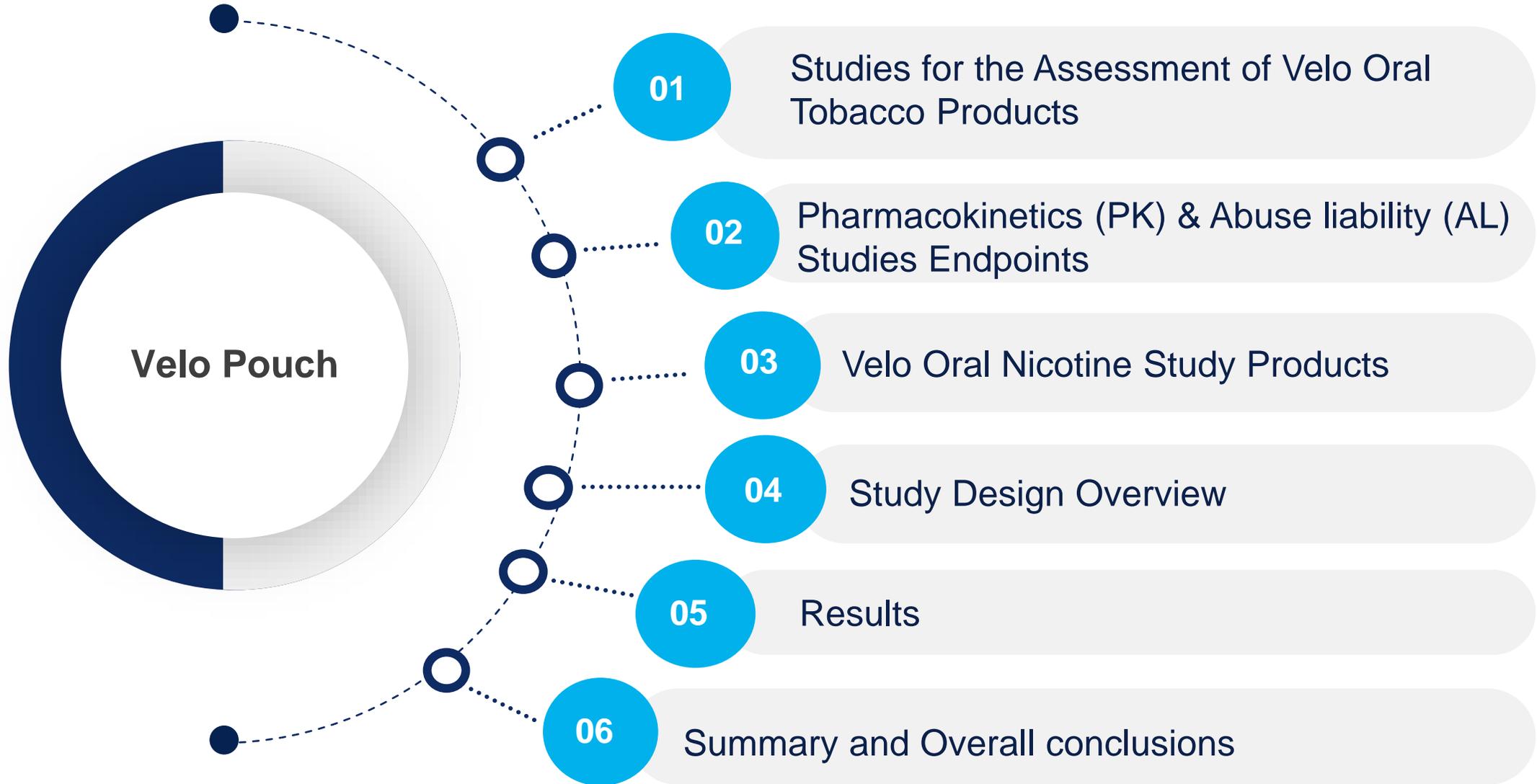


Nicotine Pharmacokinetics and Abuse Liability Assessment of Velo Oral Nicotine Pouches

