Characterization of Nicotine Pharmacokinetics and Subjective Effects During Use of Heated Tobacco Products in Adults Who Smoke

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Introduction

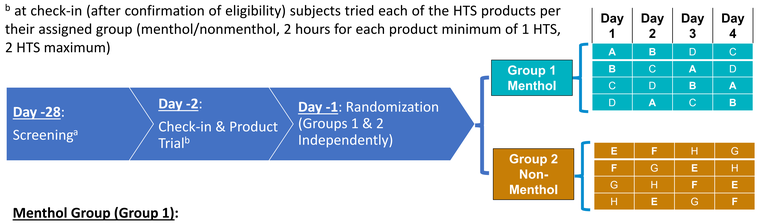
The Ploom® system is comprised of a rechargeable Ploom® heated tobacco device and heated tobacco sticks (HTS), an innovative heated tobacco product (HTP) developed by Japan Tobacco International SA. Horizon Innovations LLC is a joint venture between Philip Morris USA Inc. and Japan Tobacco International (US) Holding Inc. for the commercialization of the Ploom® system in the U.S. market; thereby providing adults 21+ who smoke (AS) with an additional choice for tobacco harm reduction. To gain insights on a Ploom® system prototype, nicotine PK profiles and its impact on subjective effects, we designed a six-day pilot study in confinement using a Ploom prototype device and HTS (two tobacco and two menthol flavor variants) compared to the subject's usual brand combustible cigarette (UBCC) and a comparator HTP in adult smokers. To use, a single HTS is inserted into the Ploom® device which heats the HTS in a controlled manner to an operating temperature without combustion to generate an inhalable 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. Once the predetermined use duration is reached, the device will automatically shut off, and the HTS can be removed and discarded.

Methods

Study objectives were to: 1) Characterize PK parameters following use of the study products (3 HTPs and 1 UBCC in each Group), 2) Compare the subjective effects after using the study products, 3) Determine the number of puffs taken during the use of each HTP during a 5-minute *ad libitum* use session (PK test sessions on Days 1-4), and 4) collect and evaluate safety information associated with use of the study products. The study recruited healthy male and female adults who smoke combustible cigarettes exclusively (n=24 per group), with the goal of completing 20 subjects per group. To participate in the study, adults who smoke had to be between the ages of 22 to 65 years of age inclusive at screening, self-reported smoking 10-30 cigarettes daily in the last 12 months, and were current menthol (Group 1) or non-menthol (Group 2) combustible cigarette smokers. Adults who smoke that met all the inclusion criteria and none of the exclusion criteria were checked-in on Day -2 and participated in a 6-hour *ad libitum* product trial, during which they tried at least one of each of the three HTP products based on their usual brand cigarette flavor category. Subjects that completed the product trials were randomized on Day -1 to a product use sequence. On the afternoon of Day -1, after randomization and on Days 1-3, after the morning PK test session, subjects completed a four-hour *ad libitum* product use session using at minimum, one study product and a maximum of four study products. The products used in the four-hour afternoon *ad libitum* session were the same products to be used during the following day's PK test session. On the morning of Days 1-4, following an overnight 12-hour tobacco/nicotine product abstinence, subjects participated in PK assessments lasting 3 hours following an 5-minute *ad libitum* study product use. During the PK assessment and following the product use, subjects were asked to provide their subjective ratings on a visual analogue scales for the Tobacco/ Nicotine Withdrawal, Direct Effects of Product, and Use the Product Again. Subjects also provided Modified Cigarette Evaluation Questionnaire responses (a modified HTP version was used for HTPs) on a 7-point Likert scale at various time points after using the product.

Study Design

[a] occurred up to 28 days prior to check-in
[b] at check-in (after confirmation of eligibility) subjects tried each of the HTS products per their assigned group (menthol/nonmenthol, 2 hours for each product minimum of 1 HTS, 2 HTS maximum)



	Day 1	Day 2	Day 3	Day 4
Group 1 Menthol	A	B	D	C
	B	C	A	D
	C	D	B	A
	D	A	C	B
Group 2 Non-Menthol	E	F	H	G
	F	G	E	H
	G	H	F	E
	H	E	G	F

Menthol Group (Group 1):

Product A: Ploom® HTS Menthol-Flavored Variant 1; **Product B**: Ploom® HTS Menthol-Flavored Variant 2; **Product C**: Menthol HTP comparator; **Product D**: Menthol usual brand combustible cigarettes.

