Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States (PMSS-COH-01-US)

Appendix 3 – Statistical Analysis Plan (SAP)

Study Title:	Postmarket Adult IQOS Consumer Cohort Study (US Adult COH) in the United States
Protocol Number:	PMSS-COH-01-US
Product Name:	IQOS
Sponsor	Philip Morris Products S.A. Avenue de Rhodanie 50 1007 Lausanne Switzerland
CRO	[CRO Name] [CRO Address]
Version:	1.0
Version Date:	May 03, 2024
Approving Program Manager at Sponsor:	Pierpaolo Magnani, Philip Morris Products S.A., Lausanne, Switzerland
Approving Statistician at Sponsor:	Emery Ngamasana, Philip Morris Products S.A., Washington DC, United States of America

Advisor at Sponsor:	Jessica Seifert, Philip Morris Products S.A., Washington D.C., United States of America Emery Ngamasana, Philip Morris Products S.A., Washington D.C., United States of America
Study Statistician at CRO:	[Statistician Name, CRO]

Document History

Status and Version	Version Date	Change Reference (page/chapter)	Reason for Change/Description of Change
1.0	05/03/2024	NA	NA

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

N/A

DEFINITIONS OF TERMS

Terms are arranged in alphabetic order. Italicized parts of definitions have their own definition in this section. Users are defined by use behaviors. For example, a current established tobacco or nicotine product (TNP) user is someone who reports current tobacco product use (i.e., past 30-day use) and meets the lifetime criterion for that TNP (i.e., established use). Unless otherwise specified, IQOS refers to IQOS Tobacco Heating System and IQOS heated tobacco sticks in this document.

Complete Switching

Complete switching generally refers to transitioning from *established use* of a given TNP to reporting no past 30-day use of that TNP and *current established* use of a different TNP at follow-up. Outcomes related to complete switching in this study include:

1. **Complete switching from cigarettes to IQOS** – Baseline current established smokers who, at a future follow-up survey, report current established IQOS use and no past 30-day smoking.
2. **Complete switching from IQOS to cigarettes** – Baseline current established IQOS users who, at a future survey, report current established smoking and no past 30-day IQOS use.

Consistent Basis

Consistent basis refers to reporting "Yes" to "Have you ever used [tobacco product] routinely or with some type of regularity. Examples might include using the product every day, a few times every week, only on the weekend."

Current Established IQOS User

Participants will be assigned to the Current Established IQOS User study group if they report the following at Baseline:

1. Having met the *lifetime use criterion* for IQOS (i.e., 100 or more lifetime IQOS heated tobacco sticks),
2. Having used IQOS for a period of 6 months or less (regardless of any other TNP use), AND,
3. Having used IQOS during the past 30 days.

Current Established Smoker

Participants will be assigned to the Current Established Smoker study group if they report the following at Baseline:

1. Never used IQOS, not even once,
2. Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more lifetime cigarettes), AND
3. Having smoked cigarettes in the past 30 days (irrespective of use of any other tobacco product).

Current Established Tobacco or Nicotine Product Use
Current established use of a given TNP will be defined as reporting:

1. Having met the *lifetime established use criterion* for the given TNP, AND
2. Having used the given TNP in the past 30 days at time of assessment.

Current Tobacco or Nicotine Product Use
Current TNP use will be defined as reporting having used a given TNP in the past 30 days at time of assessment. Irrespective of whether the lifetime established use criterion was met.

Ever Established Tobacco or Nicotine Product Use
Ever established TNP use refers to meeting the *lifetime established use criterion* (see definitions below) for a given TNP.

Ever Tobacco or Nicotine Product Use
Ever TNP use refers to reporting "Yes" to "Have you ever [used / smoked] [TNP] even one time?" Irrespective of whether the lifetime established use criterion was met.

Former Established Tobacco or Nicotine Product Use
Former established TNP use will be defined as reporting:

1. Having met the *lifetime established use criterion* for a given TNP, AND
2. No past 30-day use for a given TNP at time of assessment.

Former Tobacco or Nicotine Product Use
Former TNP use refers to reporting:

1. Having *ever used* a given TNP, AND,
2. Not having used the given TNP in the past 30 days.

Irrespective of whether the lifetime established use criterion was met.

Initiation
Initiation generally refers to the first use of a given TNP. Outcomes related to initiation in this study include:

- Ever use (even one time) of a given TNP never used at baseline, OR
- Ever established use of a given TNP never used at baseline.

Lifetime Established Use Criterion
The lifetime established use criterion for each TNP will be defined for:

1. Cigarettes: as reporting having ever smoked 100 or more cigarettes.
2. IQOS: as reporting having ever used 100 or more heated tobacco sticks.
3. Cigars (including regular cigars, cigarillos, or little filtered cigars): as reporting having ever used 50 or more cigars (including regular cigars, cigarillos, or little filtered cigars).
4. Smokeless tobacco (including chewing tobacco, dip, snuff, or snus pouch): as reporting having ever used smokeless tobacco 20 or more times per product.
5. Regular pipe: as reporting having ever smoked 50 bowls or more.
6. Traditional hookah: as reporting having ever smoked tobacco in a hookah on a "*consistent basis."*
7. Electronic cigarettes (e-cigarettes) and other e-vapor products: as reporting having ever vaped e-cigarettes on a *"consistent basis."*
8. Oral nicotine pouches: as reporting having ever used oral nicotine pouches on a *"consistent basis."*

Quit Duration
Quit duration is the length of time since a former established TNP user last used the given established TNP and will be dichotomized into:

> **Short-term TNP quitter** will be defined as reporting not having used given established TNP for less than 12 months.
>
> **Long-term TNP quitter** will be defined as reporting not having used given established TNP for 12 months or longer.

Quitting Established Tobacco or Nicotine Product Use
Quitting established TNP use will be defined as reporting:

1. Having used a given TNP to the *lifetime established use criterion*, AND
2. Having "completely stopped/quit" using the given TNP.

Quitting All Established Tobacco or Nicotine Product Use
Quitting all established TNP use will be defined as reporting:

1. Having used any TNP to the *lifetime established use criterion*, AND
2. Having "completely stopped/quit" using all TNP ever used.

Re-Initiation of Cigarette Smoking
Re-initiation of cigarette smoking refers to reporting at time of assessment:

1. Having not smoked cigarettes for 12 months or longer,
2. Having met the *lifetime established use criterion* for cigarettes, AND
3. Past 30-day cigarette smoking.

Relapse to Cigarette Smoking
Relapse to cigarette smoking refers to reporting:

1. Having not smoked cigarettes for less than 12 months,
2. Having met the *lifetime established use criterion* for cigarettes, AND
3. Past 30-day cigarette smoking.

Tobacco or Nicotine Products
Tobacco or nicotine products include products containing tobacco and/or nicotine. These products may be combustible or non-combustible, depending on intended use.

1. **Combustible Tobacco or Nicotine Products** burn tobacco and produce smoke when consumed / used as intended and include cigarettes, cigars (regular cigars, cigarillos, and little filtered cigars), regular pipes, and traditional hookah (or water pipe).

2. **Non-Combustible Tobacco or Nicotine Products** do not burn tobacco or produce smoke when consumed / used as intended and include heat-not-burn products (e.g., IQOS), smokeless tobacco (dip, snuff, chewing tobacco, and snus pouches), electronic cigarettes (e-cigarettes), and oral nicotine products (excluding nicotine replacement therapy products).

Novel TNP categories may be added to these lists, as well as assessed in this study as they emerge in future US markets.

United States (US) IQOS Customer Loyalty Program Database

Once the modified-risk tobacco product is commercialized in the US, adult IQOS consumers will be able to voluntarily register their device with the US IQOS Customer Loyalty Program (CLP). The CLP database will function as the primary sampling frame for this study.

1 INTRODUCTION

1.1 Background

Philip Morris Products S.A. (PMP) submitted a Modified Risk Tobacco Application (MRTPA) to the US Food and Drug Administration (FDA) seeking authorization to market the IQOS Tobacco Heating System and IQOS tobacco sticks (formerly "Marlboro HeatSticks") as modified risk tobacco products. The IQOS Tobacco Heating System is an electronic device that heats IQOS heated tobacco sticks, generating a nicotine-containing aerosol with significantly fewer harmful and potentially harmful chemicals than the smoke generated by combustible tobacco products. Based on the evidence provided in the MRTPA, the FDA issued two "Modified Risk Granted Orders – Exposure Modification" authorizing PMP to market IQOS with a reduced exposure claim (FDA, 2020, 2022).

The Orders are conditioned upon agreement to conduct postmarket surveillance and studies (PMSS) in accordance with protocols approved by FDA. This document is prepared as part of the PMSS program for IQOS pursuant to the Orders.

1.2 Rationale

The Federal Food, Drug and Cosmetic Act (FDCA) directs the FDA to condition an exposure modification order received under FDCA § 911(g)(2) on the MRTP applicants' agreement to conduct PMSS (FDCA §§ 911(g)(2)(C)(ii)). "The outcomes evaluated in postmarket surveillance and studies should focus on the effect of the MRTP on consumer perception, behavior and health under real world conditions of use" (FDA, 2012). For this reason, PMP[1], plans to conduct certain components of PMSS to assess the effect of the MRTP among US consumers. The program will consist of a collection of data over time that supports an assessment of IQOS in the postmarket setting. The current study, Postmarket Adult IQOS Consumer Cohort Study in the US (US Adult COH), is one such study.

1.3 Study Purpose

The purpose of the Postmarket Adult IQOS Consumer Cohort Study in the US (US Adult COH) is to provide real-world data evaluating longitudinal tobacco or nicotine product (TNP)

[1] *Note.* Prior to April 2024, Altria Client Services developed and executed the IQOS PMSS program on behalf of PMP. The IQOS PMSS program will be managed and executed by PMP beginning May 2024.

use behaviors and transitions, as well as health-related risk perceptions and outcomes among adult current established IQOS users relative to adult current established smokers.

1.4 Study Objectives

The objectives of this study are to conduct the following among US adult current established IQOS users and current established smokers over time:

1. Characterize tobacco or nicotine product (TNP) use behaviors (e.g., past 30-day use, dual product use).
2. Describe behavioral transitions, including product use initiation, complete switching from cigarettes or other TNP to IQOS, transitioning to (never smokers) or back (former smokers) to cigarettes, and quitting.
3. Assess self-reported health-related quality of life, signs, and symptoms by product use.
4. Assess relative risk perceptions related to IQOS and cigarettes.
5. Assess perception of nicotine harmfulness in IQOS and cigarettes.

2 STUDY DESIGN, DEVELOPMENT AND METHODS

2.1 Overview

This prospective longitudinal study will follow a cohort of US adult (≥21 years) current established IQOS users (i.e., meets IQOS lifetime use criterion and reports past 30-day IQOS use at Baseline) and current established smokers (i.e., meets cigarette lifetime use criterion and reports past 30-day smoking, and never used IQOS at Baseline) over a 24-month observational period.

This study intends to recruit adult current established IQOS users from the annual Adult IQOS Use Postmarket Cross-sectional Study (US Adult PMX; see PMSS-PMX-01-US for more details). We intend to conduct US Adult COH in geographies in concert with the second annual US Adult PMX, which we anticipate being approximately two years after IQOS is launched into the US marketplace. By this time, we assume IQOS to be in distribution in diverse geographies and used among a consumer base large enough to facilitate recruitment of participants that meet the study inclusion criteria. Participants in the US Adult PMX will be invited to participate in the US Adult COH if they meet criteria for the current established IQOS user study group. Current established smokers will be recruited via online panels.

