TITLE: A prospective non-interventional study to evaluate reduction of cigarette and tobacco product use after initiation with VLN™ cigarettes
PRODUCT: VLN™ King and VLN™ Menthol King cigarettes
STUDY No.: <to be determined>

Rationale and Background	VLN™ cigarettes have very low levels of nicotine in the tobacco. Published studies report reductions in cigarette consumption per day (CPD). This study is being done to address FDA requirements for post-approval evidence of real-world reduction of tobacco use after initiation of VLN™ cigarettes. The proposed study utilizes a prospective study design of 300 individuals followed for 12 months after initiation of VLN™ cigarettes.

Research question and objectives	The specific objectives are:
	• Primary objectives
	  ○ assess use of VLN™ cigarettes (number per day)
	  ○ assess use of all other types of cigarettes (type of cigarette, number per day)
	  ○ assess use of all other types of smoked and non-smoked tobacco product (type of product, frequency used per day)
	  ○ assess use of any other nicotine containing product (type of device, frequency and amount of usage per day)
	• Secondary objectives:
	  ○ assess subjects' stated desire to quit or reduce tobacco use
	  ○ describe cigarette, tobacco and nicotine containing product prior to initiation of VLN™ cigarettes
	  ○ describe tobacco reduction rates by levels of prior tobacco use and user demographic characteristics (age, gender, geography)

Study design	This is a longitudinal cohort study to evaluate reduction of smoking and tobacco use among new users of VLN™ cigarettes who have initiated the product in the period after FDA approval for general retail sale in the USA. The study will be conducted among USA individuals who have initiated VLN™ cigarettes. The target number of users completing the study is 300. Users will be recruited from users of VLN™ cigarette who have agreed to participate in a cross-sectional survey of knowledge and use of VLN™ cigarettes (study number XXX) which is also being submitted to the FDA as part of the post-approval study requirements for VLN™ cigarettes. Users who have completed the cross-sectional study will be asked to participate in this longitudinal cohort study. Each user agreeing to be in the longitudinal study will be sent a link to an online study portal. The study portal will include the process for the user to: 1) consent to participate in the study; 2) consent for the contract research organization running the study to contact the user for additional personal contact information and contact details of additional people to contact about the user in case the user cannot be reached. 3) complete the web-based data collection forms for the subject to fill out on all study information

	4) information about who to contact with any issues in use of the study portal or completion of the data collection form 5) Prior to launching the study, the draft data collection forms will undergo cognitive pre-testing in a small separate group of VLN™ cigarette users (n=10). The goals of cognitive pre-testing are to identify any questions that require clarification or revision based on areas of confusion or miscomprehension revealed by subjects in the cognitive pre-test interviews. 6) Users will be paid for completion of the study data collection forms for the entire study based on guidelines in the USA for appropriate compensation for their time to complete all study related activities. This is estimated to be USD $50.00.
Population	Inclusion criteria: • Participation in the cross-sectional study (study number XXX, for which this longitudinal study is a sub-study) • Initiation of VLN™ cigarettes after FDA approval for general sale in the USA • Provide permission to share their responses in aggregate with FDA or tobacco regulatory authorities within and outside of the USA, if requested Exclusion criteria: • Participated in the cognitive pre-testing of the survey questionnaire
Variables	The survey questionnaire will include the following: • Questions regarding user demographic characteristics (age, gender, ethnicity, USA postal zip code of residence – first three digits only) – At enrollment • Questions to assess usage of tobacco and nicotine containing products o At enrollment ▪ Estimated usage in past three months: • cigarettes (usual brand of cigarettes including roll your own, average number of cigarettes per day), • cigars (number per day), pipe usage (number of times per day), • other non-smoked tobacco products (average amount of oral and nasal tobacco products), • and nicotine containing products (type of product and average amount used). o At each follow-up data collection point, users will be asked to provide: ▪ Estimated number of VLN™ cigarettes smoked per day on each of the preceding 7 days. This question will require the user to estimate the number of VLN™ cigarettes smoked on each day of the week. ▪ Estimated number of other cigarettes smoked per day on each of the preceding 7 days (brand and number smoked per day). This question will require the user to estimate the number of other types of cigarettes smoked on each day of the week.

	▪ Estimated number of cigars smoked per day in preceding 7 days. This is the number of cigars smoked on each day of the week. ▪ Estimated usage of pipe tobacco smoking per day in the preceding 7 days. This is the number of times per day a pipe was smoked on each day of the week. ▪ Estimated usage of other non-smoked tobacco products in the past 7 days. This question will require the user to estimate the frequency of other types of non-smoked tobacco on each day of the week (route of ingestion, brand and number of times used per day). ▪ Estimated usage of nicotine containing products in the past 7 days. This question will require the user to estimate the type and frequency of use on each day of the week. ▪ At Enrollment and at each data collection point - Questions on intention to reduce and/or quit cigarette smoking and tobacco use.
Data sources	All data will be collected by on-line data capture. • The user population will be asked to complete a data collection form at enrollment and every 2 months for 12 months after enrollment (2, 4, 6, 8, 10, 12 months).
Study size	A sample of 300 completed subjectss is targeted for this study. This sample size was based on both feasibility and statistical considerations.
Data analysis	The primary analysis population will include all subjects who have completed at least four of the assessments inclusive of the enrollment assessment, the two- or four-month assessment, the six or eight month assessment and the final assessment. This is a descriptive single arm study. Frequency distributions and means (with standard deviation) will be used to report information reported as ordinal data (ie number of cigarettes smoked). Information on decline in tobacco and nicotine delivery device use will be reported as proportions (with 95% confidence intervals) of the total population enrolled in the study at each time point after the enrollment visit. <u>Sample Size</u> Previous studies have demonstrated cigarette per day reduction rates between 10% and 46% after 6 weeks after initiation of very low nicotine cigarettes. Hatsukami reported 50% reduction after 20 weeks[1]. A sample size of 300 subjects would estimate a 30% CPD reduction rate with a precision of 5.2%. See table attached.
Milestones	Start of data collection: End of data collection : Final report of study results

[1] Effects of Immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure. Hatsukami et al. JAMA 2018:320(9):880-891

.**Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Tobacco Use Levels**

Sample Size	10%		30%		50%		60%	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
100	5.90%	4.1-15.9	9.00%	21.0-30.0	9.80%	40.2-59.8	9.60%	50.4-69.6
300	3.40%	6.6-13.4	5.20%	24.8-35.2	5.70%	44.3-55.7	5.50%	54.5-65.5
500	2.60%	7.4-12.6	4.00%	26.0-34.0	4.40%	45.6-54.4	4.30%	55.7-64.3

Note: Calculated using PASS 13 software,* confidence intervals for 1 proportion, simple asymptotic formula. Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.