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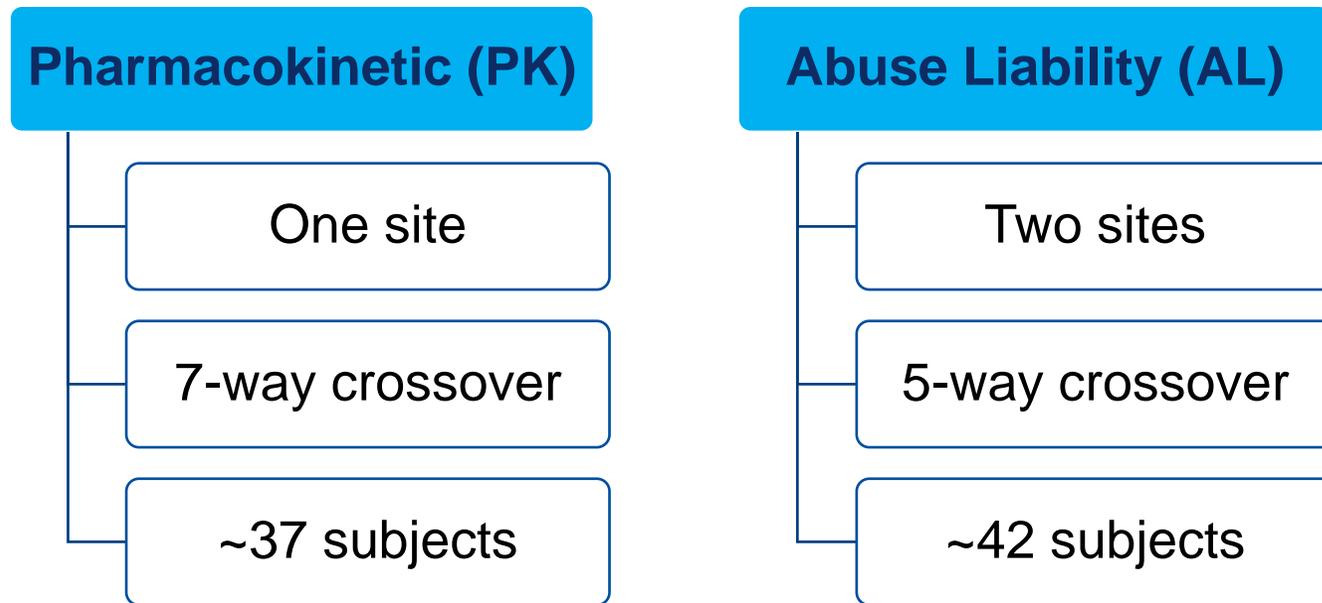
11-14Sep2022

Agenda



Studies for the Assessment of Velo Oral Nicotine Pouches

Two randomized, open label, crossover studies were conducted:



Results from both studies will be presented

PK and AL Studies Endpoints

Subjective Measures

- Product Effects (PE)
- Urge to Smoke (UTS)
- Overall Product Liking (OPL)*
- Overall Intent to use Again (OUIA)

Pharmacokinetics

- Maximal Plasma Nicotine Concentration (C_{max})*
- Time to Maximal Plasma (T_{max})*
- Total Nicotine Uptake (AUC)*

Physical Measures

- Heart Rate
- Blood Pressure

*Measures in PK Study

Velo Oral Nicotine Study Products



Velo Oral Nicotine PK Study

7 Investigational Products (IPs)

- 8 mg nicotine (6 IPs, differ in flavor)
- 10 mg nicotine

Velo Oral Nicotine AL Study

3 Investigational Products

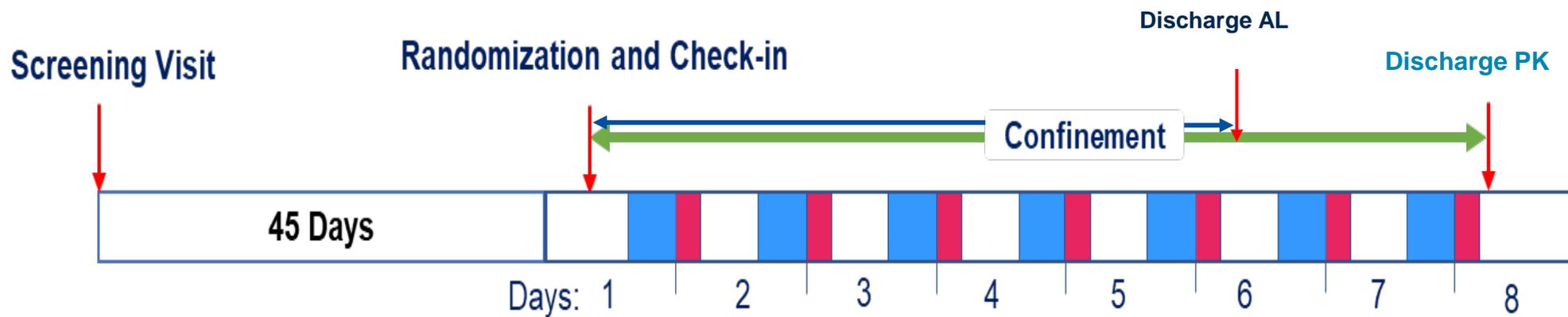
- 4 mg, 8 mg, or 10 mg nicotine

Comparator Products for AL Study

High AL: Usual Brand combustible cigarette (UB CC)

