Abuse Liability Assessment of the Ploom® System

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[1]Altria Client Services; [2]Japan Tobacco International.

Horizon Innovations LLC is a joint venture between Philip Morris USA Inc. and JTI (US) Holding Inc. for the commercialization of Ploom® in the U.S. market

PARTNERSHIP

Between JT Group and Altria

to Bring Ploom® System to U.S. Adults Who Smoke Age 21+



Abuse Liability

What it is

"The potential of a substance to result in addiction and be used repeatedly or even sporadically resulting in undesirable effects."

FDA, PMTA final rule[1]

Informs the likelihood that:

- Users of one nicotine product would use/switch to another[2]
- New users of a product will progress to regular use[2]

FDA Suggested Assessment

- Within-subject comparison against a product of known abuse liability; peak liking as the usual primary outcome[1]
- Use topography, PK/PD under prescribed and ad libitum use, and real-world actual-use data[1]
- Conclusions rest on all outcome measures together—independently and relative to products of known abuse liability[2]

Two reference products with known abuse liability

High-abuse-liability
UBCC
Positive control

NEW PRODUCT

Low-abuse-liability
Nicotine Gum
Negative control

Neither high nor low abuse liability is the goal[2]

[1]PMTA final rule, 86 FR 55300 [2]Hull & Schroeder, 2023.
FDA=Food and Drug Administration; PMTA=Premarket Tobacco Application; PK=pharmacokinetic; PD=pharmacodynamic; UBCC=usual brand combustible cigarette.

The Ploom® System

Ploom® Device

Generates aerosol without burning of tobacco

Single-use HTS

Five-minute use session with no puff limit



Heated Tobacco Sticks (HTS)

Tobacco-Flavored

- Tobacco 1
- Tobacco 2

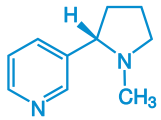
Menthol-Flavored

- Menthol 1
- Menthol 2

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Abuse Liability Assessment Framework

ALA relied on nicotine exposure and subjective effects from using the Ploom® System



NICOTINE EXPOSURE | Pharmacokinetics



SUBJECTIVE RESPONSES | Pharmacodynamics, Product Liking, Satisfaction, Craving, Withdrawal

