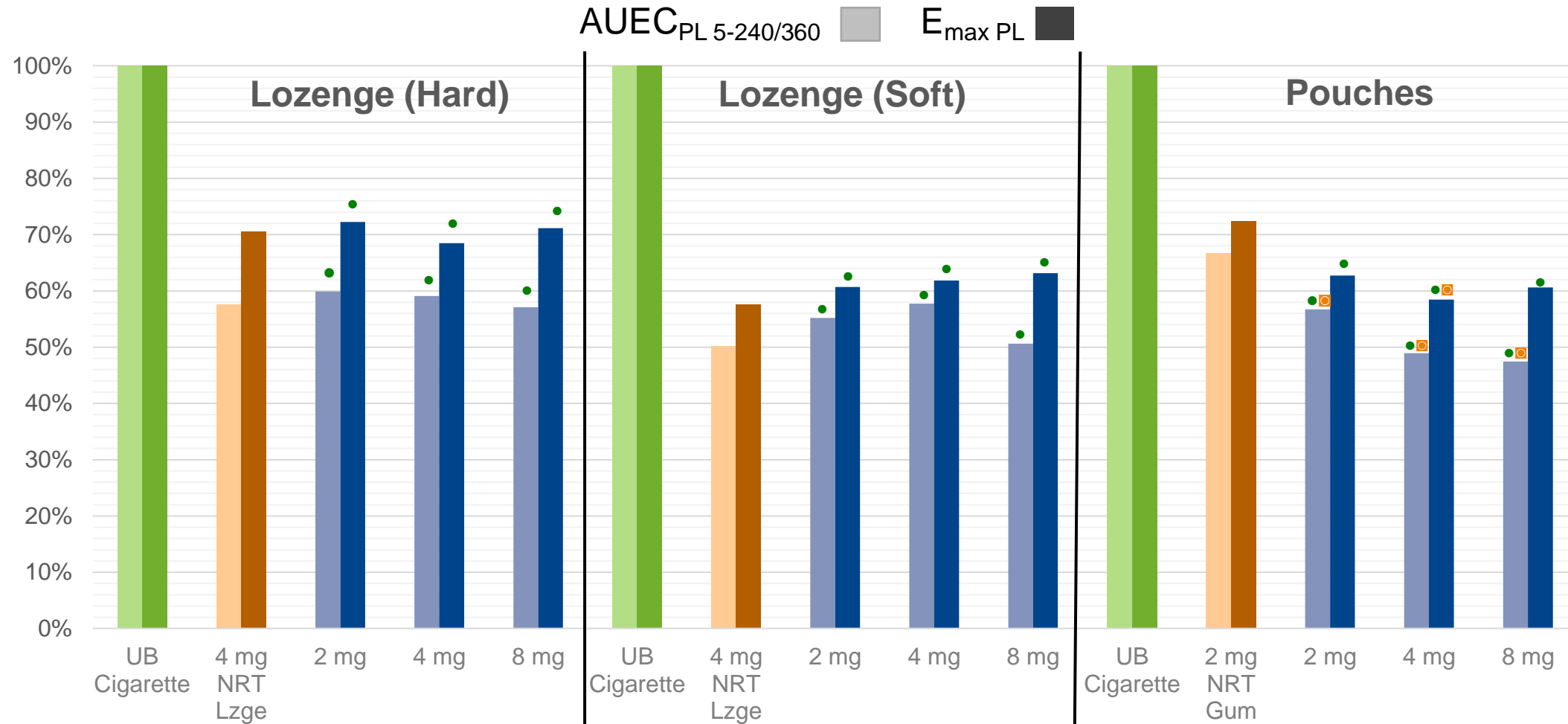
● Statistically significantly different from High-AL comparator; ■ Statistically significantly different from Low-AL comparator.
 $p \leq 0.05$ is considered significant for secondary endpoints. Statistical comparisons are based on geometric LS means

