Nicotine Pharmacokinetics and Subjective Effects During Use of Ploom® System Compared to Combustible Cigarettes and Nicotine Gum Among Adults Who Smoke

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INTRODUCTION

- The Ploom® System is an innovative Heated Tobacco Product (HTP) developed by Japan Tobacco Inc. Horizon Innovations LLC is a joint venture between Philip Morris USA Inc. and JTI (US) Holding Inc. for the commercialization of Ploom® system in the U.S. market; thereby providing adult (21+ years old) who smoke an additional potential tobacco harm reduction choice.
- To gain insights on the Ploom® System's nicotine pharmacokinetics (PK) profiles and its impact on subjective effects, we designed a randomized, six-way crossover clinical study in confinement to characterize the plasma nicotine PK and subjective effects of four Ploom® Heated Tobacco Sticks (HTS) (2 menthol variants and 2 tobacco flavor variants) in adult menthol and non-menthol combustible cigarette smokers who have never used HTPs. The study included participants' Usual Brand Combustible Cigarettes (UBCC) and a 4 mg mint flavored Nicorette® nicotine gum as high and low abuse liability comparator products, respectively.
- The Ploom® System is comprised of a rechargeable Ploom® heated tobacco device and heated tobacco sticks. To use, a single HTS is inserted into the Ploom® device which heats the HTS to an operating temperature without combustion to generate an inhalable nicotine-containing aerosol. An HTS consists of several ingredients including tobacco (cut-filler), humectants, water, and additives. Each HTS' use duration is limited to approximately five minutes by the device. After use, the device will automatically shut off, and the HTS can be removed and discarded without special care.

METHODS

- A total of 60 generally healthy adult smokers of menthol and non-menthol combustible cigarettes who met all inclusion and no exclusion criteria were enrolled and randomized across three clinical sites. Eligible participants received the Ploom® System along with four heated tobacco sticks (HTS) flavor variants six days prior to site check-in, along with instructions for product acclimation. Participants were expected to use each HTS flavor variant ad libitum at least once before check-in.
- On Day -1, participants checked in for a 6-day confinement period and were randomized to one of six product use sequences based on a Latin square design for this crossover study. That afternoon, participants began their first ad libitum product use session according to their assigned sequence. The product used on Day -1 was also used in the following morning's PK test session.
- From Days 1 to 6, each day included a morning PK test session followed by an afternoon ad libitum product use session to prepare for the next day's PK session. Use of the Ploom® system and usual brand combustible cigarettes (UBCC) was limited to 5 minutes per session, while nicotine gum use was limited to 30 minutes, in accordance with product instructions. Venous blood samples were collected at specified time points (-5 minutes prior to product use and at 3, 5, 7, 10, 15, 30, 45, 60, 120 and 180 minutes after product use) for PK analysis for nicotine and N-Nitrosonornicotine (NNN) as an exploratory endpoint.
- Participants also completed subjective assessments during each morning PK session, including Product Liking (PL), Tobacco/Nicotine Withdrawal (TNW), Direct Effects of Product (DEP), and the Modified Cigarette Evaluation Questionnaire (mCEQ).

STUDY DESIGN

Study Design
Randomized, six-way cross-over study including:

PLOOM® SYSTEM

COMPARATOR PRODUCTS

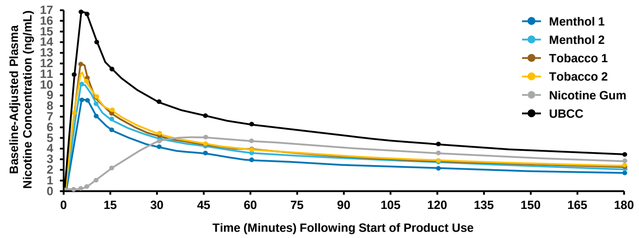
Key Outcomes
Plasma nicotine pharmacokinetics of study products assessment of subjective effects:

- ✓ Nicotine /Tobacco Withdrawal Symptoms
- ✓ Direct Effects of the Product (DEP)
- ✓ Product Liking
- ✓ Modified Cigarette Evaluations Questionnaire (mCEQ) (modified for HTP)

DATA CATEGORY		OVERALL Mean (SD)/ Range (min/max)
Mean Age (SD)		39 (7.63)
Body Mass Index (kg/m²) (SD)		30.62 (5.63)
Usual Brand Cigarette Flavor Category (%)	Menthol	30 (50%)
	Non-Menthol	30 (50%)
Cigarettes per Day (min/max)		15.7 (10/30)
Years of Cigarette use (min/max)		21.1 (2/40)