ALA is also informed by switching potential and potential health risks



USE BEHAVIORS | Actual Use, Product Substitutability

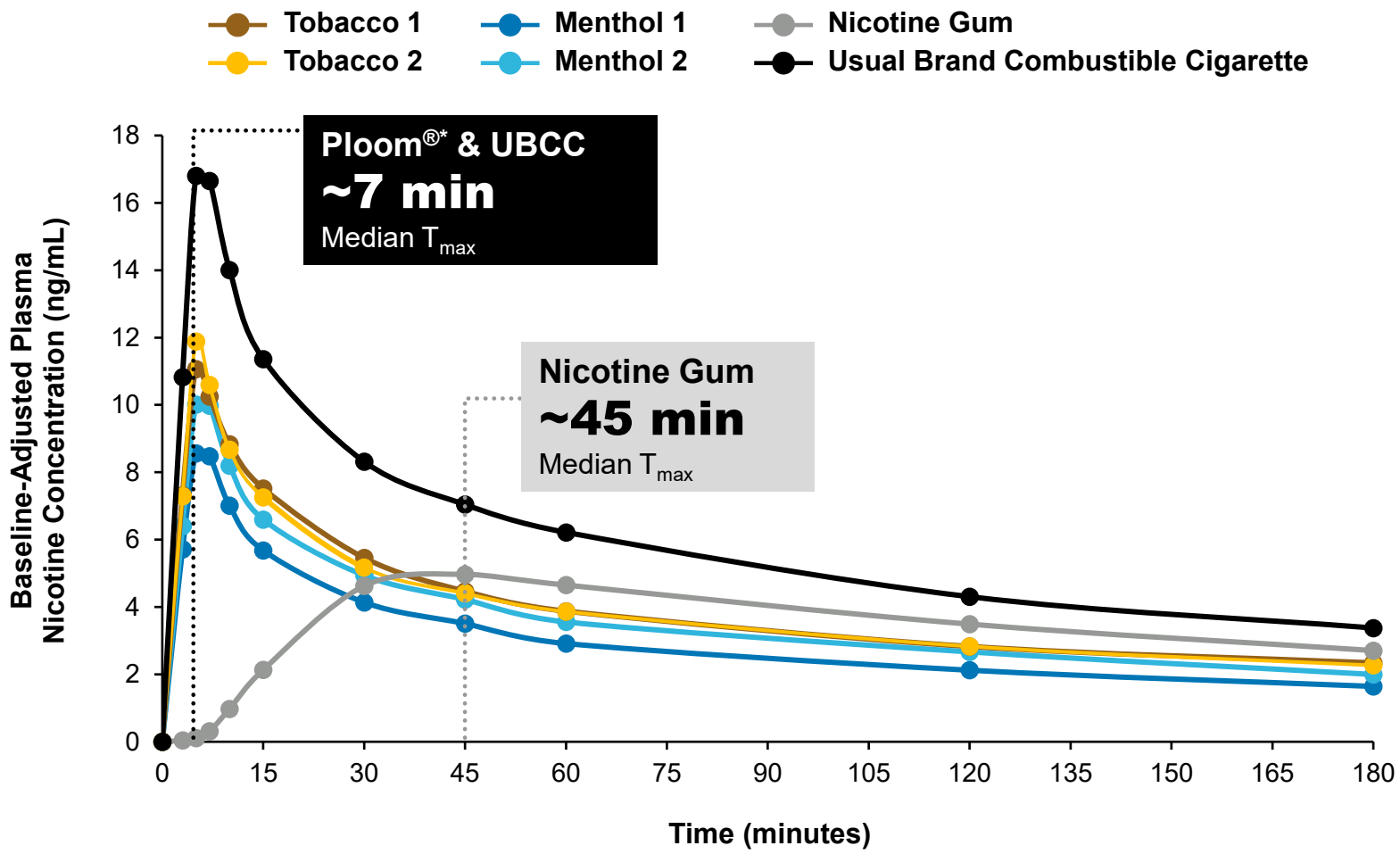


HEALTH RISK | Chemical Analyses, BOE Study

Scan each QR code to see study details and results

ALA= Abuse Liability Assessment; BOE=Biomarkers of Exposure.

Ploom® System Delivers Nicotine at Similar Rate (T_{max}) as Combustible Cigarettes, but Lower in Magnitude (C_{max})



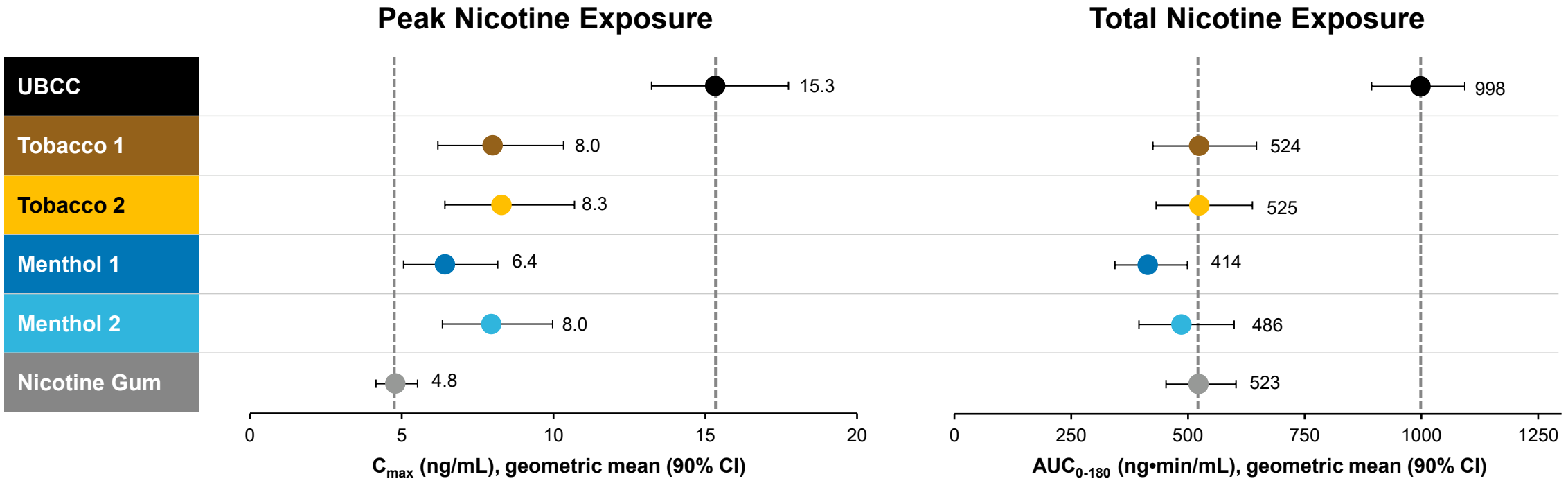
Compared to combustible cigarettes

Rate of nicotine delivery (T_{max}) is similar

Magnitude delivered (C_{max}) is not

Median T_{max} : Ploom® System 6.8–7.0 min
Cmax=maximum nicotine concentration; Tmax=time to maximum concentration.