After agreeing to participate in the study, potential participants will complete the Participant Screener Survey to determine their eligibility for the study. Age verification is a prerequisite

for registration in the US IQOS Customer Loyalty Program (CLP) – the sampling frame for US Adult PMX – so eligible current established IQOS users recruited for this study via the US Adult PMX will not require additional age verification. Current established IQOS users not recruited via the US Adult PMX and current established smokers will be age verified during screening.

Eligible participants who agree to participate will be asked to complete the baseline survey (Time 0)[2,3]. Participants will have 7 days to complete the baseline survey. Follow up surveys will be administered at months 3, 6, 12, 18, and 24 (Table 1). The study length was selected to enable the ability to detect changes in behaviors and health over time. A 3- and 6-month interval is a sufficient timeframe for measuring changes in tobacco use behaviors (Halpern et al., 2018; Mantey et al., 2017; McKeganey et al., 2018; O'Connor et al., 2005; O'Connor et al., 2011; Pulvers et al., 2018; Pulvers et al., 2015). The initial 3-month follow-up and subsequent 3-month follow-up (6 months post-baseline) will provide more opportunity to detect changes in early tobacco use behavior for new IQOS users. Detecting changes in some clinical and self-reported health status was seen in studies with a harm reduction focus within 6 months in one study (Campagna et al., 2016) and within a year or less in other studies (Cibella et al., 2016; Farsalinos et al., 2014; Polosa et al., 2014; Polosa et al., 2016). Thus, we selected a 24-month study period with follow-up at 3 months for the first 6 months then every 6 months thereafter.

The survey will take a modular approach to minimize survey length and time to complete. For example, diagnoses will be asked yearly. Checklist items will be randomized. Skip logic will be incorporated into surveys to reduce participant burden. The baseline and five follow-up surveys will include measures grouped in the following modules:

- Sociodemographic and health-related characteristics.
- Tobacco or nicotine product (TNP) use behaviors.
- Quitting behaviors.
- Risk perceptions.
- Perception and understanding of IQOS and harmful or potentially harmful constituent (HPHC) exposure reduction.

[2] After completion of the US Adult PMX main survey, all eligible current established IQOS user cohort participants will be asked to complete the following survey modules: Quality of Life, Signs and Symptoms, and Diagnoses. See Section 2.2.8 for additional details.

- Product dependence (IQOS and cigarettes).
- Conditions and diagnoses.
- Health-related quality of life (HRQOL).
- Signs and symptoms.

Participants will complete all surveys online and will receive e-mail invitations and reminders to complete each survey. Participants will have a 14-day window to complete each follow-up survey and will receive reminders to do so up to/until they complete the survey. Participants will receive compensation for each survey that they complete. If a participant misses a survey, they will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule. The study modules at each study phase are summarized in Table 1.

Table 1: Survey Module Administration Schedule for Baseline and All Follow Up Survey Months (3, 6, 12, 18, and 24)

Survey Module	Baseline	Follow Up Month				
		3	6	12	18	24
Sociodemographics	✓					
TNP Use Behaviors	✓	✓	✓	✓	✓	✓
Quitting Behaviors	✓	✓	✓	✓	✓	✓
Risk Perceptions	✓			✓		✓
Perceived Exposure to HPHCs	✓	✓	✓	✓	✓	✓
Product Dependence	✓	✓	✓	✓	✓	✓
Conditions & Diagnoses	✓			✓		✓
Quality of Life	✓	✓	✓	✓	✓	✓
Signs & Symptoms	✓	✓	✓	✓	✓	✓

TNP = Tobacco or nicotine product; HPHC = Harmful or potentially harmful constituents
Note. Check marks indicate inclusion of survey module in survey.

2.2 Survey Module Overview

2.2.1 Sociodemographic and Health-Related Characteristics Module

The baseline survey will capture participants' sociodemographic and health-related characteristics, including:

- Sex
- Gender Identity
- Age
- Race
- Ethnicity
- Education level
- Income
- Sexual Orientation
- Marital Status
- Pre-existing medical conditions or co-morbidities
    - Cardiovascular disease
    - Respiratory disease
    - Cancer
    - Diabetes
    - Mental illness
- Pregnancy status (among women 21 to 49 years of age)
- Military or Veteran Status

2.2.2 Tobacco or Nicotine Product Use Behaviors Module

Survey items will capture participants historical (e.g., ever use) and current (e.g., past 30-day use) IQOS and other TNP use, including:

- Ever use of a given TNP (even one time).
- Lifetime use of a given TNP.
- Past 30-day use of a given TNP.
- Number of days of used a given TNP in the past 30 days.
- Amount of product used on days used in the past 30 days (IQOS, cigarettes, and e-cigarettes).
- IQOS heated tobacco stick flavor(s) ever used, currently using, and used most often used.
- Menthol use (current and former smokers only)
- Types of TNP completely quit.

2.2.3 Quitting Behaviors Module

Current Established Smokers' will be asked to provide the number of previous quit attempts they have made at time of assessment. Their motivation to stop smoking will be measured using the Motivation To Stop Smoking (MTSS) scale (Kotz et al., 2013). MTSS responses include the following seven items:

- "I don't want to stop smoking" (1)
- "I think I should stop smoking but don't really want to" (2)
- "I want to stop smoking but haven't thought about when" (3)
- "I REALLY want to stop smoking but I don't know when I will" (4)
- "I want to stop smoking and hope to soon" (5)
- "I REALLY want to stop smoking and intend to in the next 3 months" (6)
- "I REALLY want to stop smoking and intend to in the next month" (7)

Higher score on the MTSS scale indicate higher motivation to stop smoking cigarettes.

Use of tobacco cessation treatment will be captured for all participants as: Never; past 30 days; >30 days to 12 months; > 12 months at baseline; and past 30 days and > past 30 days at last assessment for each follow-up survey.

2.2.4 Risk Perceptions Module

At baseline, participants' lifetime health risk perceptions will be measured using the ABOUT™—Perceived Risk instrument (Cano et al., 2018). ABOUT™ is based on an underlying conceptual framework developed from a range of extensive qualitative studies with different populations (adult current smokers, adult former smokers, and adult never smokers), literature review, and input from expert panels (Cano et al., 2018). The short 9-item scale version will be used in this study. This version contains psychometrically valid measures for the assessment of health risk perceptions for different types of tobacco products and various levels of smoking status. In addition, given the prevailing misconceptions about the role of nicotine in relation to cancer and other tobacco-related diseases, the study also outsourced two questions from the PATH adult study on the perception of perception of harmfulness of nicotine in cigarettes compared to nicotine in IQOS .

2.2.5 IQOS and HPHC Exposure Reduction Module

Participants' perception and understanding of IQOS and HPHC exposure reduction will also be assessed, specifically:

- Perception of harmful or potentially harmful chemical exposure when switching from cigarettes to IQOS.
- Understanding of what smokers must do to reduce harmful or potentially harmful chemical exposure.

2.2.6 Product Dependence Module

Tobacco dependence for IQOS and cigarettes will be measured using the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1989). FTND has been validated for use across TNP categories other than cigarettes and has demonstrated good psychometric properties for measuring the intensity of physical dependence on nicotine (Mushtaq & Beebe, 2017; Piper et al., 2020; Sharma et al., 2021).

2.2.7 Cardiovascular Diseases, Diabetes, Respiratory Diseases, Malignancy, and Mental Health Diagnoses Module

A set of diagnoses were selected that relate to TNP use and could impact health and tobacco use behaviors (U.S. Department of Health and Human Services [DHHS], 2020). Survey items were sourced from national surveys (e.g., Behavioral Risk Factor Surveillance System [BRFSS], NHIS, NSDUH), and include the following diagnoses:

- Cardiovascular disease diagnoses
  - Myocardial infarction
  - Stroke
  - Angina
  - Coronary heart disease
  - Congestive heart failure
  - Hyperlipidemia
  - Hypertension
  - Other cardiovascular diseases
- Diabetes diagnosis
- Respiratory disease diagnoses
  - Chronic obstructive pulmonary disorder (COPD)
  - Asthma
  - Chronic bronchitis
  - Emphysema
  - Apnea
  - Other respiratory diseases
- Malignancy diagnoses
- Mental illness
  - Diagnoses
  - Taking medicine or receiving treatment

2.2.8 Health-Related Quality of Life, Signs, and Symptoms Module

Health-Related Quality of Life (HRQOL) is a multidimensional concept that includes positive and negative aspects of life as well as physical health, and measures of physical, social, and psychological functioning that directly relate to health (World Health Organization [WHO], 1998). HRQOL has been shown in literature to be correlated with health outcomes including cardiovascular and respiratory diseases. HRQOL will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS©) Global Health short form. The PROMIS© Global Health was designed to measure patient-reported outcomes related to physical, mental, and overall health using a 10-item bank. The HRQOL, signs, and symptoms module will include:

- Health-Related Quality of Life – Physical and Mental Health Signs and symptoms – Cardiovascular and Respiratory

3 STUDY POPULATION

3.1 Study Groups

Participants will include adult (≥ 21 years) current established IQOS users recruited from the US Adult PMX study and current established smokers recruited from commercial, online panels. Participants for both study groups will be recruited simultaneously.

Current established IQOS users will be defined as adult IQOS users who report at baseline:

1. Having met the *lifetime established use criterion* for IQOS heated tobacco sticks (i.e., 100 or more lifetime sticks), AND
2. Having used IQOS in the past 30 days at baseline, AND
3. Having used IQOS for six or fewer months (regardless of other tobacco or nicotine product [TNP] use).

Current established smokers will be defined as adult cigarette smokers who report at baseline:

1. Having met the *lifetime established use criterion* for cigarettes (i.e., 100 or more), AND
2. Having smoked cigarettes in the past 30 days at baseline (regardless of other TNP use), AND
   Have never tried IQOS.

3.2 Propensity weighting for covariate balance

Propensity scores, or the probability of treatment group assignment, can be used to reduce confounding between groups and limit bias when randomization is not possible, or not ethically acceptable (Austin, 2011; Rosenbaum & Rubin, 1983).

Inverse probability of treatment weighting (IPTW) is one technique that leverages propensity scores to control for confounders. IPTW offers an advantage over matching in that it allows the ability to maintain the sample size and not drop study participants because of the inability to find an exact match (Chesnaye et al., 2022; Li & Greene, 2013). IPTW will involve two steps: First, propensity scores will be calculated using a logistic regression model estimating the likelihood of being in the IQOS group versus in the cigarette group as a function of select demographic characteristics and other set variables likely to predict current IQOS® versus cigarette use (Leas et al., 2018; Timberlake et al., 2009). Second, individual weights will be calculated as the inverse of propensity scores:

- For the IQOS group: $\frac{1}{propensity\ for\ IQOS\ group}$
- For the cigarettes groups: $\frac{1}{1-(propensity\ for\ IQOS\ group)}$

As such, individuals in the IQOS group with lower probability of being in that group (and cigarettes smokers with higher probability of being IQOS users) receive larger weights so that their relative influence on the comparison is increased. These two steps will create a pseudo population in which measured confounders are equally distributed across groups. Final analyses will be weighted using the new weights obtained from the IPTW procedure (Cefalu et al., 2021; Ridgeway et al., 2022).