Non-Menthol Group (Group 2):

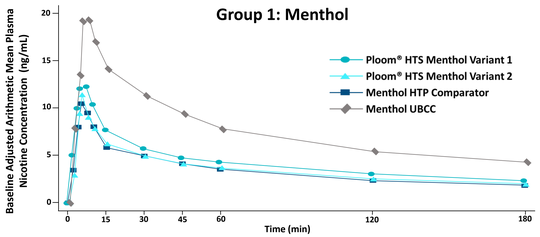
Product E: Ploom® HTS Tobacco-Flavored Variant 1; **Product F**: Ploom® HTS Tobacco-Flavored Variant 2; **Product G**: Non-menthol HTP comparator; **Product H**: Non-menthol usual brand combustible cigarettes.

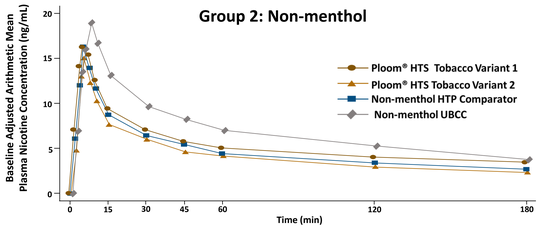
Results

Study Subject Summary

Demographics	Group 1 (Menthol) Mean (SD)	Group 2 (Non-menthol) Mean (SD)
Age	37.0 (7.34)	39.5 (9.83)
Sex (M/F)	12/12	13/10
BMI	30.1(5.18)	31.2 (5.79)
Number of cigarettes smoked per day	13.5 (4.67)	17.6 (5.71)
Number of years of cigarette use	17.5 (8.11)	19.5 (11.4)

Plasma Nicotine Pharmacokinetics





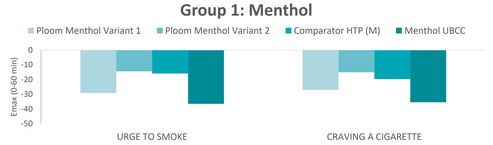
Abbreviations: HTS = heated tobacco stick; UBCC = usual brand combustible cigarette; **Note**: Ploom® device and heated tobacco sticks used in this study are prototypes.

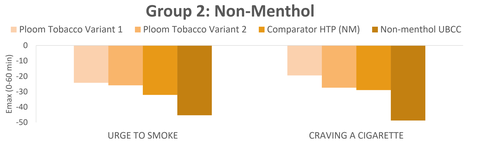
Summary of Baseline-Adjusted Plasma Nicotine PK Parameters and Puff Count by Study Products with 5-Minute *Ad Libitum* Product-Use

Study Group	Study Product	$AUC_{nic\ (0\text{-}180)}$ (min*ng/mL)	$C_{max(0\text{-}180)}$ (ng/mL)	Puff Count Per Unit
Group 1: Menthol GM (SD)	Ploom® HTS Menthol-Flavored Variant 1	528* (628)	8.24* (14.1)	18.9 (9.31)
	Ploom® HTS Menthol-Flavored Variant 2	411* (477)	6.16* (11.4)	19.8 (8.90)
	Menthol HTP Comparator	488* (453)	8.41* (12.9)	17.0 (5.78)
	Menthol UBCC	1135 (812)	17.9 (18.1)	14.5 (4.02)
Group 2: Non-Menthol GM (SD)	Ploom® HTS Tobacco-Flavored Variant 1	884 (353)	15.1 (11.6)	21.5 (6.75)
	Ploom® HTS Tobacco-Flavored Variant 2	722* (408)	12.7* (11.6)	19.5 (7.71)
	Non-menthol HTP Comparator	639* (373)	11.9* (12.8)	19.4 (5.22)
	Non-Menthol UBCC	1117 (596)	17.6 (11.8)	15.5 (5.23)