Total Nicotine Exposure Similar to Nicotine Gum; Peak Sits Between Gum and Combustible Cigarettes



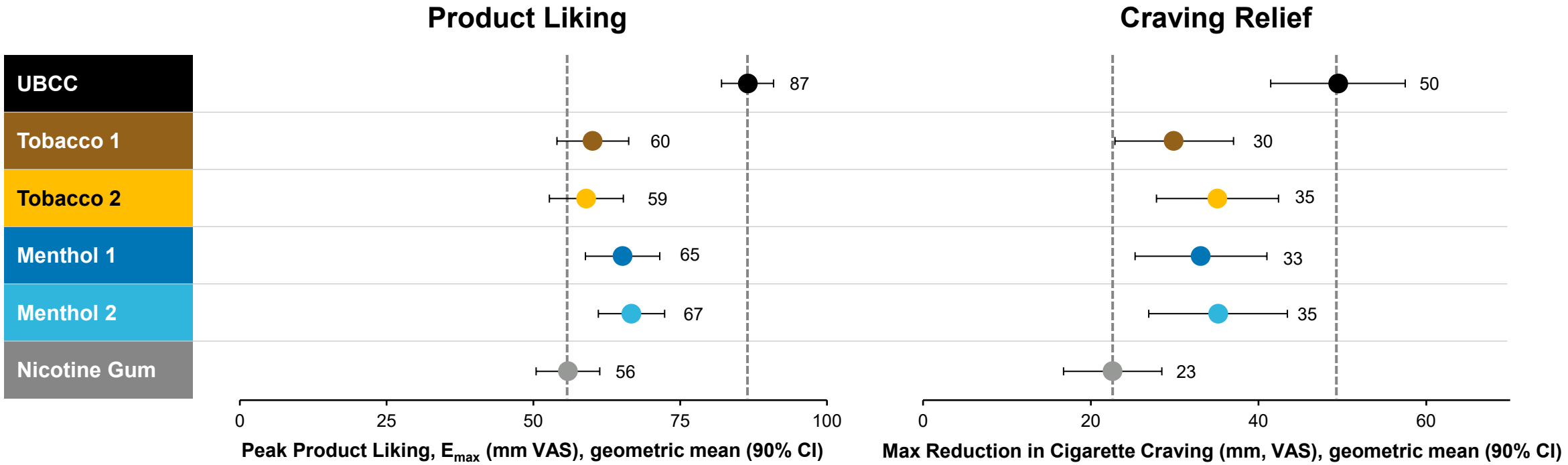
Geometric LS mean ratios: vs. UBCC: C_{max} 42–53%, AUC 42–53% | **vs. Nicotine Gum:** C_{max} 134–169%, AUC 76–100%

Ploom® System exhibits significantly lower magnitude (C_{max}) and extent (AUC) of nicotine exposure than combustible cigarettes

Extent of exposure from Ploom® System was not significantly greater than 4 mg nicotine gum

Dashed lines = UBCC (black) and Nicotine Gum (grey) reference values.
AUC=Area Under the Curve; CI=confidence interval; C_{max}=maximum nicotine concentration; LS=least squares; UBCC=usual brand combustible cigarette.

Liking and Craving Relief: Lower than Combustible Cigarettes; at or Above Nicotine Gum