Standardized mean differences (SMD) will be used, to assess covariate balance between the two groups. Given the nature of the study (e.g., observational), SMD < 0.20 will be considered adequate balance (Markoulidakis et al., 2023).

$$smd = \frac{\bar{X}_{exposed} - \bar{X}_{control}}{\sqrt{\frac{S^2_{exposed} - S^2_{control}}{2}}}$$

where, $\bar{X}$ refers to the weighted average effect in the exposed (e.g., quit rate in the IQOS group), and control group (cigarette smoker group), while S captures the standard deviation for the exposed and the unexposed groups.

Visuals representation of the weights will allow to investigate lack of overlap (e.g., violation of positivity assumption). In case there is lack of overlap, extreme weight will be trimmed.

The following variables will be used as predictors in the logistic regression with group membership (IQOS® versus cigarette smokers) as the dependent variable:

- Demographic (age, sex, race/ethnicity, education, marital status)
- Smoking exposure related (years smoked, tobacco poly-use)
- Behavioral related (binge drinking, mental health concern, cessation advice from a health professional)
- Health related (presence of any chronic health condition)

Other variables may be included if significant and meaningful differences are seen between groups.

3.3 Sample Size and Power Considerations

A power analysis was conducted to determine the necessary ending sample size. We selected one of the primary outcomes, quitting cigarette smoking, because it has received substantial attention both among regulators and in the scientific community (U.S. Department of Health and Human Services [DHHS], 2020). A recent comprehensive study by Kasza et al. (2024), leveraged the large sample from the Population Assessment of Tobacco and Health (PATH) adults to compare cigarette smoking quit rates between baseline (wave 5) dual users of cigarettes and e-cigarettes products against exclusive smokers using the most recent waves of data collection: 2018/19 for wave 5 to 2021 for wave 6.

Specifically, Kasza et al. (2024) found that over the two years (using wave 5 as the baseline), exclusive cigarette smokers quit smoking at a cumulative rate of 21% while those combining cigarettes with e-cigarettes quit smoking at a cumulative rate of 29.7%. Given these estimates and the exponential nature of the distribution of quit rates (Getsios, 2013), instantaneous smoking quit rates were obtained using the natural log of the above survival rates for two years follow-up:

- In the cigarette group, given that 79.0% (i.e., 1-0.21) continued to smoke after two years follow-up, the instantaneous quit rate can be obtained as: $\frac{-\ln(0.79)}{2} = 0.1179.$
- In the e-cigarette group, given that 70.3% (i.e., 1-0.297) continued to smoke after two years follow-up, the instantaneous quit rate can be obtained as: $\frac{-\ln(0.703)}{2} = 0.1762.$

- Given these instantaneous quit rates, the hazard ratio of cigarette smoking can be obtained as: $\frac{Instantaneous\ Quit\ Rate\ in\ Test\ Group}{Instantaneous\ Quit\ Rate\ in\ Control\ Group} = \frac{0.1762}{0.1179} = 1.4950$

At these prevailing rates, and extending these findings to the IQOS® and cigarette study groups for the same study time (two years), results from the power analysis using a *logrank* test (with Schoenfeld method) for comparison of two survival functions revealed that 260 events (~ overall number of subjects who quit smoking) and an initial sample size of 1,026 participants (n=513 per study group) would be required to detect a difference (e.g., bi-annual hazard ratio of 1.4950) with a statistical power of 90% and Type I Error of α=0.05. That power analysis was conducted for a two-sided *logrank* test, with Schoenfeld method for determining the number of events and power using Stata 18 (StataCorp LLC). If sample size requirements for the current established IOQS user group are not met through US Adult PMX recruitment, then additional participants will be recruited though an internal database of IQOS users.

However, prior relevant longitudinal studies have experienced dropout rates ranging from 12% to 66% (Berg et al., 2014; Choi & Forster, 2014; Dobbie et al., 2015; Grana et al., 2014; McRobbie et al., 2015; Nides et al., 2014; Norton et al., 2014; Pacifici et al., 2015; Polosa et al., 2014). Given the likelihood of dropout, we allowed the sample to be inflated to account for a potential dropout rate of 50% (instantaneous rate of drop out: $\frac{-\ln(0.50)}{2} = 0.3466$), thereby yielding a sample size of 1,570, rounded at 1,600 participants (n=800 per study group) with an expected count of 260 participants reporting the event of interest (i.e., cigarette cessation).

Considering the potential loss of power with propensity score weighting, and the plan to present stratified analyses comparing menthol versus non-menthol IQOS users in the IQOS group, we allowed an additional sample inflation of 30%:

- In the current established IQOS group: [800 * 1.30] * 2 ≈ 2,100 (multiplying by two for menthol and non-menthol users).
- In the current established smoker group: [800 * 1.30] * 2 ≈ 2,100 (multiplying by two for menthol and non-menthol smokers).
- Hence a total baseline line sample of 4,200 respondents.

3.4 Recruitment Method

Recruitment is expected to launch when the number of established IQOS users is sufficient to support the study. This study will leverage two recruitment sources: 1) US Customer Loyalty Program (CLP) database to recruit current established IQOS users and 2) commercial, online panels to recruit current established smokers from geographies where IQOS is sold.

3.4.1 Recruiting Current Established IQOS Users – US Customer Loyalty Program

It is anticipated that PMP will establish and maintain a US CLP and requisite database which will contain age-verified adult IQOS purchasers. Based on experience with similar international markets, the CLP is expected to enroll ≥ 80% of all adult IQOS users and is intended as the primary recruitment source for this study.

US Adult PMX Study Recruitment

This study intends to recruit adult (≥ 21 years) current established IQOS users who were invited and eligible to participate in the US Adult PMX Study (PMSS-PMX-01-US), PMP's repeated, online, cross-sectional survey.

Study invitations for the US Adult PMX study will be delivered via email, direct mail, and/or text to adult IQOS purchasers who have registered their device in the CLP and opted in to receive communications from PMP. Interested individuals who follow the study invitation link will be directed to begin the Participant Screener. Those not terminated at the initial screen will then be directed to review the US Adult PMX Informed Consent Statement (ICS) detailing the study purpose, the voluntary nature of their participation, data privacy and confidentiality guidelines, and contact information for the Institutional Review Board (IRB) and Contract Research Organization (CRO).

US Adult COH

Study invitations for the US Adult COH will be administered at the end of the US Adult PMX main survey to individuals who meet the current established IQOS user study group criteria. Participants will be recruited using a non-probability method on a schedule that matches the US Adult PMX during the single time that the US Adult COH will recruit participants. If the current established IQOS user group sample targets cannot be met through the US Adult PMX, additional participants will be recruited from the CLP database. To better maximize participation, potential participants may be contacted multiple times via multiple channels when possible (e.g., emails, text messages, and mailings).

3.4.2 Recruiting Current Established Smokers – Online panels

Current established smokers will be recruited from multiple online consumer panel companies to increase the likelihood of achieving a more diverse sample and completing screening requirements in a timely manner. For these and other reasons, the main contract research organization (CRO) will evaluate and select the online consumer panel companies based on several quality criteria, including having established a history of compliance with industry codes and standards and processes for:

- Registering panelists,
- Validating member information via external databases,
- Periodic updating of panel member information,
- Appropriate sample deployment (e.g., batching), and
- Identifying straightliners, speeders, and other fraudulent data (e.g., bot traffic).

Online survey panel companies use a variety of methods to recruit members to minimize the inherent bias that could result from using one or a few recruiting sources. These methods can include face-to-face, telephone, online, social media, classified newspaper advertisements, and referral programs. Those who agree to join the panel are periodically sent e-mail invitations to complete surveys. Panelists may or may not decide to opt-in to a survey. They also may discontinue participation at any point, for any reason.

4 OUTCOME MEASURES

4.1 Objective 1 – Characterize tobacco or nicotine product (TNP) use behaviors.

The following outcome measures will be used to characterize participants' TNP use behaviors:

a) At baseline, participants' TNP use before first trying IQOS, specifically:
   - Having never used any TNP
   - Long-term former established tobacco use
   - Current established smoking
   - Other current established TNP use

b) Past 30-day exclusive, dual, or poly use at follow-up months 3,6,12,18, and 24:
   - Exclusive: IQOS only.
   - Exclusive: Cigarettes only.
   - Dual: IQOS plus one other TNP:
     - IQOS and one combustible TNP.
       - IQOS and cigarettes.
     - IQOS and one other non-combustible TNP.
   - Poly: IQOS plus two or more other TNP:
     - IQOS and at least one combustible TNP.
       - IQOS, cigarettes, and one or more other TNP.
     - IQOS and two or more other non-combustible TNP (i.e., participants reporting poly-tobacco use does not include any combustible TNP).

c) Mean number of days used IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24.

d) Mean number of days smoked cigarettes at baseline and follow-up months 3, 6, 12, 18, and 24.

e) Mean number of IQOS heated tobacco sticks used per day at baseline (Current established IQOS users only) and at follow-up months 3, 6, 12, 18, and 24.

f) Mean number of cigarettes smoked per day at baseline and at follow-up months 3, 6, 12, 18, and 24 months (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only).

g) Mean number of IQOS heated tobacco sticks used and cigarettes smoked per day at baseline and follow-up months 3, 6, 12, 18, and 24 months (Current established IQOS users reporting dual IQOS and cigarette use at baseline and Current established smokers reporting dual IQOS and cigarette use at follow ups).

h) Percent change in cigarettes smoked per day from baseline for follow-up months 3, 6, 12 ,18, and 24 (Current established IQOS users reporting dual IQOS and cigarette smoking at baseline only):
    a. Reduced cigarettes smoked per day by ≥50%
    b. Increased cigarettes smoked per day by ≥50%
    c. Maintained cigarettes smoker per day (i.e., change < ±50%)

i) Prevalence of current established smoking at baseline and at follow-up months 3, 6, 12, 18, and 24.

j) Mean score of the FTND for IQOS at baseline (Current established IQOS users only) and follow-up months 3, 6, 12, 18, and 24.

k) Mean score of the FTND for cigarettes at baseline (Current established smokers and Current established IQOS users reporting dual IQOS and cigarette use at baseline) and follow-up months 3, 6, 12, 18, and 24.

4.2 Objective 2 – Describe behavioral transitions, including: product use initiation, completely switching from cigarettes to other TNP or to IQOS, transitioning to (never smokers) or back (former smokers) to cigarettes, and quitting.

The following outcome measures will be used to describe participants' IQOS and other TNP use behavioral transitions:

a) Product initiation:
   - Ever use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24.
   - Established use at follow up of a TNP never used at baseline for follow-up months 3, 6, 12, 18, and 24.

b) Complete switching to IQOS (i.e., baseline current established smokers from either study group reporting current established IQOS use and no past 30-day smoking at follow up) at follow-up months 3, 6, 12, 18, and 24.

c) Complete switching from IQOS to cigarette smoking (i.e., current established IQOS users reporting current established smoking and no past 30-day IQOS use at follow up) at follow-up months 3, 6, 12, 18, and 24.

d) Follow up behavioral transitions among current established IQOS users who report dual IQOS and cigarette use at baseline for follow-up months 3, 6, 12, 18, and 24:
   - Exclusive IQOS use
   - Exclusive cigarette smoking
   - Dual IQOS and cigarette use
   - No past 30-day IQOS use or cigarette smoking (regardless of other TNP use).

e) Transition to cigarette smoking at follow-up months 3, 6, 12, 18, and 24 months:
   - Relapse to cigarette smoking among baseline current established IQOS users who report short-term former established smoking at baseline.
   - Re-initiation of cigarette smoking among baseline current established IQOS users who report long-term former established smoking at baseline.

f) Quitting behaviors:
   - Quit smoking after first trying IOQS – Baseline current established IQOS users who report former established smoking at baseline who smoked in the 30-days prior to first trying IQOS.