Low AL: Nicorette[®] White Ice Mint 4 mg nicotine polacrilex gum (NRT gum)

Study Design Overview



□ Product Familiarization and Ad libitum UB CC use

■ 12-hr Tobacco/Nicotine abstinence

■ 4-hr Test Session: PK and PD assessments

UB: Usual Brand
CC: Combustible Cigarette
PK: Pharmacokinetics
PD: Pharmacodynamics

Main 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.

RESULTS



Demographics and Baseline Characteristics

Characteristic

Enrolled Subjects

Avg. age (years)

Race (%)

Gender (%)

Avg. years smoked

Avg. no. cigarettes
smoked/day

PK Study

36*

40.4 (27-57)

83.3 Caucasian
13.9 African American
2.8 Other

69.4 Male
30.6 Female

23.8 (6-45)

16.6 (10-35)

AL Study

41**

42.4 (23-59)

78.0 Caucasian
19.5 African American
2.4 Other

63.4 Male
36.6 Female

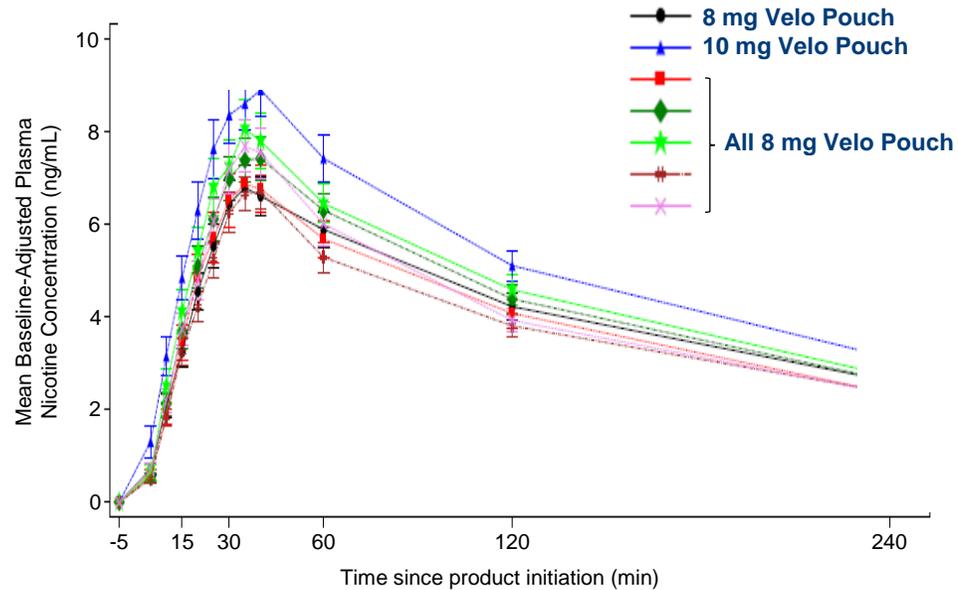
23.7 (4-39)

18.1 (10-40)

One subject discontinued from each of the studies; one due to consent withdrawn by subject (*); another withdrawn due to an AE (**).