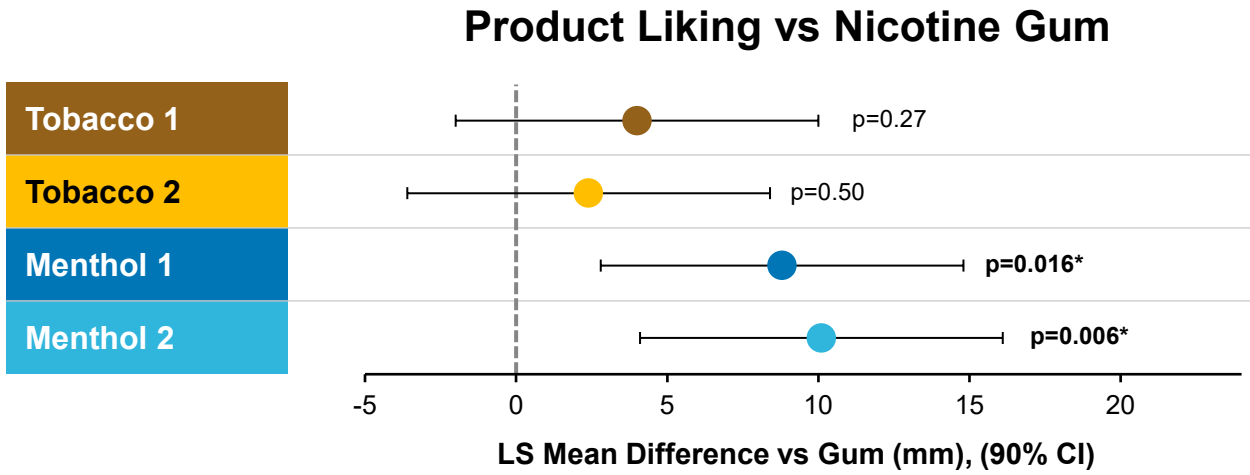
LS mean difference vs. UBCC: Liking E_{max} −20.5 to −28.1; Maximum Craving Relief −14.3 to −19.8 (all p<0.01)

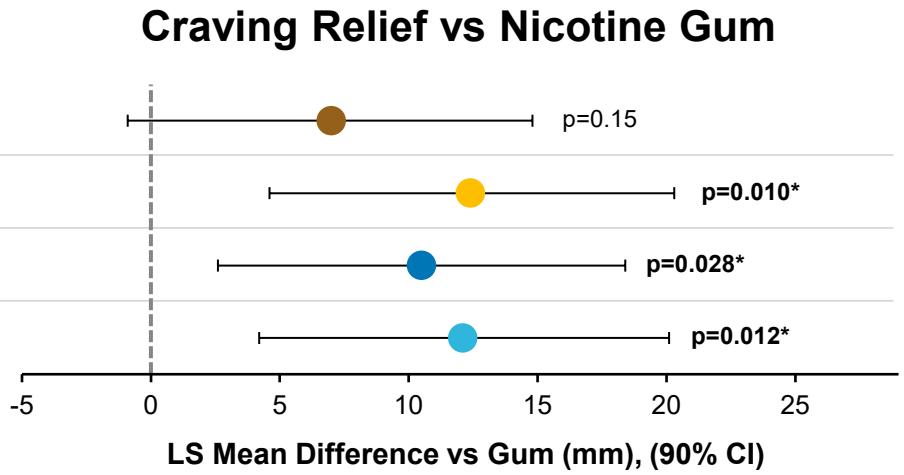
LS mean difference vs. Nicotine Gum: Liking E_{max} +2.4 to +10.1; Maximum Craving Relief +7.0 to +12.4

Reinforcement sits well below combustible cigarettes and at/modestly above an approved NRT

Dashed lines = UBCC (black) and Nicotine Gum (grey) reference values.
CI=confidence interval; E_{max}=peak rating; LS=least squares; mm=millimeter; NRT=nicotine replacement therapy; VAS=visual analog scale.

Impact of Menthol-Flavored Ploom® System on Product Liking and Craving Relief Relative to Nicotine Gum





Converging evidence for flavor

Product Liking:

- Menthol-flavored Ploom® System liked significantly more than Nicotine Gum (p's<0.02)
- Neither tobacco-flavored Ploom® System differed significantly from Nicotine Gum (p's≥0.27)

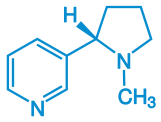
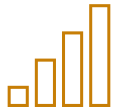
Craving Relief:

- Menthol-flavored Ploom® System reduced craving to a significantly greater degree than Nicotine Gum (p's<0.03)
- One tobacco-flavored Ploom® System variety differed significantly from Nicotine Gum (p=0.01), but not the other (p=0.15)

Flavor influenced subjective responses but not nicotine delivery; exposure was similar across all four HTS

Dashed lines = no difference from nicotine gum. Points right of the line favor Ploom®
*Indicates p<0.10. LS=least squares; HTS=heated tobacco sticks

Abuse Liability Assessment Framework

	**NICOTINE EXPOSURE**	Pharmacokinetics
	**SUBJECTIVE RESPONSES**	Pharmacodynamics, Product Liking, Satisfaction, Craving, Withdrawal
	**USE BEHAVIORS**	Actual Use, Product Substitutability
	**HEALTH RISK**	Chemical Analyses, BOE Study

Scan each QR code to see study details and results

BOE=biomarkers of exposure.