- Quit attempts in the past 12 months – Baseline current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers who attempted a quit attempt in the 12 months prior to baseline.
- Use of cessation treatment at baseline and follow-up months 3, 6, 12, 18, and 24.
- Completely quit smoking cigarettes at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users who report dual IQOS and cigarette use at baseline and baseline current established smokers).
- Completely quit IQOS use at follow-up months 3, 6, 12, 18, and 24 (current established IQOS users).
- Complete quit all TNP at follow-up months 3, 6, 12, 18, and 24.

4.3 Objective 3 – Assess self-reported health-related quality of life, signs, and symptoms by product use.

The health-related outcomes include HRQOL, signs, and symptoms. The facets of quality of life[4] that will be measured as outcomes in this study include:

a) Mean physical health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24.

b) Mean mental health-related quality of life scores at baseline and follow-up months 3, 6, 12, 18, and 24.

c) Change in mean physical health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

d) Change in mean mental health-related quality of life scores from baseline at follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

[4] The QOL outcomes will be measured using the PROMIS© Global Health 10 and scored using the PROMIS© scoring manual. Please see health module section for details.

e) Difference in mean physical health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24.

f) Difference in mean mental health-related quality of life scores between study groups at follow-up months 3, 6, 12, 18, and 24.

g) Mean number of cardiovascular symptoms at baseline and follow-up months 3, 6, 12, 18, and 24.

h) Mean number of respiratory symptoms at baseline and follow-up months 3, 6, 12, 18, and 24.

i) Change in mean number of cardiovascular symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

j) Change in mean number of respiratory symptoms from baseline to follow-up months 3, 6, 12, 18, and 24 among current established smokers who completely switched to IQOS.

k) Difference in mean number of cardiovascular symptoms between study groups at follow-up months 3, 6, 12, 18, and 24.

l) Difference in mean number of respiratory symptoms between study groups at follow-up months 3, 6, 12, 18, and 24.

4.4 Objective 4 – Assess risk perceptions related to IQOS and cigarettes.

The following outcome measures will be used to assess participants' risk perceptions related to IQOS and cigarettes:

a) Percent and count (n, %) of participants in each category of the ABOUT™ scale assessing risk perception related to IQOS use, cigarette smoking, and complete smoking cessation at baseline and follow-up months 12 and 24.

b) Percent distribution of perceived harmful or potentially harmful chemical (HPHC) exposure following switching from cigarettes to IQOS ("More", "Same", "Less", "No", or "Don't know") at follow-up months 3, 6, 12, 18, and 24.

Percent distribution of the understanding of what smokers must do to reduce HPHC exposure among participants who perceive reduced ("Less") HPHC exposure following switching from cigarettes to IQOS at follow-up months 3, 6, 12, 18, and 24.

5 PLANNED STATISTICAL ANALYSIS[5]

Analyses within this section align with the outcome measures defined in Section 4. Overall, analyses will consist of the following steps:

1. First disposition summary reporting participation proportions will be reported for the overall sample and stratified by sex and age.
2. Second, descriptive statistics will be used to describe baseline demographics characteristics and all study outcomes for each time period stratified by the study group where appropriate (e.g., use history, current tobacco use, days used and units used, risk perception, perception and understanding of IQOS and exposure reduction). Descriptive statistics will include means, medians, standard deviations, and interquartile range for continuous variables (e.g., age) and proportions and frequencies for categorical variables (e.g., sex).
3. A series of GEE models (e.g., GEE log-binomial regression, GEE Poisson regression) will be employed to address study objectives with comparisons between groups or over time (e.g., tobacco use, transitions, health-related quality of life, signs, and symptoms). Some outcomes are only relevant to certain tobacco subpopulations; the population(s) included in the analysis will be described within the outcome.

GEE models will be employed using the SAS GENMOD procedure. LSMEANS and ESTIMATE statements will be constructed to estimate statistics of interest (e.g., group and time-specific proportions and means) as well as to test specific contrasts (e.g., mean differences between groups across time points). For all GEE models, the covariance structure will employ

[5] All references to Baseline within this section = survey 1-Time 0

an unstructured covariance structure. The tenability of all assumptions will be evaluated. In the event assumptions are not met, more appropriate statistical models will be utilized.

All statistical tests will be conducted at a Type I Error Rate of α=.05. Corrections for the potential inflation of Type I Error will not be made due to the potential inflation of Type II error (Perneger, 1998). Significant *p*-values will be reported with high precision (to the 3rd decimal place) to allow reviewers to evaluate significance.

All inferential analyses (e.g., GEE models) analyses will be weighted using the weights obtained through propensity score weighting (e.g., IPTW or entropy balancing), except for sensitivity analysis that will use propensity score matching.

The following standards will be implemented in reporting small study ns:

1. All non-zero counts less than 10 will be suppressed.
2. All rates or proportions derived from suppressed counts will also be suppressed.
3. When possible and appropriate, data will be aggregated to minimize the need for suppression.
4. Estimates with denominators less than 50 or having a relative standard error greater than 30.0% will be reported with a note of low statistical precision.

5.1 Characterization of tobacco use behaviors

1. **Tobacco or nicotine product use status prior to first trying IQOS** – Descriptive statistics will be used to summarize the percent and count of participants who report use of other TNPs before first trying IQOS.

   The following categories will be used to classify current established IQOS users based on the reported TNP used prior to first trying IQOS: Never TNP user; Long-term former established TNP user; current established smoker; and other current established TNP user (Table 2).

2. **Past 30-day use of tobacco or nicotine products (TNP)** – Descriptive statistics will be used to summarize the percent and count of participants who report past 30-day TNP use. The following categories will be used to classify users based on their past 30-day use of tobacco products:

   a. Exclusive IQOS Use,

   b. Exclusive Cigarette Smoking,

c. Dual Use – IQOS and 1 other TNP

d. Dual Use – IQOS and 1 Combustible TNP

e. Dual Use – IQOS and Cigarette Smoking

f. Poly Use – IQOS plus use of 2 or more Other TNP

g. Poly Use – IQOS plus use of 2 or more Other TNP where at least 1 TNP is combustible.

h. Poly Use – IQOS, Cigarettes, and at least 1 or more Other TNP

i. Poly Use – IQOS plus use of 2 or more Other Non-Combustible TNP (i.e., participants' poly-tobacco use does not include any combustible TNP).

The past 30-day TNP use categories will be stratified by menthol IQOS heated tobacco use predominant use (i.e., used menthol used most often in the past 30-days, yes / no) and use of a cessation treatment in the past 30 days (Table 3).

3. **Change in cigarettes per day among dual users** – A GEE with a cumulative logit link will be used to estimate the changes in cigarettes per day among Current Established IQOS Users who dual use IQOS and cigarettes at baseline, as a function of whether they used menthol IQOS heated tobacco sticks most often in the past 30 days, used a cessation treatment in the past 30 days, or smoked mentholated cigarettes most often in the past 30 days.

   Change in cigarettes per day will be classified in three ordered categories: reduced cigarettes per day by at least 50%, the same cigarettes per day (less change than ±50%), or increased cigarettes per day by at least 50% compared to the prior wave (Descriptive statistics, Table 4; Model results, Table 5). The standardized calculation for cigarettes per day (CPD) is given by:

$$CPD = \frac{(Cigarettes\ smoked\ per\ day\ on\ days\ used)\ x\ (Days\ used\ in\ past\ 30\ days)}{30}$$

For CPD calculations, a response of "<1" cigarettes will be coded as 1, and a response of ">50" cigarettes will be coded as 80[6]. Changed in cigarettes per day at current wave of data collection compared to prior wave will be calculated as follows:

$$\%\Delta CPD = \frac{CPD_t - CPD_{t-1}}{CPD_{t-1}} x100$$

Where CPD_t captures CPD at current wave, and CPD_{t-1}represents CPD at prior wave.

Change in cigarettes per day will then be categorized as:

a. Reduced CPD by at least 50% (if $-100 \leq \%\Delta CPD \leq -50\%$)

b. Smoked about the same amount (if $-49 \leq \%\Delta CPD \leq 0\%$)

c. Increased cigarettes per day by less than 50% (if $0\% < \%\Delta CPD < 49\%$)

d. Increased cigarettes per day by at least 50% (if $\%\Delta CPD \geq 50\%$)

4. **Cigarettes per day over time among dual users by menthol status** – A GEE traditional linear model will be used to estimate the cigarettes per day among Current Established IQOS Users who report dual IQOS and cigarette use at baseline by time point. The model will include time, menthol IQOS heated tobacco stick use, menthol cigarette use, and cessation treatment use. The parameters derived from the statistical model will be used to estimate and test for differences in average standardized cigarettes per day over time compared to baseline (Descriptive statistics, Table 6; Model results, Table 7).

   The standardized calculation for cigarettes per day for this measure is defined as:

$$\frac{(Cigarettes\ smoked\ per\ day\ on\ days\ used)\ x\ (Days\ used\ in\ past\ 30\ days)}{30}$$

   For cigarette per day calculation, a response of "<1" will be coded as 1, and a response of ">50" will be coded as 80.

5. **Average Number of Days Used IQOS/Cigarettes in the past 30 days** – Descriptive statistics will be employed to summarize the mean number of days [out of 30 days] each study group reported using IQOS and cigarettes at each time point stratified by

[6] Based on data from PATH adult wave 4 data, the median number of cigarettes smoked per day is 80 among the 16 individuals who reported smoking more than 50 cigarettes per day.

menthol IQOS heated tobacco stick use (i.e., used most often in the past 30 days) and menthol cigarette use (i.e., used most often in the past 30 days). The mean number of days used is defined as the sum of the number of days product was used for each participant divided by the number of participants who reported having used the tobacco product during the past 30 days (Table 8).

Formula: $\bar{x} = \frac{\sum x}{n}$

Where:

x = number of days product used for each participant

n = participants who reported having used the product during the past 30 days

Summary statistics will include means, standard deviations, medians, first and third quartiles (Q1 and Q3, respectively) and range (min/max).

6. **Number of IQOS Heated Tobacco Sticks Used/Cigarettes Used per Day on Days Used and per Day in Past 30 Days** – Descriptive statistics will be employed to summarize the number of units of each tobacco product [IQOS and cigarettes] used on average in a given day and on days used [out of 30 days] at each time point stratified by menthol IQOS heated tobacco stick use (i.e., used most often in the past 30 days) and menthol cigarette use (i.e., used most often in the past 30 days).

   The number of units for each product will be calculated among participants who used the product in the past 30 days. Summary statistics will include mean, standard deviation, 95% confidence interval, median, Q1, Q3, and range (Table 9).

   The standardized calculation for monthly average IQOS heated tobacco sticks or cigarettes per day (calculated separately) for this measure is defined as:

$$\frac{(Sticks/Cigarettes\ used\ per\ day\ on\ days\ used)\ x\ (Days\ used\ in\ past\ 30\ days)}{30}$$

   For cigarette per day and IQOS heated tobacco sticks per day calculation, a response of "<1" will be coded as 1, and a response of ">50" will be coded as 80.