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

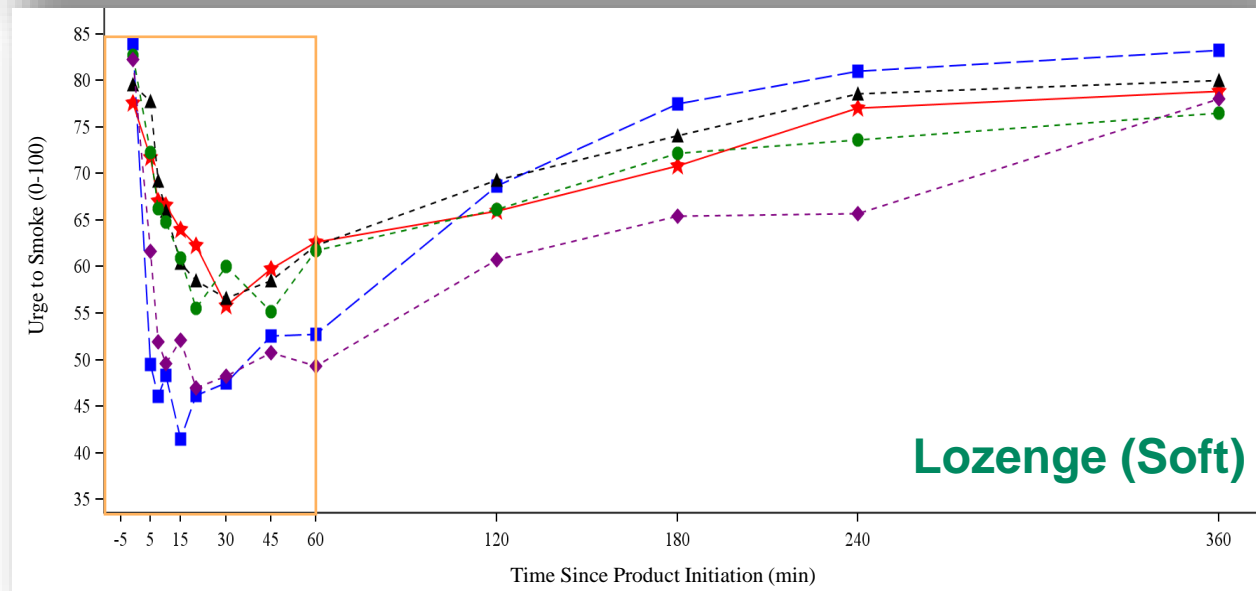
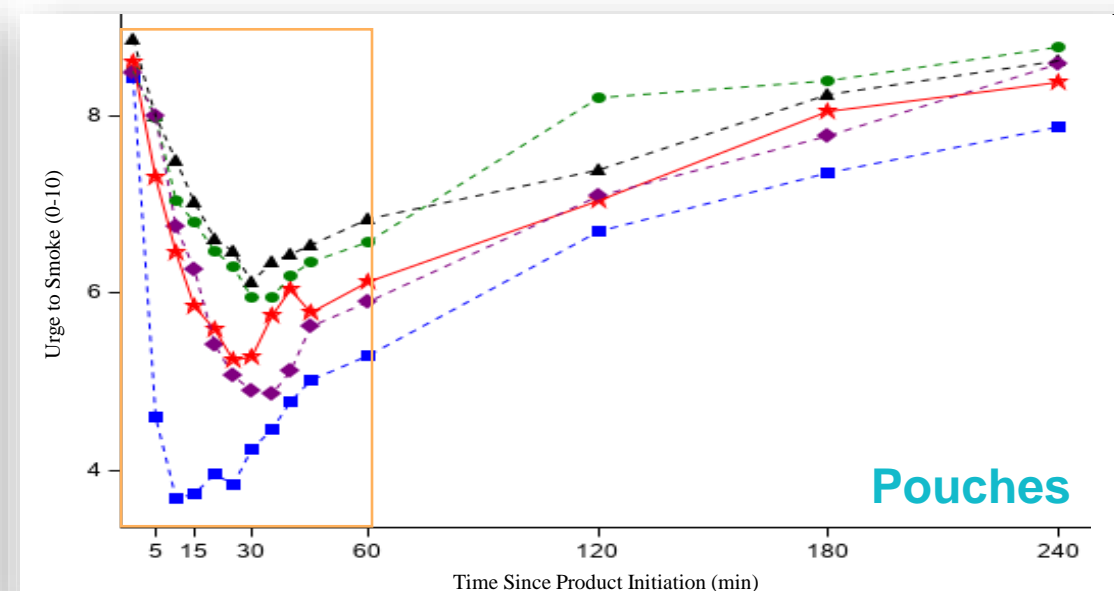
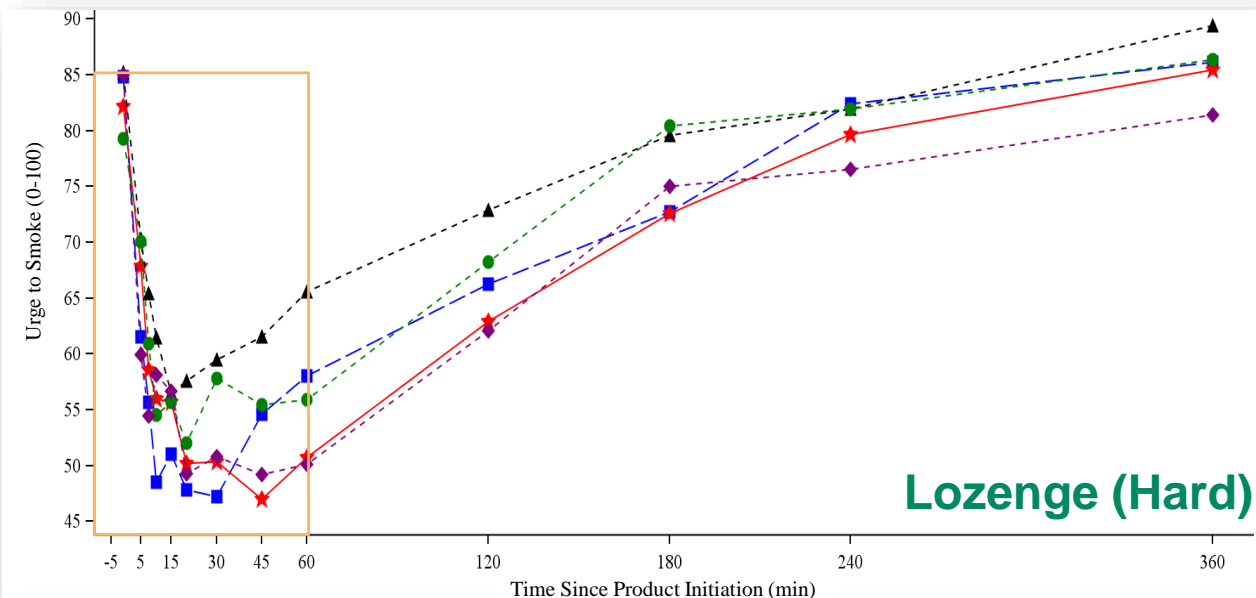


● Statistically significantly different from High-AL comparator; ■ Statistically significantly different from Low-AL comparator.

p ≤ 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

Summary and Conclusions

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

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

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

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EXTERNAL STUDY PARTNERS

CROs

- United BioSource (UBC)
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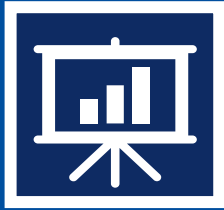
Sites

- 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?