RESULTS

Baseline-Adjusted Plasma Nicotine Concentrations Over Time

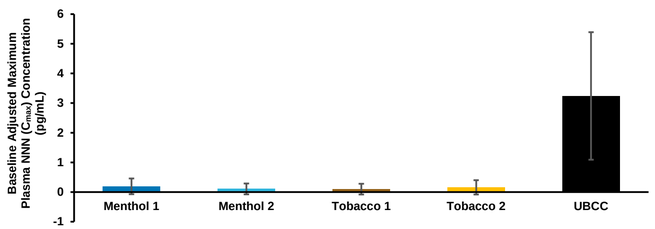


Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters

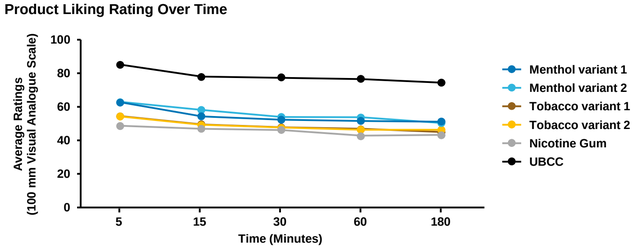
Study Product	n	$AUC_{(nic\ 0\text{-}180)}$ (ng*min/mL) GM (SD)	C_{max} (ng/mL) GM (SD)	T_{max} (min) (Median)
Menthol 1	57	414.10 (307.71)	6.43 (7.39)	6.80
Menthol 2	57	486.40 (373.77)	7.95 (8.50)	6.97
Tobacco 1	60	524.90 (409.42)	8.29 (10.78)	7.00
Tobacco 2	59	524.20 (400.21)	7.99 (9.59)	6.90
Nicorette® 4 mg Mint Nicotine Gum	57	522.70 (363.23)	4.79 (3.45)	45.00
Usual Brand Combustible Cigarettes	57	988.00 (465.43)	15.32 (14.51)	7.00

Abbreviations: $AUC_{(nic0\text{-}180)}$=baseline-adjusted area under the plasma nicotine concentration-versus-time curve from time zero to 180 minutes after the start of study product use; C_{max}=maximum baseline-adjusted plasma nicotine concentration; GM=geometric mean; SD=standard deviation; T_{max}= time to baseline adjusted maximum plasma nicotine concentration.

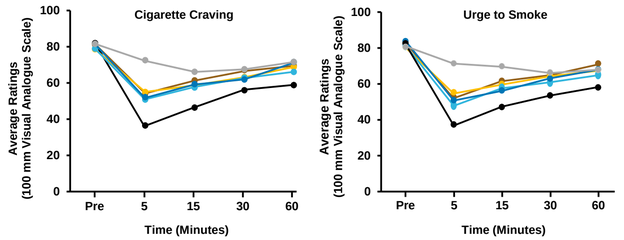
Baseline-Adjusted Maximum Plasma NNN Concentrations (C_{max})



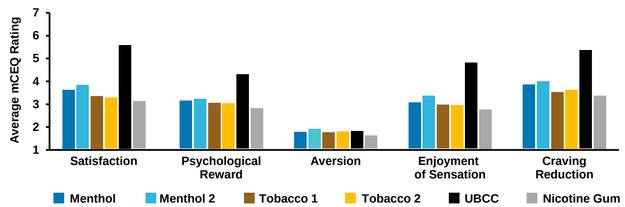
Product Liking Rating Over Time



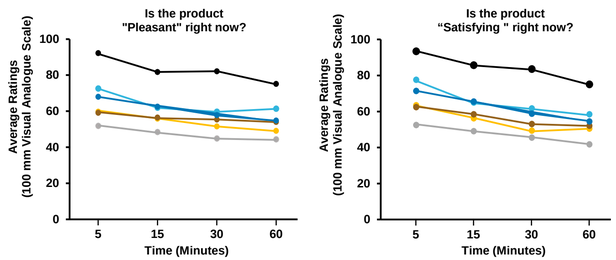
Nicotine/Tobacco Withdrawal Symptoms



Modified Cigarette Evaluations Questionnaire



Direct Effects of Product



SAFETY

A total of 22 AEs were reported, seven of which were considered likely related or related to Ploom® System use; one of which occurred (dyspepsia) during the product trial and six during clinical confinement. Of the six, dyspepsia (Menthol Variant 2), dizziness (Menthol Variant 1 and 2), nausea (Menthol Variant 1), vomiting (Menthol Variant 1) were considered likely related to candidate product use, and a headache (Tobacco Variant 1) was considered to be definitely related to Ploom® System use. All AEs were determined to be mild in severity and similar to those typically reported for use of other nicotine-containing products .

CONCLUSIONS

Maximum plasma nicotine concentration (C_{max}) is lower with the Ploom® system compared to UBCC across all four flavor varieties.

Total nicotine exposure (AUC) is lower with the Ploom® system compared to UBCC but similar to NRT gum.

Maximum plasma NNN concentration is lower with the Ploom® System, with reductions ranging from 94 to 97% compared to UBCC.

The Ploom® System effectively reduced cigarette craving and urge to smoke to levels close to combustible cigarettes and greater than nicotine gum across all flavor variants.

Product liking scores for the Ploom® System were comparable to nicotine gum but lower than combustible cigarettes.

Positive subjective responses in Direct Effects of Product (DEP) and Modified Cigarette Evaluation Questionnaire (mCEQ), were higher for the Ploom® system than for nicotine gum, but lower than for combustible cigarettes.

Overall, these findings suggest that the Ploom® System is a potentially satisfying and acceptable alternative for adults who smoke, with lower abuse liability compared to combustible cigarettes.

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