7. **Current (Past 30-day) Use of Cigarettes** – A GEE log-binomial regression model will be employed to estimate the percent of participants who are current (past 30-day) established cigarette smokers by group and time point. The model will include study

group (i.e., baseline current established IQOS users and baseline current established smokers), time and group-BY-time, years smoking cigarettes, menthol IQOS heated tobacco stick use, menthol cigarette use, and cessation treatment use. The dependent variable will be yes/no endorsement of current (past 30-day) established cigarette smoking at follow up. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, current use Table 10; Descriptive statistics, current menthol and regular IQOS heated tobacco sticks and Cigarette use Table 11; Model results, Table 12).

5.2 Characterization of product use transitions

1. **Change in current IQOS and cigarette use status at follow up among dual IQOS and cigarettes users** – Descriptive statistics will be employed to summarize the percent and count of prior wave IQOS and cigarette dual users from the current established IQOS user study group who at follow-up months 3, 6, 12, 18, and 24 are exclusive IQOS users, exclusive smokers, dual IQOS and cigarette users, or users of neither product, irrespective of other tobacco product use and stratifying by menthol IQOS heated tobacco stick use and cessation treatment use (Table 13).
2. **Complete switching from cigarettes to IQOS** – A GEE log-binomial regression model will be employed to estimate the percent of participants who use IQOS while transitioning from cigarettes to not at all use of cigarettes. The model will include time and baseline menthol IQOS heated tobacco stick use, baseline menthol cigarette use, and baseline cessation treatment use. The dependent variable will be calculated based on (1) having smoking cigarettes during the 30 days before first trying IQOS and became former smokers after first trying IQOS at baseline and (2) reporting no cigarette smoking in the 30 days prior to the survey and current established use of IQOS in a subsequent survey(s). Tables include descriptive statistics for switching within and between menthol and non-menthol products. (Descriptive statistics, Table 14; Model results, Table 15)
3. **Complete switching from IQOS to cigarettes** – A GEE log-binomial model will be employed to estimate the percent of participants in the current established IQOS user study group who, at a follow up, report current established smoking and no IQOS use. The model will include time and baseline menthol IQOS heated tobacco stick use, baseline menthol cigarette use, and baseline cessation treatment use. The dependent variable will be calculated based on (1) current established use of IQOS at baseline and (2) reporting no IQOS use at the time of follow-up survey, and current established use

of cigarettes in a subsequent follow-up survey(s) (Descriptive statistics, Table 16; Model results, Table 17).

4. **Ever use of a [tobacco or nicotine product (TNP)] never used at baseline** – A GEE log-binomial model will be employed to estimate the percent of participants who report ever use at follow up survey months 3, 6, 12, 18, or 24 of a TNP never used, even one time, at baseline by group and time point. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, and menthol IQOS heated tobacco sticks use (i.e., used most often in the past 30 days, yes / no). The dependent variable will be whether or not participants initiated use of a TNP during the study. The parameters derived from the statistical model will be used to estimate and test for differences in proportions across time points by group (Descriptive statistics, with IQOS heated tobacco sticks preference, Table 18; Model results, Table 19).
5. **Established use of a [tobacco or nicotine product (TNP)] never used at baseline** – A GEE log-binomial model will be employed to estimate the percent of participants who report ever established use at follow-up survey months 3, 6, 12, 18, or 24 of a TNP never used, even one time, at baseline by study group and time point. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, and menthol IQOS heated tobacco sticks use (i.e., used most often in the past 30 days, yes / no). The dependent variable will be whether or not participants who initiated use and reached the lifetime established use criterion for a tobacco product during the study. The parameters derived from the statistical model will be used to estimate and test for differences in proportions across time points by group (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 21; Model results, Table 22).The parameters derived from the statistical model will be used to estimate and test for differences in proportions across time points by group (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 20; Model results, Table 21).
6. **Smoking relapse** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the current established IQOS user group that experience smoking relapse. The model will include time, years smoked cigarettes, menthol IQOS heated tobacco sticks use (i.e., used most often in the past 30 days, yes / no), and cessation treatment use. The dependent variable will be the percent of participants who report established use of cigarettes but report not currently using cigarettes at baseline, and, at a follow-up survey report resuming current use of cigarettes within 12 months

of not using (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 22; Model results, Table 23).

7. **Smoking re-initiation** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the current established IQOS user group that experience smoking re-initiation. The model will include time, years smoked cigarettes, menthol IQOS heated tobacco sticks use (i.e., used most often in the past 30 days, yes / no), and cessation treatment use. The dependent variable will be the percent of participants who report established use of cigarettes but report not currently using cigarettes at baseline, and at a subsequent follow-up survey report resuming current use of cigarettes 12 months or more after not using (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 24; Model results, Table 25).
8. **Quit smoking after first trying IQOS at baseline** – Descriptive statistics will be employed to summarize the percent and count of the current established IQOS user group who were established smokers and smoked in the 30 days before first trying IQOS and quit smoking at baseline stratified by baseline menthol IQOS heated tobacco stick use and baseline cessation treatment use (Table 26).
9. **Quit attempts** – A GEE log-binomial regression model will be employed to estimate the percent of baseline current (past 30-day) smokers who attempted to quit smoking cigarettes in the past 12/6/3 months at baseline and at each interval between subsequent follow-up surveys between groups over time. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, quit status, years smoking cigarettes, menthol IQOS heated tobacco sticks use (i.e., used most often in the past 30 days, yes / no). The dependent variable will be yes/no response to past 12/6/3 month quit attempts for cigarettes. The parameters derived from the statistical model will be used to estimate and test for study group differences in proportions of participants over time (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 27; Model results, Table 28).
10. **Use of cessation treatment** – Descriptive statistics will be employed to summarize the percent and count of participants who report: (1) use of cessation treatment at baseline (Never, Past 30 Days, >30 Days but < 12 Months, >12 Months) (Table 29); (2) use of cessation treatment (Past 30 Days, > Past 30 Day to Last Assessment) at follow-up months 3, 6, 12, 18, or 24 (Table 30); and (3) incident use of a cessation treatment (yes / no) at follow-up months 3, 6, 12, 18, or 24 (Table 30).

11. **Completely quit smoking** – A GEE log-binomial regression model will be employed to estimate the percent of baseline current (past 30-day) smokers who completely quit smoking cigarettes at follow-up between groups over time. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, years smoking cigarettes, menthol IQOS heated tobacco stick use (i.e., used most often in the past 30 days), and cessation treatment use. The dependent variable will be yes/no response to completely quit smoking cigarettes. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, Table 31; Model results, Table 32).
12. **Completely quit IQOS** – A GEE log-binomial regression model will be employed to estimate the percent of participants in the current established IQOS user group who completely quit IQOS use over time. The model will include time and years of IQOS use, menthol IQOS heated tobacco stick use (i.e., used most often in the past 30 days), and cessation treatment use. The dependent variable will be yes/no response to completely quit IQOS (Descriptive statistics, with stratification of IQOS heated tobacco sticks preference, Table 31; Model results, Table 33).
13. **Completely quit all tobacco** – A GEE log-binomial regression model will be employed to estimate the percent of participants who completely quit all TNP at follow-up survey months 3, 6, 12, 18, or 24. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, menthol IQOS heated tobacco stick use (i.e., used most often in the past 30 days), and cessation treatment use. The dependent variable will be coded yes/no based on whether the participant met the criteria for "completely quit" all TNPs. The parameters derived from the statistical model will be used to estimate and test for group differences in proportions over time (Descriptive statistics, Table 31; Model results, Table 34).

5.3 Assessment of health-related quality of life and signs and symptoms

1. **Health-related Quality of Life (Physical)** – A GEE traditional linear model will be employed to estimate the mean physical health T-score between study groups over time. The model will include group study group (i.e., baseline current established IQOS users, baseline current established smokers), time, and group-BY-time, years smoked cigarettes, and number of diagnoses. The dependent variable will be the physical health T-score. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 35; Model results, Table 36).

2. **Health-related Quality of Life (Mental)** – A GEE traditional linear model will be employed to estimate the mean mental health T-score between study groups over time. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, and group-BY-time, years smoked cigarettes, and number of diagnoses. The dependent variable will be the mean mental health T-score. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 35; Model results, Table 36).
3. **Cardiovascular signs and symptoms** – A GEE Poisson regression model will be employed to estimate the mean number of cardiovascular symptoms present between study groups over time. The model will include study group (i.e., baseline current established IQOS users, baseline current established smokers), time, group-BY-time, years smoked cigarettes, and number of diagnoses. The dependent variable will be the number of cardiovascular symptoms present. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 35; Model results, Table 36).
4. **Respiratory signs and symptoms** – A GEE Poisson regression model will be employed to estimate the mean number of respiratory symptoms present between study groups over time. The model will include group (Test, Reference), time, group-BY-time, years smoked cigarettes, and number of diagnoses. The dependent variable will be the number of respiratory symptoms present. The parameters derived from the statistical model will be used to estimate and test for group differences in means over time (Descriptive statistics, Table 36; Model results, Table 37).

5.4 Assessment of risk perceptions and perception and understanding of IQOS and exposure reduction

1. **Risk perceptions** – Descriptive statistics will be employed to summarize the distribution (count, percentages, and 95% CI) of participants across ABOUT scale composite scores [IQOS and cigarettes] at baseline and follow-up surveys 12 and 24 (Table 37).
2. **Perception of switching completely to IQOS and HPHC exposure reduction** – A GEE log-binomial regression model will be employed to estimate the percent of participants in each study group that perceive that switching completely to IQOS results in reduced harmful or potentially harmful constituent (HPHC) exposure over time compared to baseline. The model will include time. The dependent variable will be correct

perception/misperception response to reduced HPHC perception. (Descriptive statistics, with complete distribution of response options, Table 38; Model results, Table 39).

3. **Understanding of what to do to reduce exposure** – A GEE log-binomial regression model will be employed to estimate the percent of participants in each study group that have an understanding of what smokers must do to reduce HPHC exposure over time compared to baseline. The model will include time. The dependent variable will be correct perception/misperception response to what smokers must do to reduce HPHC exposure. This model will include participants who perceive that switching completely to IQOS results in reduced HPHC exposure. (Descriptive statistics, with complete distribution of response options, Table 40; Model results, Table 41).

All regression models will be weighted using the weights obtained through the IPTW to control for confounding.

6 ADDITIONAL DATA SUMMARIES

6.1 Participation Proportions

Recruitment and participation will be reported in total and by sex, age, and study group (as applicable).

- **Contact Proportion**: The number of persons screened for eligibility divided by the total number of persons attempted to be reached for eligibility screening (i.e., the number of invitations sent).
- **Eligibility Proportion**: The number of persons eligible for enrollment (i.e., persons who meet all inclusion criteria and no exclusion criteria) divided by the total number of persons screened for eligibility.
- **Completion Proportion**: The number of completed interviews divided by the number of attempted interviews (completed plus partial).
- **Response Proportion**: The number of completed interviews divided by the number of invitations sent.

7 SURVEY PERFORMANCE EVALUATION

7.1 Overview

Survey development, testing, and evaluation are viewed as iterative processes that frequently entail examining the performance of the survey instruments. The purpose of this section is to provide an analytical plan to evaluate the performance of the survey instruments used in this study. The summary of results will be reported as part of the Detailed Study Report. The full report of the survey performance evaluation will be provided under separate cover.