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Nearly All Adults Who Smoked Adopted Ploom® System And Intended To Keep Using It

By the end of a 6-week Actual Use Study among adults who smoked and were not planning to quit (n=416)

98.3%

met "started using" criteria by Week 6 (used ≥20 sticks)

5.1–5.3

mean product liking at end of study (out of 7)

65.9%

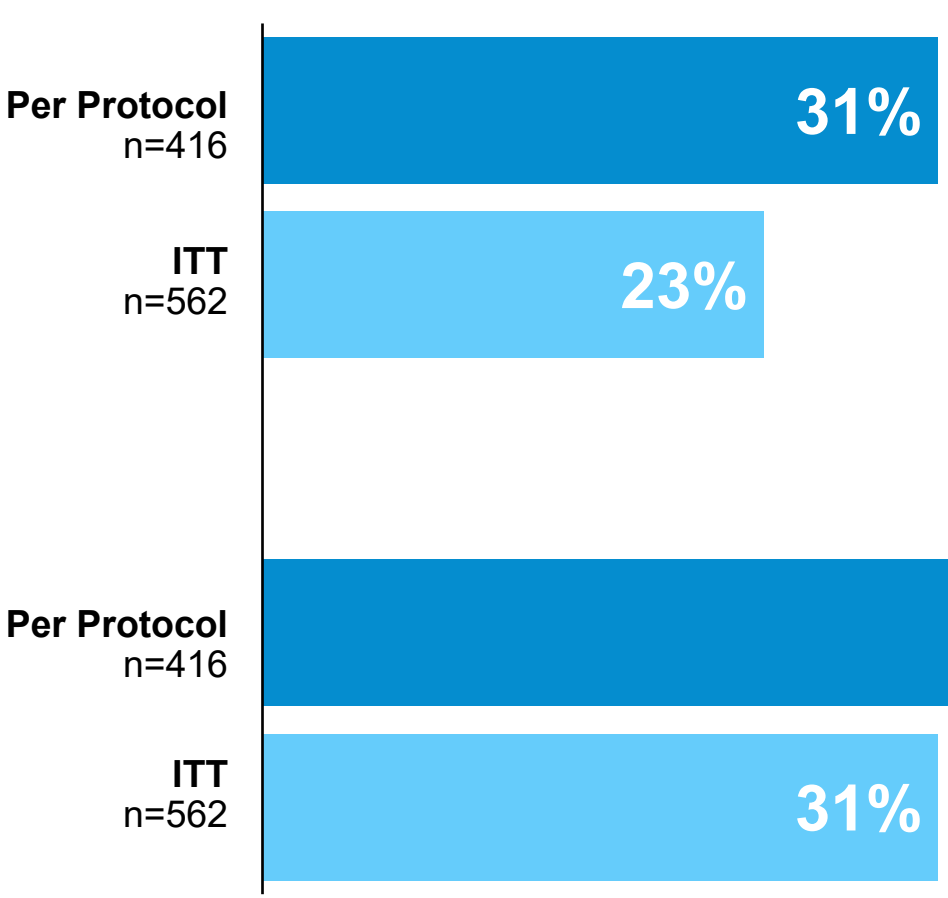
intended to switch to Ploom® System

57.7%

intended to purchase Ploom® System

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Many Adults Who Smoke Switched Completely or Substantially Reduced Combustible Cigarette Consumption by ≥50%