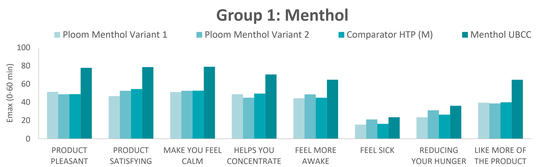
Abbreviations: AUCnic(0-180) = baseline-adjusted area under the plasma nicotine concentration-versus-time curve from time zero to 180 minutes after the start of study product use; Cmax(0-180) = maximum baseline-adjusted plasma nicotine concentration; HTS = heated tobacco stick; UBCC = usual brand combustible cigarette; GM: geometric mean; SD: standard deviation; *: p-value less than 0.05 and statistically significant compared to UBCC. **Note**: Ploom® device and heated tobacco sticks used in this study are prototypes; Per Unit = 1 heated tobacco stirk or 1 subject's usual brand of combustible cigarette.

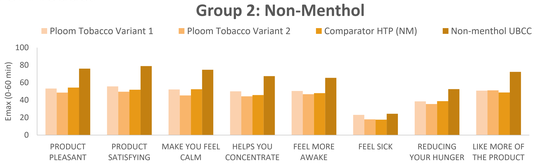
Tobacco/Nicotine Withdrawal



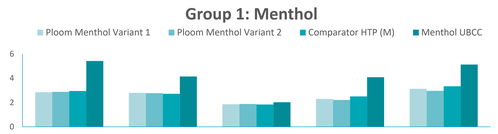


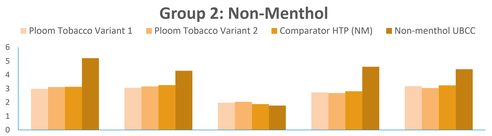
Direct Effects of Product





Modified Cigarette Evaluation (mCEQ) at 180 minutes after study product use





For all graphs, (M) = Menthol , (NM) = Non-menthol, Ploom Menthol Variant 1 = Ploom® HTS Menthol Variant 1, Ploom Menthol Variant 2 = Ploom® HTS Menthol Variant 2, Comparator HTP (M) = Menthol HTP Comparator, Ploom Tobacco Variant 1 = Ploom® HTS Tobacco Variant 1, Ploom Tobacco Variant 2 = Ploom® HTS Tobacco Variant 2. and Comparator HTP (NM) = Non-menthol HTP Comparator. All Ploom® device and heated tobacco sticks used in this study are prototypes.

Use the Product Again

	Ploom Menthol Variant 1	Ploom Menthol Variant 2	Menthol HTP Comparator	UBCC Menthol	Ploom Tobacco Variant 1	Ploom Tobacco Variant 2	Non-menthol HTP Comparator	UBCC Non-menthol
-50 to < 0 (%)	60.9	58.3	58.3	25	50	45.5	38.1	13.6
0 (%)	0	8.3	16.7	0	13.6	18.2	9.5	13.6
> 0 to 50 (%)	39.1	33.3	25	75	36.4	36.4	52.4	72.7

Note: Visual Analogue Scale from 0 through **100: -50** = Definitely Would Not; **0** = Don't Care, **50** = Definitely Would. The bipolar score is calculated by subtracting 50 from the original score (0 - 100).

Adverse Experiences: Two subjects reported two adverse experiences (AE) during the study (1 incidence of dyspepsia and 1 incidence of nausea). Ploom® System related adverse experience, a single incidence of dyspepsia, was mild and transient in nature. No serious adverse experience occurred during the study.

Conclusion

Among the adults who smoke cigarettes exclusively, prototype Ploom® System:

- Delivered nicotine at levels comparable to comparator HTPs but less than subjects' usual brand of combustible cigarettes (UBCC).
- Reduced urge to smoke and cigarette cravings were similar to comparator HTPs; however, reductions were less than subjects' UBCC
- Showed potential to be a satisfying and pleasant alternative to cigarettes for adults who smoke.
- Tolerated well by all subjects.

The data suggests the prototype Ploom® System can provide U.S. Adults who smoke with options for achieving Tobacco Harm Reduction.

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