7.2 Examine Survey Administration Meta-Data

The survey administration meta-data file contains the number of seconds a participant takes to complete each question across each entire survey. Survey administration meta-data (e.g., the average and fastest survey completion time by study group) will be examined for irregularities to identify issues associated with how participants engaged with the survey.

a. The total time required to complete each survey will be calculated and depicted graphically using histograms in total and by study group. Means, medians, standard deviations, minimums and maximums will also be reported in total and by study group.

b. The 5% fastest participants for each survey will be identified and their demographics and tobacco product use patterns will be examined for irregularities relative to the other participants.

7.3 Data Quality Checks

A variety of data quality checks will be implemented to identify and flag records that contain forms of data falsification or missing data. These records will be examined to understand their influence on study results and for possible exclusion from analysis. Data falsification forms include “speeding,” nondifferentiation, and gibberish/non-sensical verbatim response. The number of respondents that are flagged for each data falsification form will be included in the final survey report.

“Speeding” is completing a questionnaire very quickly, without giving thought to answers. In this study, a participant who completes the main questionnaire in less than 30% of the median completion time of participants with a similar number of tobacco products used is flagged for review. The amount of time to complete each questionnaire is expected to vary depending on the number of tobacco products used. Median questionnaire duration will be calculated and compared among participants that:

- Use no tobacco products.
- Use one tobacco product.
- Use two tobacco products.
- Use more than two tobacco products.

Nondifferentiation of rating, or "straightlining" is when a participant does not differentiate between response options and selects the same response for multiple questions (e.g., selecting the first option for a question series). Participants who have answers with 100% similarity for scaled attribute questions with 15 or more dimensions are flagged for review.

Free text fields and verbatim responses that are poor quality (e.g. gibberish, non-sensical responses, single characters, profanity) are flagged for possible removal. The main questionnaire does not contain open-ended questions and includes program logic to ensure valid values, so this review will be applied to typed-in "other" responses. The questionnaire is designed to minimize outliers by defining ranges for numeric responses. For example, cigarettes smoked per day has a minimum of '<1' and a maximum of 'more than 50,' and the number of days used in the past 30 days can only range from 0 to 30. Therefore, we do not expect any outliers relevant to this analysis plan.

The main analysis will be conducted with the full dataset and sensitivity analyses will be conducted without the flagged responses to determine if the potentially invalid data substantially influence the results. These sensitivity analyses will be performed to assess the robustness of the results with the exclusion of flagged data. If there are no substantial changes observed, results are considered robust to invalid data. Treatment of invalid data and inconsistencies will be noted in the Final Study Report as applicable.

8 ADDITIONAL ANALYSES

As needed, additional analyses may be conducted to clarify or further contextualize study outcomes measures. These analyses may be exploratory in nature. These additional supportive analyses will be documented, amended to the SAP and reported in the final study report.

9 STATISTICAL METHODOLOGIES

9.1 General Consideration

The data will be analyzed and reported both descriptively – primarily using percentages, frequency distributions, means, standard deviations and medians, and using inferential statistics such as generalized linear models.

9.2 Missing Data

Adult participants who discontinue a survey before completion will be allowed to re-enter and complete during their allotted survey completion time. Participants who fail to return and fail to complete will not be replaced. If a participant misses a survey, he/she will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule. Only completed surveys will be used for analysis and reporting. Missing data or surveys will not be imputed and results will be analyzed using available complete data.

A comprehensive analysis of attrition and its possible consequences for introducing bias in the results will be carried out. At each time point, those who complete the survey versus those who do not will be compared on the basis of demographics (age, race, education, income) and study group (IQOS versus cigarette smokers). A logistic regression will be performed with survey completion as the dependent variable; the demographics and study group variables will be the independent variables. A significant omnibus chi-squared test and any significant estimates for the individual variables would indicate potential bias for that wave. If the model and any estimates are significant, post-stratification weights will be created based on iterative proportional fitting to make the respective wave's sample more similar to the baseline sample. Weighting efficiencies will then be examined and, if less than 90%, descriptive statistics based on the weighted data will be provided in the appendix. This analysis will be repeated separately at each time point.

To address the potential bias due to attrition in the GEE models, the weighted GEE estimator originally proposed by (Robins et al., 1995) will be performed.[7] This approach uses logistic regression to estimate the probability that a subject's survey is missing at a given wave and

[7] Implemented in SAS's proc gee with the missmodel statement or in the R package wgeesel Xu, C., Li, Z., Xue, Y., Zhang, L., & Wang, M. (2019). An R package for model fitting, model selection and the simulation for longitudinal data with dropout missingness. *Commun Stat Simul Comput*, *48*(9), 2812-2829. https://doi.org/10.1080/03610918.2018.1468457 .

reweights the data based on the inverse of these probabilities. Results from the weighted and unweighted models will be compared. The unweighted results will be presented, but any changes in inference due to the weighting will be clearly noted in the report.

9.3 Statistical Analysis of Data

9.3.1 Analysis of Categorical Data

All summaries of categorical data will present sample sizes, proportions, and 95% confidence intervals for each study group.

9.3.2 Analysis of Continuous Data

All summaries of continuous data will present sample sizes, mean, standard deviation, median, interquartile range and 95% confidence intervals by study group.

9.3.3 Analysis Using GEE Models

All summaries of models will include number of observations used, estimate, standard error, *Z* value, and *p*-value for the model and variables in the model.

9.4 Coding of Open-Ended Data

Certain survey questions allow participants to provide an answer other than what is pre-listed in the response set (e.g., signs and symptoms). These verbatim responses are reviewed, evaluated and coded as follows: 1) verbatim responses that were provided as an "other" response, but fit into one of the pre-listed responses are "up-coded" (e.g., response is typed in as an "other" response, but it is provided in the pre-list); 2) responses provided that cannot be "up-coded" are categorized, and frequency of these responses are evaluated. Responses with a frequency beyond a certain threshold (e.g., 2-5%) are then assigned a code, and the coded response is analyzed and reported as part of the response set for that question. Responses with frequencies below the threshold are reported as "other."

9.5 Reporting Conventions

All summary statistics, including percentages, means, standard deviations, medians and confidence intervals will be reported to the second decimal place. Standard rounding conventions will be used (e.g., 12.567 rounded to 12.57; 12.564 rounded to 12.56). Significant *p*-values will be reported with high precision (to the 4th decimal place) to allow reviewers to evaluate significance after applying a Bonferroni correction, if desired.

10 FIGURES AND TABLES

Examples of table shells for the analyses are provided.

Table 2: Current Established IQOS User at Baseline – Tobacco or Nicotine Product Use Status Prior To First Trying IQOS

	Baseline		
	n = XXX		
TNP Use Status Prior to First Trying IQOS	n	%	CI
Never used any TNP[1]			
Long-term former established tobacco user[2]			
Current established smoker[3]			
Current established other TNP user[4]			

TNP = Tobacco or Nicotine Product; CI = 95% Confidence Interval

1. At baseline reporting never having used any TNP before first trying IQOS.
2. At baseline, reporting having used a given TNP to its lifetime use criterion and have not used the given TNP 12 or more months before first trying IQOS.
3. At baseline, reporting having smoked cigarettes to its lifetime use criterion (100 or more cigarettes) and having smoked cigarettes in the 30 days before first trying IQOS.
4. At baseline, reporting having used a given TNP (excluding cigarettes) to its lifetime use criterion and having used the given TNP in the 30 days before first trying IQOS.

Table 3: Past 30-day Exclusive, Dual, or Poly Use at Baseline and Follow Up Months 3, 6, 12, 18, and 24 – Current Established IQOS Users and Current Established Smokers

Measure		Follow-Up Survey				
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Current Established IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Tobacco Use Behaviors						
Exclusive IQOS Use						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Exclusive Cigarette Smoking	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Dual – IQOS and 1 Other TNP						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Dual – IQOS and 1 Combustible TNP						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Dual – IQOS and Cigarettes						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Poly – IQOS and ≥ 2 Other TNP						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Poly – IQOS and ≥ 1 combustible TNP						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						

Poly – IQOS, Cigarettes, and ≥ 1 Other TNP						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Poly – IQOS and ≥ 2 Other Non-Combustible TNP[3]						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Tobacco Use Behaviors						
Exclusive IQOS Use	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Exclusive Cigarette Smoking						
Menthol IQOS Heated Tobacco Stick Use[1]						
Cessation Treatment Use[2]						
Dual – IQOS and 1 Other TNP	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Dual – IQOS and 1 Combustible TNP	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Dual – IQOS and Cigarettes	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Poly – IQOS and ≥ 2 Other TNP	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					

Poly – IQOS and ≥ 1 combustible TNP	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Poly – IQOS, Cigarettes, and ≥ 1 Other TNP	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Poly – IQOS and ≥ 2 Other Non-Combustible TNP[3]	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					

CI = 95% Confidence Interval; NA = Not applicable; TNP = Tobacco or Nicotine Product

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.
3. Participants' poly-tobacco use does not include any combustible TNP.

Table 4: Change in Cigarettes Smoked per Day among Current Established IQOS Users Reporting Dual IQOS and Cigarette Smoking at Baseline – Follow Up Months 3, 6, 12, 18, and 24

	Percent Change in Cigarettes Smoked Per Day								
	Reduced by ≥ 50%			Maintained[1]			Reduced by ≥ 50%		
Measure	**N**	**%**	**CI**	**N**	**%**	**CI**	**N**	**%**	**CI**
Baseline to Month 3									
Menthol IQOS Heated Tobacco Stick Use[2]									
Menthol Cigarette Use[3]									
Cessation Treatment Use[4]									
Month 3 to Month 6									
Menthol IQOS Heated Tobacco Stick Use[2]									
Menthol Cigarette Use[3]									
Cessation Treatment Use[4]									
Month 6 to Month 12									
Menthol IQOS Heated Tobacco Stick Use[2]									
Menthol Cigarette Use[3]									
Cessation Treatment Use[4]									
Month 12 to Month 18									
Menthol IQOS Heated Tobacco Stick Use[2]									
Menthol Cigarette Use[3]									
Cessation Treatment Use[4]									
Month 18 to Month 24									
Menthol IQOS Heated Tobacco Stick Use[2]									
Menthol Cigarette Use[3]									
Cessation Treatment Use[4]									

CI = 95% Confidence Interval

1. Same cigarettes per day (less change than ±50%).
2. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
3. Menthol cigarette use is defined as reporting having smoked menthol cigarettes most often in the past 30 days at time of assessment.
4. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 5: Results from Generalized Estimating Equation: Percent Change in Cigarettes Smoked per Day among Current Established IQOS Users Reporting Dual IQOS and Cigarette Smoking at Baseline

Term	Estimate	SE	Z value	*p* value
Threshold 1				
Threshold 2				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Menthol IQOS Heated Tobacco Stick Use[1]				
Menthol Cigarette Use[2]				
Cessation Treatment Use[3]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Menthol cigarette use is defined as reporting having smoked menthol cigarettes most often in the past 30 days at time of assessment.
3. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 6: Cigarettes Per Day Over Time Among Baseline Dual IQOS and Cigarette Smokers – Follow Up Months 3, 6, 12, 18, and 24.

	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Measure	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Cigarettes per day						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						

M = Mean; SD = Standard Deviation; CI = Confidence Interval; Q1 = First Quartile; Q3 = Third Quartile

Note: This table repeated by past 30-day menthol IQOS heated tobacco sticks use and past 30-day cessation treatment at time of assessment.

