A two-arm randomized, within-arm crossover study in confinement to assess abuse liability of glo heated tobacco products

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Abstract

FDA guidance recommends assessment of abuse liability (AL) as part of a Premarket Tobacco Product Application. Recent studies on next-generation nicotine delivery systems suggest product liking, sufficient nicotine delivery, and availability of flavors are important elements in aiding the adoption and transition of smokers to non-combustible alternatives. glo is a heated tobacco product (HTP) that produces inhalable aerosol containing nicotine without combustion of tobacco. Publications on HTPs have demonstrated large and significant reductions in biomarkers of exposure (BOE) to chemical toxicants from HTP aerosol in subjects switched to HTP.

Introduction

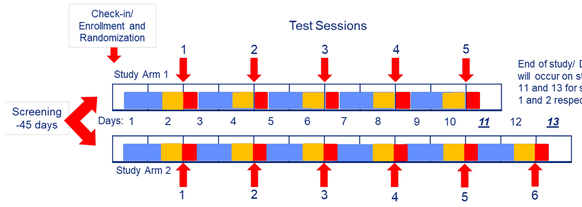
Cigarette smoking is a leading cause of preventable death in the US and significantly increases the risk of developing lung cancer, heart disease, chronic obstructive pulmonary disease, and other serious diseases and adverse health conditions. The risk for serious disease is significantly affected by the type of tobacco product used and the frequency, duration, and manner of use. Research indicates that it is the combustion of tobacco (i.e., cigarette smoking) rather than the nicotine that exposes tobacco consumers to the most risk and suggests the existence of a pronounced “continuum of risk” of tobacco and nicotine replacement products.

At the higher end of the risk continuum are traditional combustible tobacco products. During cigarette smoking, the tobacco leaf is combusted at temperatures typically greater than 600°C and commonly around 800°C, resulting in incomplete pyrolysis of the plant material. As well as releasing nicotine into the cigarette smoke, combustion also causes the formation of over 8,000 chemical compounds, many of which are known human toxicants and carcinogens when inhaled. At the lower end of the risk continuum are nicotine replacement therapies (NRTs). Nicotine is the active ingredient in these products, but they do not expose the user to the carcinogens present in combustible tobacco products. Although it is addictive, nicotine alone is not considered a significant threat to health. Within the context of this tobacco risk continuum, more research needs to be done to secure a firm place for heated tobacco products (HTPs) being evaluated in this study on the risk continuum by public health experts. Encouraging smokers to switch to products that have potential to reduce risk from smoking.

Despite the known health risks of smoking, roughly one in five adults still smokes, and a subset of those adults is expected to maintain long-term nicotine use of nicotine-containing products. The 2014 Surgeon General’s report, as well as various tobacco control experts, have concluded that alternative nicotine delivery products may be useful and appropriate to benefit public health by delivering sufficient nicotine, and with sufficient appeal and abuse potential, to be adopted by current smokers in place of combustible cigarettes. This study provides information on the elements of abuse liability (AL) of HTP investigational products (IPs) by studying the initial experiences of these products with smokers.

Study Design

This was a single center, open-label, randomized, two-arm, within-arm crossover study designed to evaluate elements of AL including subjective effects and physiological measures (pharmacodynamics [PD]), along with plasma nicotine uptake (PK) during and following ad libitum use of the HTP IPs in generally healthy smokers.



Abbreviations: hr=hour; IP=Investigational Product; PD=pharmacodynamic; PK=pharmacokinetic; UB=usual brand

Investigational Products Used

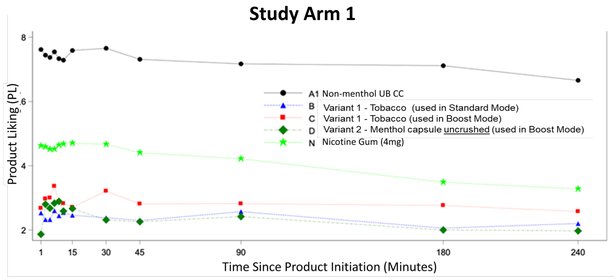
Study Arm 1: glo Heated Tobacco Products	
B	Variant 1 - Tobacco (used in Standard Mode)
C	Variant 1 - Tobacco (used in Boost Mode)
D	Variant 2 - Menthol capsule uncrushed (used in Boost Mode)
Study Arm 2: glo Heated Tobacco Products	
E	Variant 3 - Menthol (used in Standard Mode)
F	Variant 3 - Menthol (used in Boost Mode)
G	Variant 4 - Menthol (used in Boost Mode)
H	Variant 2 - Menthol capsule crushed (used in Boost Mode)
Comparator Products	
A1, A2	Usual brand filtered, non-menthol (Study Arm 1) or menthol (Study Arm 2) combustible cigarette
N	NRT: Nicorette White Ice Mint 4 mg nicotine polacrilex gum

Results

- Key primary and secondary endpoint measures are presented below in graphs with pertinent data below the graphs.