Switched Completely
to the Ploom® System



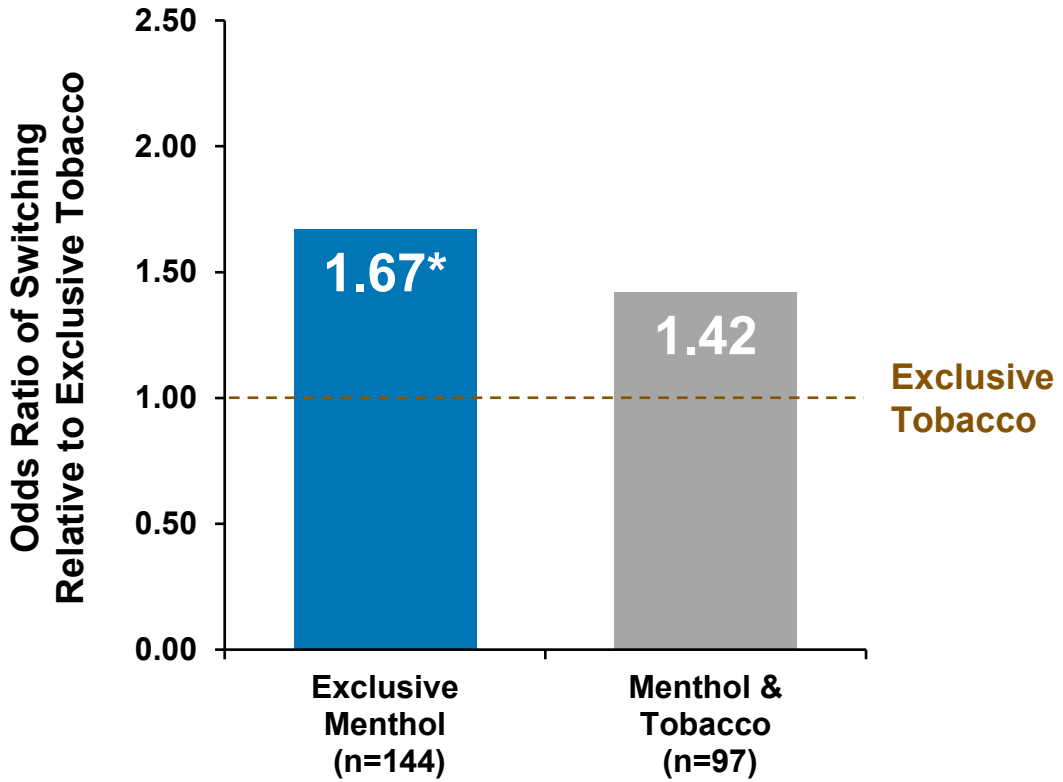
Reduced Cigarette Consumption by ≥50%
(exclusive of switching)

ITT=intention to treat. Per Protocol Sample included only those who completed the study; ITT sample included all enrolled at Week 1.

Impact of Menthol-Flavored Ploom® System Use on Switching or Reducing Smoking Relative to Tobacco-Flavored

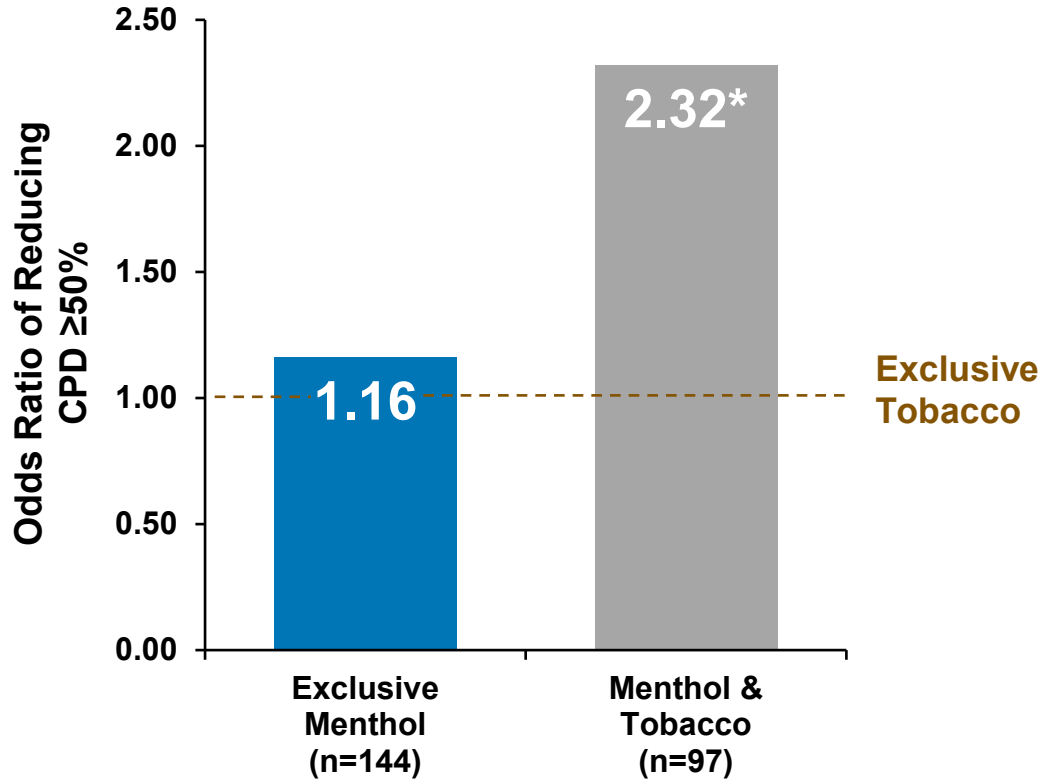
Odds of Complete Switching at Week 6

(based on those who used Ploom® System in Week 6; n=413)