Table 7: Results from Generalized Estimating Equation: Change in Cigarette Per Day as a function of Time (in months), and IQOS Flavor Preference, Cigarette Flavor Preference, and Use of Cessation Treatment Among Dual Users

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
IQOS Heated Tobacco Stick Use[1]				
Menthol Cigarette Use[2]				
Cessation Treatment Use[3]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Menthol cigarette use is defined as reporting having smoked menthol cigarettes most often in the past 30 days at time of assessment.
3. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 8: Average Number of Days Used IQOS and Number of Days Smoked Cigarettes in the past 30-days among Current Established IQOS Users at Baseline and Follow-up Months 3, 6, 12, 18, & 24

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Past 30-day IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Number of days used IQOS						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						
Past 30-day Cigarette Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Number of days smoked cigarettes						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						

M = Mean; SD = Standard Deviation; CI = Confidence Interval; Q1 = First Quartile; Q3 = Third Quartile

Note: This table repeated for Current Established Smokers and by past 30-day menthol IQOS heated tobacco stick use and past 30-day menthol cigarette use.

Table 9: Number of IQOS Heated Tobacco Sticks Used and Number of Cigarettes Used Per Day on Days Used in the Past 30 Days among Current Established IQOS Users

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Past 30-day IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Number of IQOS heated tobacco sticks on days used						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						
Number of IQOS heated tobacco sticks used per day						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						
Past 30-day Cigarette Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Number of cigarettes on days used						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						
Number of cigarettes used per day						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						

M = Mean; SD = Standard Deviation; CI = Confidence Interval; Q1 = First Quartile; Q3 = Third Quartile

Note: This table repeated for Current Established Smokers and by past 30-day menthol IQOS heated tobacco stick use and past 30-day menthol cigarette use.

Table 10: Current (Past 30-day) Established Smoker Status at Time of Assessment by Baseline Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Past 30-day established smokers						
Menthol IQOS Heated Tobacco Stick Use[1]						
Menthol Cigarette Use[2]						
Cessation Treatment Use[3]						
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Past 30-day established smokers						
Menthol IQOS Heated Tobacco Stick Use[1]						
Menthol Cigarette Use[2]						
Cessation Treatment Use[3]						

CI = 95% Confidence Interval

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Menthol cigarette use is defined as reporting having smoked menthol cigarettes most often in the past 30 days at time of assessment.
3. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 11: Past 30-day Menthol IQOS Heated Tobacco Stick Use and Past 30-day Menthol Cigarette Smoking among Current Established IQOS Users at Baseline

	Past 30-day Menthol Cigarette Smoking			
	Non-menthol	Menthol	Non-current Smoker	Total
Past 30-day Menthol IQOS Heated Tobacco Stick Use	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Current IQOS User				
Non-menthol, n (%)				
Menthol, n (%)				
Non-current IQOS User, n (%)				
Total				

Note. Table repeated for Current Established Smokers and follow-up survey months 3, 6, 12, 18, and 24.

Table 12: Results from Generalized Estimating Equation: Change in Current (Past 30-day) Cigarettes Smoking as a function of Time (months), Baseline Study Group, Years Smoked Cigarettes, IQOS Flavor Preferences, Cigarette Flavor Preference, and Cessation Treatment Use.

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 3*CEIU				
Month 6* CEIU				
Month 12* CEIU				
Month 18* CEIU				
Month 24* CEIU				
Years smoked cigarettes				
Menthol IQOS Heated Tobacco Stick Use[1]				
Menthol Cigarette Use[2]				
Cessation Treatment Use[3]				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
Test v. Reference (Baseline)				
Test v. Reference (Month 3)				
Test v. Reference (Month 6)				
Test v. Reference (Month 12)				
Test v. Reference (Month 18)				
Test v. Reference (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Menthol cigarette use is defined as reporting having smoked menthol cigarettes most often in the past 30 days at time of assessment.
3. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 13: Change in IQOS and Cigarette Use Status at Follow-up Months 3, 6, 12, 18, and 24

Measure	Current IQOS and Cigarette Use Status				
	Exclusive IQOS Use	Exclusive Smoking	Dual IQOS and Cigarette Use	Neither Product	
	n, % [95% CI]	n, % [95% CI]	n, % [95% CI]	n, % [95% CI]	Total Number
Baseline Dual Users at Month 3					
Menthol IQOS Heated Tobacco Stick Use[1]					
Cessation Treatment Use[2]					
Month 3 Dual Users at Month 6					
Menthol IQOS Heated Tobacco Stick Use[1]					
Cessation Treatment Use[2]					
Month 6 Dual Users at Month 12					
Menthol IQOS Heated Tobacco Stick Use[1]					
Cessation Treatment Use[2]					
Month 12 Dual Users at Month 18					
Menthol IQOS Heated Tobacco Stick Use[1]					
Cessation Treatment Use[2]					
Month 18 Dual Users at Month 24					
Menthol IQOS Heated Tobacco Stick Use[1]					
Cessation Treatment Use[2]					

CI = Confidence Interval

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Note: Behavior classification is irrespective of other tobacco product use other than IQOS and cigarettes.

Table 14: Complete Switching from Cigarettes to IQOS at Baseline and Follow-up Months 3, 6, 12, 18, and 24 by Study Group

		Follow-up Survey				
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Current Established IQOS User	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Total Switched to IQOS						
Switched to menthol IQOS						
From regular cigarette						
From menthol						
Switched to regular IQOS						
From regular cigarette						
From menthol						
Baseline Menthol IQOS Heated Tobacco Stick Use[1]						
Baseline Menthol Cigarette Use[2]						
Baseline Cessation Treatment Use[3]						
Current Established Smoker	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Total Switched to IQOS	NA					
Switched to menthol IQOS	NA					
From regular cigarette	NA					
From menthol	NA					
Switched to regular IQOS	NA					
From regular cigarette	NA					
From menthol	NA					
Baseline Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Baseline Menthol Cigarette Use[2]	NA					
Baseline Cessation Treatment Use[3]	NA					

CI = 95% Confidence Interval

1. Baseline menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at baseline.
2. Baseline menthol cigarette use is defined as reporting smoking menthol cigarettes most often in the past 30 days at baseline.
3. Baseline cessation treatment use is defined as reporting any cessation treatment in the past 30-days at baseline.

Note: Behavior classifications are irrespective of other tobacco product use other than IQOS and cigarettes.

Table 15: Results from Generalized Estimating Equation: Complete Switching from Cigarettes to IQOS among Current Established IQOS Users

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Baseline Menthol IQOS Heated Tobacco Stick Use[1]				
Baseline Menthol Cigarette Use[2]				
Baseline Cessation Treatment Use[3]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Baseline menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at baseline.
2. Baseline menthol cigarette use is defined as reporting smoking menthol cigarettes most often in the past 30 days at baseline.
3. Baseline cessation treatment use is defined as reporting any cessation treatment in the past 30-days at baseline.

Note: This table repeated for Current Established Smoker study group.

Table 16: Complete Switching from IQOS to Cigarettes at Baseline and Follow-up Months 3, 6, 12, 18, and 24 among Current Established IQOS Users

		Follow-up Survey				
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
	n = XXX	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Measure	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Baseline Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Baseline Menthol Cigarette Use[2]	NA					
Baseline Cessation Treatment Use[3]	NA					

CI = 95% Confidence Interval; NA = Not applicable.

1. Baseline menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at baseline.
2. Baseline menthol cigarette use is defined as reporting smoking menthol cigarettes most often in the past 30 days at baseline.
3. Baseline cessation treatment use is defined as reporting any cessation treatment in the past 30-days at baseline.

Note: IQOS Behavior classification are irrespective of other tobacco product use other than IQOS and cigarettes.

Table 17: Results from Generalized Estimating Equation: Complete Switching from IQOS to Cigarettes among Current Established IQOS Users as a Function of Time, Baseline IQOS Flavor Preference, Baseline Cigarette Flavor Preference, and Baseline Cessation Treatment Use

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Baseline Menthol IQOS Heated Tobacco Stick Use[1]				
Baseline Menthol Cigarette Use[2]				
Baseline Cessation Treatment Use[3]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Baseline menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at baseline.
2. Baseline menthol cigarette use is defined as reporting smoking menthol cigarettes most often in the past 30 days at baseline.
3. Baseline cessation treatment use is defined as reporting any cessation treatment in the past 30-days at baseline.

Table 18: Ever Use of a [Tobacco or Nicotine Product (TNP)] Never Used at Baseline by Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS User	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Ever use of [TNP] never used at Baseline						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-cigarettes	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					
Menthol IQOS Heated Tobacco Stick Use	NA					
Current Established Smoker	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Ever use of [TNP] never used at Baseline						
Cigarettes	NA	NA	NA	NA	NA	NA
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-cigarettes	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					

CI = 95% Confidence Interval; NA = Not applicable

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.

Table 19: Results from Generalized Estimating Equation: Ever Use of a [Tobacco or Nicotine Product (TNP)] Never Used at Baseline as a Function of Time, Baseline Study Group, IQOS Flavor Preference

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 6*CEIU				
Month 12*CEIU				
Month 18*CEIU				
Month 24*CEIU				
Menthol IQOS Heated Tobacco Stick Use[1]				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.

Note: This table repeated for each TNP category.

Table 20: Established Use of a [Tobacco or Nicotine Product (TNP)] Never Used at Baseline by Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS User	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Established use of [TNP] never used at Baseline						
Cigarettes	NA					
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-cigarettes	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					
Menthol IQOS Heated Tobacco Stick Use	NA					
Current Established Smoker	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Established use of [TNP] never used at Baseline						
Cigarettes	NA	NA	NA	NA	NA	NA
Regular cigars, cigarillos, or little filtered cigars	NA					
Smokeless tobacco products (chewing tobacco, "dip"/snuff or snus pouches)	NA					
Regular pipe	NA					
E-cigarettes	NA					
Hookah	NA					
Oral tobacco-derived nicotine products	NA					
Net any product	NA					

CI = 95% Confidence Interval; NA = Not applicable

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.

Table 21: Results from Generalized Estimating Equation: Established Use of a [Tobacco Product] Never Used at Baseline as a Function of Time, Baseline IQOS Flavor Preference, Baseline Study Group, and IQOS Flavor Preference

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS Use (CEIU)				
Month 6*CEIU				
Month 12*CEIU				
Month 18*CEIU				
Month 24*CEIU				
Menthol IQOS Heated Tobacco Stick Use[1]				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.

Note: This table repeated for each TNP category.

Table 22: Smoking Relapse at Follow-up Months 3, 6, 12, 18, and 24 among Current Established IQOS Users Who Report Former Established Smoking at Baseline

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
	n = XXX	n = XXX	n = XXX	n = XXX	n = XXX	n = XXX
	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)
Total Relapse to Cigarette Smoking	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					

CI = 95% Confidence Interval; NA = Not applicable.

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 23: Results from Generalized Estimating Equation: Smoking Relapse among Current Established IQOS Users Who Report Former Established Smoking at Baseline as a Function of Time, IQOS Flavor Preference, Years of Cigarette Smoking, and Baseline Cessation Treatment Use.

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years smoked cigarettes				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use[2]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion
1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 24: Smoking Re-initiation at Follow-up Months 3, 6, 12, 18, and 24 among Current Established IQOS Users Who Report Former Established Smoking at Baseline

		Follow-up Survey				
	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24
	n = XXX	n = XXX	n = XXX	n = XXX	n = XXX	n = XXX
Measure	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)	% (CI)
Total Re-initiation to Cigarette Smoking	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					

CI = 95% Confidence Interval; NA = Not applicable.
1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 25: Results from Generalized Estimating Equation: Smoking Re-initiation among Current Established IQOS Users Who Report Former Established Smoking at Baseline as a Function of Time, Years of Cigarette Smoking, IQOS Flavor Preference, and Use of Treatment Cessation

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years smoked cigarettes				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use[2]				

Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 26: Quit Smoking After First Trying IQOS – Current Established IQOS Users Who Report Having Smoked in the 30 Days Before First Trying IQOS and are Former Established Smokers at Baseline

Measure	Baseline n = XXX % (CI)
Quit Smoking After First Trying IQOS	
Menthol IQOS Heated Tobacco Stick Use[1]	
Cessation Treatment Use[2]	

CI = 95% Confidence Interval

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at baseline.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at baseline.