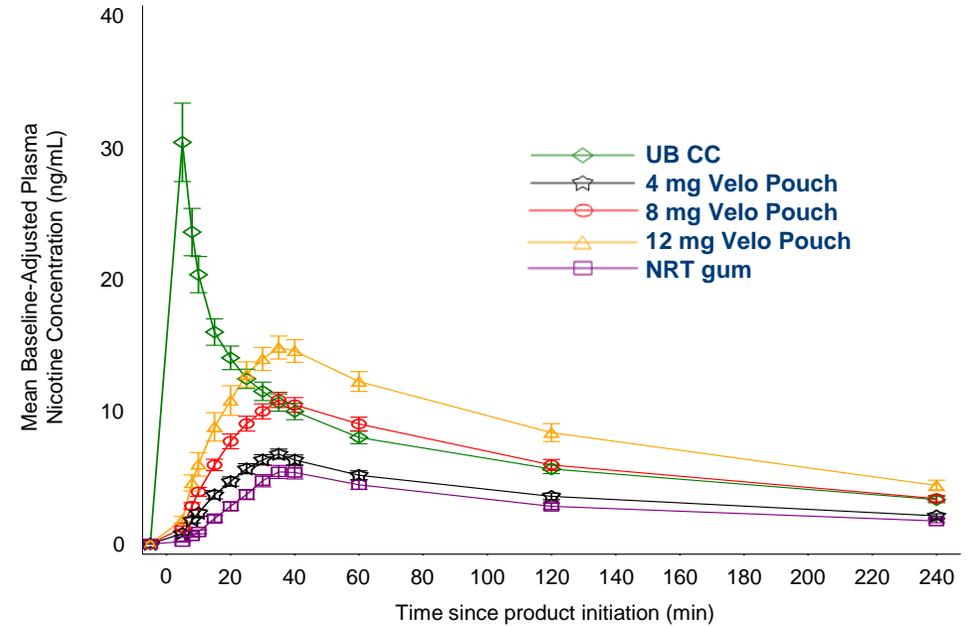
Nicotine Uptake Over Time

PK Study



- Nicotine uptake was similar for all 8 mg nicotine products, irrespective of flavor.
- The 10 mg nicotine product has the highest nicotine curve and peak compared to the 8 mg nicotine products

AL Study



- Nicotine uptake from UB CC was higher and faster compared to Velo Pouches.
- Velo Pouches have a slightly higher nicotine peak compared to NRT gum.

PK Parameters

PK Study		
PK Parameters	Velo (8 mg) N=35/36	Velo (10 mg) N=35
LS Means		
AUC _{nic 0-15} (ng*min/mL)	19.58 - 25.79	34.36
AUC _{nic 0-240} (ng*min/mL)	907.24 - 1097.42	1259.44
C _{max} (ng/mL)	7.12 - 8.67	9.76
Median		
T _{max} (minutes)	35.0	35.0

AL Study					
PK Parameters	UB CC N = 37	Velo (4 mg) N = 40	Velo (8 mg) N = 38	Velo (12 mg) N = 37	NRT (4 mg) N = 38
LS Means					
AUC _{nic 0-15} (ng*min/mL)	268.6	20.3 ^{a,b}	35.1 ^{a,b}	46.8 ^{a,b}	8.2
AUC _{nic 0-240} (ng*min/mL)	1680.5	805.6 ^{a,b}	1305.7 ^{a,b}	1763.1 ^b	648.2
C _{max} (ng/mL)	27.5	6.6 ^{a,b}	10.5 ^{a,b}	14.8 ^{a,b}	5.2
Median					
T _{max} (minutes)	5.1	35.0 ^a	35.0 ^a	35.1 ^a	35.0

a, b = Significantly different from UB and NRT gum at $p \leq 0.05$, respectively.

- Nicotine uptake parameters were generally similar across the 8 mg nicotine products; and higher for the 10 mg product.
- Nicotine uptake for Velo Pouches increased with increasing levels of nicotine.
- These PK parameters were significantly higher than NRT gum but lower than UB CC.

Pharmacodynamics (PD) Parameter – Product Liking

Question asked over 4 hours during and following study product use (5 – 240 minutes):

At this moment, how much do you like the product (0- strongly dislike to 10- strongly like).

PD Parameters	UB CC N = 37	Velo (4 mg) N = 40	Velo (8 mg) N = 38	Velo (12 mg) N = 37	NRT (4 mg) N = 39
LS Means					
AUEC _{PL 5-240}	1895.4	1351.2 ^a	1269.4 ^a	1296.1 ^a	1350.6
E _{max PL}	9.2	7.0 ^a	6.7 ^a	7.1 ^a	7.2

a = Significantly different from UB CC at $p \leq 0.05$

RESULTS:

Both PL parameters for Velo Pouches were similar to NRT gum, and significantly lower than UB CC.

PD - Overall Product Liking (OPL) and Overall Intent to Use Again (OIUA)

Question asked over 4 hours during and following study product use (5 – 240 minutes):

- (1) Overall, how much did you like the product (0- strongly dislike to 10 - strongly like).
- (2) Rate the degree to which you would like to use the product again (0 - not at all to 10 - very much).

PD Parameters	UB CC N = 37	Velo (4 mg) N = 40	Velo (8 mg) N = 38	Velo (12 mg) N = 37	NRT (4 mg) N = 39
LS Means					
E _{overall PL}	8.4	6.5 ^a	6.1 ^a	5.7 ^a	5.7
E _{overall IUA}	8.8	5.0 ^a	4.8 ^a	4.5 ^a	4.7

a = Significantly different from UB CC at p ≤ 0.05

RESULTS:

Both OPL and OIUA slightly decreased with increasing nicotine level of the product.