Odds of Reducing CPD by ≥50% at Week 6

(based on those who used Ploom® System in Week 6; n=413)



*Indicates statistically significant at p<0.05

Abuse Liability Assessment Framework

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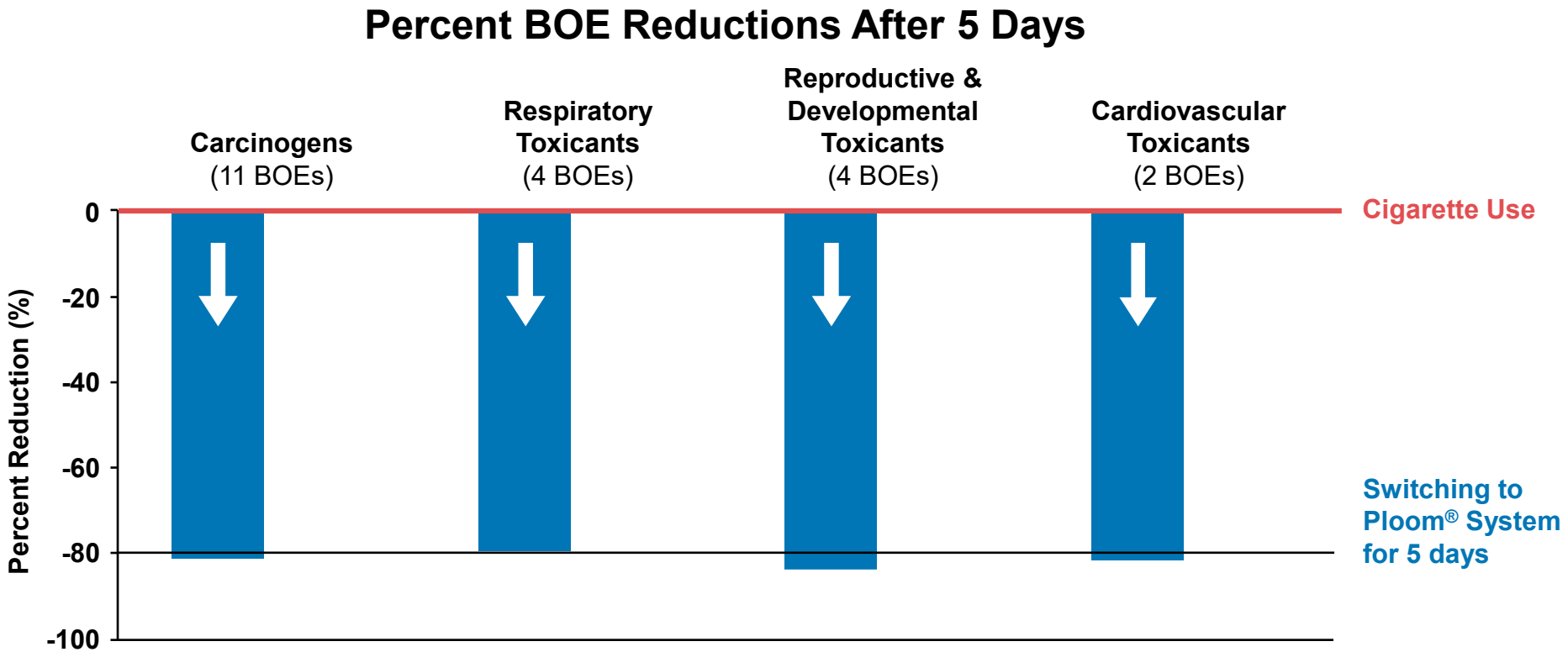
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BOE=biomarkers of exposure.