Data table incudes p-values of each comparisons: **p-value$_{UBCC}$** represent p-values of HTP IP against cigarette and **, p-value$_{NRT}$** represent p-values of HTP IP against NRT (nicotine gum).
Statistical significance was set at p ≤ 0.0042 for primary endpoints and at <0.05 for secondary endpoints (adjusted for multiple comparisons).

Study Arm 1



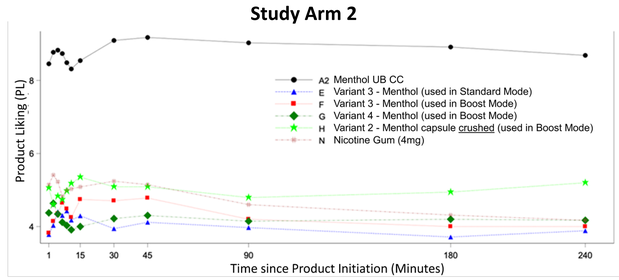
Variant 1 - Tobacco in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 1 – Tobacco in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule uncrushed in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUEC$_{PL\ 5\text{-}240}$				
529.73 (<0.0001, 0.0004)	655.92 (<0.0001, 0.0181)	518.71 (<0.0001, 0.0002)	1658.65	905.27
$E_{max\ PL}$				
3.42 (<0.0001, <0.0001)	4.11 (<0.0001, 0.0026)	3.52 (<0.0001, <0.0001)	8.25	5.64

Variant 1 - Tobacco in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 1 – Tobacco in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule uncrushed in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUC$_{nic\ 0\text{-}15}$ (ng*min/mL)				
51.50 (<0.0001, <0.0001)	42.98 (<0.0001, <0.0001)	41.26 (<0.0001, <0.0001)	158.04	6.18
AUC$_{nic\ 0\text{-}240}$ (ng*min/mL)				
388.13 (<0.0001, 0.0015)	378.94 (<0.0001, 0.0011)	389.24 (<0.0001, 0.0013)	1123.73	647.80
C_{max} (ng/mL)				
5.84 (<0.0001, 0.2544)	5.49 (<0.0001, 0.4012)	5.46 (<0.0001, 0.4030)	16.29	4.59

Variant 1 - Tobacco in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 1 – Tobacco in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule uncrushed in Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUEC$_{UTS\ 0\text{-}15}$				
127.97 (<0.0001, 0.0162*)	127.48 (<0.0001, 0.0130*)	133.26 (<0.0001, 0.1443)	100.76	140.89
AUEC $_{UTS\ 0\text{-}240}$				
1803.23 (0.1657, 0.9957)	1724.20 (0.9623, 0.1503)	1763.71 (0.5000, 0.4574)	1726.83	1803.53
$E_{min\ UTS}$				
4.86 (<0.0001, 0.2578)	4.85 (<0.0001, 0.2569)	4.94 (<0.0001, 0.3483)	2.46	5.32

* Statistically significant difference from NRT

Study Arm 2



Variant 3 - Menthol in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 3 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 4 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule crushed In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUEC$_{PL\ 3\text{-}240}$					
912.95 (<0.0001, 0.1895)	986.60 (<0.0001, 0.4838)	976.06 (<0.0001, 0.4308)	1170.94 (<0.0001, 0.4024)	2095.73	1070.53
$E_{max\ PL}$					
5.43 (<0.0001, 0.0853)	5.30 (<0.0001, 0.0488)	5.66 (<0.0001, 0.2041)	6.29 (<0.0001, 0.9744)	9.64	6.31

Variant 3 - Menthol in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 3 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 4 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule crushed In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUC$_{nic\ 0\text{-}15}$ (ng*min/mL)					
75.71 (0.0002, <0.0001)	74.49 (0.0001, <0.0001)	67.34 (<0.0001, <0.0001)	57.46 (<0.0001, <0.0001)	165.53	5.22
AUC$_{nic\ 0\text{-}240}$ (ng*min/mL)					
573.07 (<0.0001, 0.1377)	596.00 (<0.0001, 0.2435)	589.38 (<0.0001, 0.2088)	486.20 (<0.0001, 0.0051)	1283.37	687.68
C_{max} (ng/mL)					
9.00 (<0.0001, <0.0001)	8.65 (<0.0001, <0.0001)	8.05 (<0.0001, 0.0003)	6.37 (<0.0001, <0.0343)	16.76	4.60