Both OPL and OIUA were similar to NRT gum, but significantly different compared to UB CC.

PD - Positive and Negative Effects

Question asked over 4 hours during and following study product use (5 – 240 minutes):

Rate the degree to which you feel positive [negative] effects about the product at this moment (0 – I feel no positive [negative] effect to 10 – I feel extremely positive [negative] effects).

PK Parameters	UB CC N = 37	Velo (4 mg) N = 40	Velo (8 mg) N = 38	Velo (12 mg) N = 37	NRT (4 mg) N = 39
Positive Effects - LS Means					
AUEC _{PEpos 5-240}	1415.1	1048.5 ^a	969.3 ^a	991.4 ^a	886.6
E _{max PEpos}	8.9	6.5 ^a	6.5 ^a	6.4 ^a	6.3
Negative Effects - LS Means					
AUEC _{PEneg 5-240}	345.6	336.7	339.7	357.0	259.4
E _{max PENeg}	3.6	2.9	3.1	3.7 ^b	2.2

a, b = Significantly different from UB CC and NRT gum at $p \leq 0.05$, respectively; LS = Least Square.

RESULTS:

Maximum Positive Effects for Velo Pouches were similar to NRT gum but significantly lower than UB CC.

Maximum Negative Effects increased slightly with increasing nicotine levels of Velo Pouches, with the 12 mg nicotine product having significantly higher Negative Effects than NRT gum.

PD- Urge to Smoke (UTS)

Question asked over 4 hours during and following study product use (5 – 240 minutes):

How strong is your current urge to smoke your usual brand cigarette (UB CC)
(0 – No urge to 10 – Extremely strong urge).

PK Parameters	UB CC N = 37	Velo (4 mg) N = 40	Velo (8 mg) N = 38	Velo (12 mg) N = 37	NRT (4 mg) N = 39
UTS LS Means					
AUEC _{UTS 0-15}	65.6	88.8 ^a	83.5 ^a	84.1 ^a	92.8
AUEC _{UTS 0-240}	1658.5	1742.3	1623.9 ^b	1605.0 ^b	1821.3
E _{min UTS}	3.6	5.5 ^a	5.0 ^a	4.6 ^b	6.0

a, b = Significantly different from UB CC and NRT gum at p ≤ 0.05, respectively.

RESULTS:

UTS parameters for Velo Pouches were similar to those of NRT gum than to UB CC during the first 15 minutes of product use.

UTS with use Velo Pouches slightly decreased with increasing nicotine levels of the product.

Summary

1

Nicotine uptake parameters of Velo Oral Nicotine products increased with increasing levels of nicotine; nicotine uptake was generally similar across product flavors at the same nicotine level.

2

Compared to UB CC, Velo Oral Nicotine products had:

- significantly lower scores of PL endpoints and Positive PE
- generally similar Negative PE
- significantly higher UTS during the first 15 minutes of product use

3

Compared to NRT gum, Velo Oral nicotine products had:

- similar scores for PL endpoints and Positive PE
- generally similar negative PE
- generally lower UTS parameters

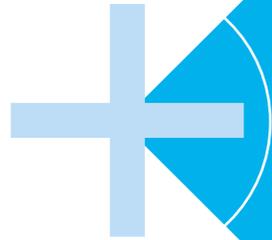
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UTS with use of Velo Oral Nicotine products slightly decreased with increasing nicotine levels of the product.

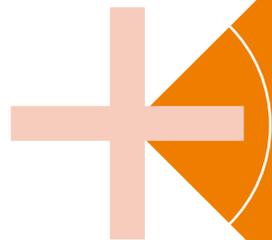
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Velo Oral Nicotine products were well-tolerated in both studies; no SAEs or death reported; AEs were similar to those observed with commercially available FDA-approved NRT gum.

Overall Conclusions



Velo Oral Nicotine products have an abuse liability profile lower than usual-brand cigarettes, and similar to that of a commercially-available NRT gum.



Similar to NRT gum, Velo Oral Nicotine products have a low risk of dependence and may provide levels of nicotine that enable some adult cigarette smokers to transition away from smoking to use of the Oral Nicotine pouches.

Acknowledgements

- **Contract Research Organizations**
 - NCGS
 - ICON
- **Study Sites**
 - Alliance for Multispecialty Research (AMR) Knoxville, TN
 - Icon Early Phase Services, LLC, San Antonio, TX
- **Bioanalytical Laboratory**
 - Celerion
- **RAIS Colleagues**
 - Clinical Studies Division
 - Submissions



Thank You!

Questions?