Biomarkers of Exposure are Significantly Reduced Among Switchers Based on Clinical Assessment

>80%

Overall average reduction



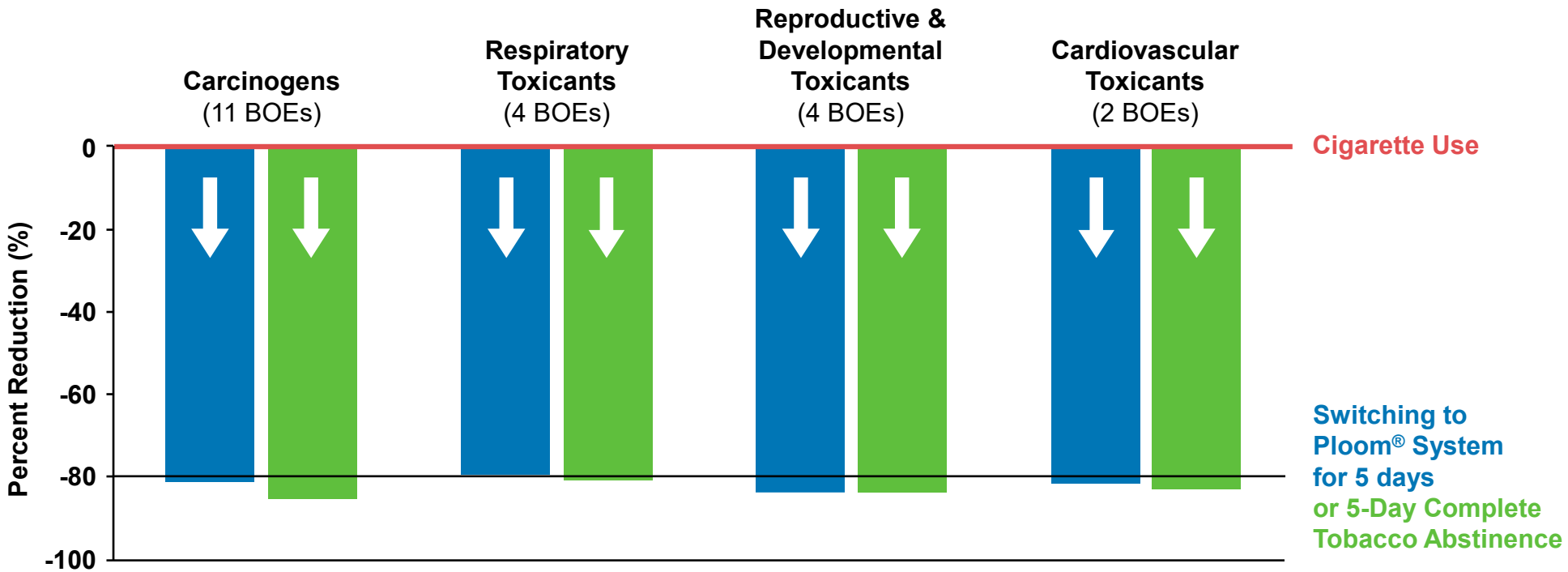
Blue Bars represent median percent reductions in measured BOEs when adult smokers completely switched to Ploom for 5 days in our clinical study. Some BOEs have more than one classification and are included for each of their classifications. Nicotine BOE is not included.
BOE=biomarkers of exposure.

BOE Reduction When AS Switch to Ploom® System Comparable to Abstaining From all Tobacco Use Except for Nicotine Exposure

>80%

Overall average reduction

Percent BOE Reductions After 5 Days



Percent Reductions in BOEs among adult smokers who **completely switched to Ploom® System** were comparable to **complete tobacco abstinence**, excluding nicotine

Blue Bars represent median percent reductions in measured BOEs when adult smokers completely switched to Ploom for 5 days in our clinical study. Green Bars represent median percent reductions in measured BOEs when adult smokers abstained from all tobacco for 5 days in our clinical study. Some BOEs have more than one classification and are included for each of their classifications. Nicotine BOE is not included.
BOE=biomarkers of exposure.

Totality of the Evidence: Abuse Liability of the Ploom® System is Likely Lower than Combustible Cigarettes, yet Sufficient to Support Switching

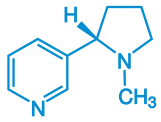
The abuse liability of Ploom® System is likely lower than Combustible Cigarettes

Nicotine exposure is lower than combustible cigarettes

Ploom® System was liked by adults who smoke, but not as much as their usual brand combustible cigarettes

Many adults who smoke switch to Ploom® System or reduce consumption of combustible cigarettes by ≥50%

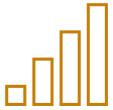
Substantially lower exposure to HPHCs compared to combustible cigarettes



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HEALTH RISK | Chemical Analyses, BOE Study

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Any Questions?