Variant 3 - Menthol in STD Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 3 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 4 - Menthol In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	Variant 2 - Menthol capsule crushed In Boost Mode (p-value$_{UBCC}$, p-value$_{NRT}$)	UB CC	NRT
AUEC$_{UTS\ 0\text{-}15}$					
136.58 (<0.0001, 0.0165*)	145.89 (<0.0001, 0.2047)	134.77 (<0.0001, 0.0093*)	137.34 (<0.0001, 0.0212*)	100.15	156.21
AUEC $_{(UTS\ 0\text{-}240)}$					
1956.82 (0.0003, 0.9409)	2012.38 (<0.0001, 0.4349)	1910.45 (0.0022, 0.6079)	1859.81 (0.0149, 0.2470)	1666.62	1950.99
$E_{min\ UTS}$					
4.96 (<0.0001, 0.0193*)	5.17 (<0.0001, 0.0462*)	4.26 (0.0030, 0.0005*)	5.58 (<0.0001, 0.1978)	2.51	6.34

* Statistically significant difference from NRT

Objectives and Endpoints

Primary Objective:

- Product Liking (PL) subjective measures over 4 hours after the start of IP use

Secondary Objectives:

- Baseline-adjusted nicotine PK parameters over 4 hours after the start of IP use
- Additional subjective measures: Product Effects [PE], and Urge to Smoke [UTS], over 4 hours after the start of IP use and Overall Product Liking [OPL], and Overall Intent to Use Again [OIUA]) assessed at the end of 4 hours after the start of IP use
- To assess maximum increase in physiological measures (i.e., heart rate and blood pressure) following IP use over 4 hours

Materials and Methods

Smokers of both non-menthol and menthol combustible cigarettes were recruited into this study to evaluate elements of AL of HTP IPs compared to combustible cigarettes and nicotine gum.

Matriculated subjects were assigned to either Study Arm 1 (non-menthol smokers) or Study Arm 2 (menthol smokers).

Starting on Day 1, subjects were confined for either 11 days (Study Arm 1) or 13 days (Study Arm 2). Based on their Study Arm assignment, subjects were randomized to a product use sequence (using a Williams design) in which they evaluated one IP in each Test Session, including both a high-AL comparator (subject’s UB cigarette) and a low-AL comparator (a commercially available NRT nicotine gum). In addition to the AL-comparators, Study Arm 1 evaluated three HTP IPs (i.e., 5 Test Sessions) and Study Arm 2 evaluated four HTP IPs (i.e., 6 Test Sessions).

Conclusions

Product Liking (Primary Endpoint)

- Overall, Product Liking parameters (AUEC$_{PL\ 5\text{-}240}$ and $E_{max\ PL}$) for HTPs were lower than cigarettes.
- HTPs scores were generally higher than NRT, but the differences were not always statistically significant.

Plasma Nicotine Uptake (PK) Endpoints (Secondary Endpoint)

- Plasma nicotine delivery profiles of HTPs (both non-menthol and menthol) were similar but lower than cigarettes.
- Nicotine uptake in first 15 minutes and overall (AUC$_{nic\ 0\text{-}15}$ and AUC$_{nic\ 0240}$) were higher than NRT, C_{max} values were not significantly different than NRT

Urge to Smoke (Secondary Endpoint)

- Mean maximum reduction in urge to smoke ($E_{min\ UTS}$) for HTPs were less than cigarettes for both non-menthol and menthol.
- Significantly lower mean maximum urge to smoke ($E_{min\ UTS}$) was seen with menthol HTPs, variants 3 (used in STD and Boost modes) and 4 compared to NRT, but not with variant 2 (menthol capsule crushed). No significant reduction was seen with non-menthol HTPs compared to NRT.
- Significantly lower mean urge to smoke was seen during first 15 minutes (AUEC$_{UTS\ 0\text{-}15}$) in non-menthol HTPs, variant 1 in STD and Boost modes; and menthol HTPs, variants 3 (used in STD and Boost modes) and 4, compared to NRT.
- The AUEC$_{UTS\ 0\text{-}240}$ scores were not statistically different that NRT for both non-menthol and menthol HTPs.

Product Effects (Secondary Endpoint)

- Positive and negative product effects for HTPs were statistically different than cigarettes (lower and higher respectively).
- Similar trends were seen in comparison of HTPs to NRT but differences were not always statistically significant.

Overall Product Liking and Overall Intent to Use Again (Secondary Endpoint)

- The OPL and OIUA scores ($E_{overall\ PL}$ and $E_{overall\ IUA}$) for the HTP IPs were statistically significantly lower for each HTP IP than the cigarettes in both Study Arms.
- The PL scores for several HTPs were statistically higher compared to NRT, but overall intent to use again was not significantly different than NRT.

Conclusion

- Product liking, overall product liking and overall intent to use again data suggest there were no significant differences between HTPs and NRT.
- Urge to smoke data suggests HTP’s suppressed urge to smoke during first 15 minutes of product use better than nicotine gum but differences in urge to smoke over the 4-hour period between HTP and nicotine gum were not statistically significant.
- Abuse liability of HTPs are lower than cigarettes, and similar to NRT

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