Table 27: Quit Attempts – Prevalence of Baseline Current Smokers Who Attempted to Quit Smoking Cigarettes in the Past 12, 6, and 3 Months at Baseline and in the 30 Days Prior to Each Follow Up by Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS User	**n = XXX** **% (CI)**	**n = XXX** **% (CI)**	**n = XXX** **% (CI)**	**n = XXX** **% (CI)**	**n = XXX** **% (CI)**	**n = XXX** **% (CI)**
Attempted to Quit Smoking						
Menthol IQOS Heated Tobacco Stick Use						
Regular IQOS Heated Tobacco Sticks Use						

Current Established Smoker	n = XXX % (CI)	n = XXX % (CI)	n = XXX % (CI)	n = XXX % (CI)	n = XXX % (CI)	n = XXX % (CI)
Attempted to Quit Smoking						
Menthol IQOS Heated Tobacco Stick Use	NA					
Regular IQOS Heated Tobacco Sticks Use	NA					

CI = 95% Confidence Interval

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Regular IQOS heated tobacco stick use is defined as reporting not using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.

Table 28: Results from Generalized Estimating Equation: Quit Attempts as a Function of Time, Years of Cigarette Smoking, IQOS Flavor Preference, and Use of Treatment Cessation as a Function of Time, Study Group, Years of cigarette smoking, IQOS Flavor Preferences, Use of Cessation Treatment Used

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 3*CEIU				
Month 6*CEIU				
Month 12*CEIU				
Month 18*CEIU				
Month 24*CEIU				
Years smoked cigarettes				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use				
Fit Statistics				
Deviance				

AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Baseline)				
CEIU v. CES (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 29: Use of Cessation Treatment at Baseline by Study Group

Measure	Baseline
Current Established IQOS Users	**n = XXX**
	% (CI)
Cessation Treatment	
Never used	
Used in the past 30 days	
Used >30 days but < 12 months ago	
Used >12 months ago	
Current Established Smokers	**n = XXX**
	% (CI)
Never used	
Used in the past 30 days	
Used >30 days but < 12 months ago	
Used >12 months ago	

CI = 95% Confidence Interval

Table 30: Use of a Cessation Treatment: Use and Incident Use at Each Follow-up Survey by Study Group

Measure	Follow-up Survey				
	Month 3	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Current Established IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Use of cessation treatment					
In the past 30 days					
>30 days to last assessment					
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Use of cessation treatment					
In the past 30 days					
>30 days to last assessment					
Current Established IQOS Users – Without a history of prior cessation treatment use	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Incident use of a cessation treatment					
Current Established Smokers – Without a history of prior cessation treatment use	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Incident use of a cessation treatment					

CI = 95% Confidence Interval

Table 31: Completely Quit – 1. Baseline Current (Past 30-day) Smokers Who Completely Quit Smoking at Follow Up; 2. Current (Past 30-day) IQOS Users who Completely Quit IQOS at Follow-Up; and 3. Participants who Completely Quit All Tobacco or Nicotine Product Use at Follow Up by Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IOQS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Completely quit smoking cigarettes	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Completely quit smoking cigarettes	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Current Established IOQS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Completely quit IQOS	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Current Established IOQS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Completely quit all tobacco	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Completely quit all tobacco	NA					
Menthol IQOS Heated Tobacco Stick Use[1]	NA					
Cessation Treatment Use[2]	NA					

CI = 95% Confidence Interval; NA = Not applicable.

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 32: Results from Generalized Estimating Equation: Completely Quit Smoking - Baseline Current (Past 30-day) Smokers Who Completely Quit Smoking at Follow Up as a function of Time, Baseline Study Group, Years of Cigarette Smoking, IQOS Flavor Preference, and Use of Cessation Treatment.

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 6*CEIU				
Month 12* CEIU				
Month 18* CEIU				
Month 24* CEIU				
Years smoked cigarettes				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use[2]				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion
1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 33: Results from Generalized Estimating Equation: Completely Quit IQOS – Current (Past 30-day) IQOS Users who Completely Quit IQOS at Follow-Up as a function of Time, Baseline Study Group, Years of IQOS Use, IQOS Flavor Preference, and Use of Cessation Treatment

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Years of IQOS use				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use[2]				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion
1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 34: Results from Generalized Estimating Equation: Completely Quit All Tobacco – Participants who Completely Quit All Tobacco or Nicotine Product Use at Follow Up as a function of Time, Baseline Study Group, IQOS Flavor Preference, and Use of Cessation Treatment

Term	Estimate	SE	Z value	*p* value
Intercept (Month 3)				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 6*CEIU				
Month 12*CEIU				
Month 18*CEIU				
Month 24*CEIU				
Menthol IQOS Heated Tobacco Stick Use[1]				
Cessation Treatment Use[2]				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

1. Menthol IQOS heated tobacco stick use is defined as reporting using menthol IQOS heated tobacco sticks most often in the past 30 days at time of assessment.
2. Cessation treatment use is defined as reporting any cessation treatment in the past 30-days at time of assessment.

Table 35: Health-related Quality of Life Scores – Physical – at Baseline and Follow-up Survey Months 3, 6, 12, 18, and 24 by Study Group

Measure		Follow-up Survey				
	Baseline	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Current Established IQOS Users	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Physical health T-score						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						
Current Established Smokers	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
Physical health T-score						
M (SD) [95% CI]						
Median (Q1, Q3)						
Min/Max						

M = Mean; SD = Standard Deviation; CI = Confidence Interval; Q1 = First Quartile; Q3 = Third Quartile

Note. This table repeated for:

- Mental health T-score
- Mean number of cardiovascular symptoms
- Mean number of respiratory symptoms

Table 36: Results from Generalized Estimating Equation: Health-related Quality of Life Score – Physical as a function of Time, Baseline Study Group, Years of Cigarette Smoking, Diagnoses.

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Group = Current Established IQOS User (CEIU)				
Month 3*CEIU				
Month 6*CEIU				
Month 12*CEIU				
Month 18*CEIU				
Month 24*CEIU				
Years smoked cigarettes				
Diagnoses				
Fit Statistics				
Deviance				
AIC				
BIC				
Contrasts				
CEIU v. Current Established Smoker (CES) (Baseline)				
CEIU v. CES (Month 3)				
CEIU v. CES (Month 6)				
CEIU v. CES (Month 12)				
CEIU v. CES (Month 18)				
CEIU v. CES (Month 24)				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Note. This table repeated for:

- Mental health T-score
- Number of cardiovascular symptoms
- Number of respiratory symptoms

Table 37: ABOUT™ – Health-Risk Perception Composite Scores for Cigarettes and IQOS at Baseline and Follow-up Survey Months 12 and 24 – Current Established IQOS Users

Measure		Follow-up Survey	
	Baseline	**Month 12**	**Month 24**
ABOUT™ scale composite score – Cigarettes	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**
Perceived Health-Risk…			
No to Low			
Low			
Low to Moderate			
Moderate			
Moderate to High			
High			
High to Very High			
Very High			
ABOUT™ scale composite score – IQOS	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**
Perceived Health-Risk…			
No to Low			
Low			
Low to Moderate			
Moderate			
Moderate to High			
High			
High to Very High			
Very High			

CI = 95% Confidence Interval

Note: This table repeated for Current Established Smokers.

Table 38: Perception of Switching Completely to IQOS and Harmful or Potentially Harmful Constituent Exposure Reduction at Baseline and Follow-up Survey Months 3, 6, 12, 18, 24 by Study Group

Measure	Baseline	Follow-up Survey				
		Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS User	**n =XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Smokers who switch completely to IQOS have…						
More exposure						
The same exposure						
Less exposure (correct answer)						
No exposure						
Don't know						
Current Established Smoker	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Smokers who switching completely to IQOS have…						
More exposure						
The same exposure						
Less exposure (correct answer)						
No exposure						
Don't know						

CI = 95% Confidence Interval

Table 39: Results from Generalized Estimating Equation: Perception of Switching Completely to IQOS and Harmful or Potentially Harmful Constituent Exposure Reduction as a function of Time.

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 40: Understanding of What to do to Reduce Exposure among Participants Who Perceived that Switching Completely to IQOS results in Reduced Exposure to Harmful or Potentially Harmful Constituents at Baseline and Follow-up Survey Months 3, 6, 12, 18, and 24 by Study Group

Measure		Follow-up Survey				
	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24
Current Established IQOS User	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Stop smoking cigarettes completely and only use IQOS (correct answer)						
Smoke fewer cigarettes and also use IQOS						
Keep smoking the same amount of cigarettes and also use IQOS						
Don't know						
Current Established Smoker	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**	**n = XXX**
	% (CI)	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**	**% (CI)**
Stop smoking cigarettes completely and only use IQOS (correct answer)						

Smoke fewer cigarettes and also use IQOS						
Keep smoking the same amount of cigarettes and also use IQOS						
Don't know						

CI = 95% Confidence Interval

Table 41: Results from Generalized Estimating Equation: Correct Comprehension: Must Switch Completely from Cigarettes to IQOS

Term	Estimate	SE	Z value	*p* value
Intercept (Baseline)				
Month 3				
Month 6				
Month 12				
Month 18				
Month 24				
Fit Statistics				
Deviance				
AIC				
BIC				

SE = Standard Error; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

11 SUMMARY OF CHANGES TO THE PROTOCOL AND/OR STATISTICAL ANALYSIS PLAN

Version	Date of Revision	Revision	Reason for Revision
1.0	3 May 2024	Original SAP	N/A

12 REFERENCES

Austin, P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*, *46*(3), 399-424. https://doi.org/10.1080/00273171.2011.568786

Berg, C. J., Barr, D. B., Stratton, E., Escoffery, C., & Kegler, M. (2014). Attitudes toward E-Cigarettes, Reasons for Initiating E-Cigarette Use, and Changes in Smoking Behavior after Initiation: A Pilot Longitudinal Study of Regular Cigarette Smokers. *Open J Prev Med*, *4*(10), 789-800. https://doi.org/10.4236/ojpm.2014.410089

Campagna, D., Cibella, F., Caponnetto, P., Amaradio, M. D., Caruso, M., Morjaria, J. B., Malerba, M., & Polosa, R. (2016). Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *Eur J Clin Invest*, *46*(8), 698-706. https://doi.org/10.1111/eci.12651

Cano, S., Chrea, C., Salzberger, T., Alfieri, T., Emilien, G., Mainy, N., Ramazzotti, A., Lüdicke, F., & Weitkunat, R. (2018). Development and validation of a new instrument to measure perceived risks associated with the use of tobacco and nicotine-containing products. *Health Qual Life Outcomes*, *16*(1), 192. https://doi.org/10.1186/s12955-018-0997-5

Cefalu, M., Ridgeway, G., Mccaffrey, D., Morral, A., Griffin, A. B., & Burgette, L. (2021). Toolkit for weighting and analysis of nonequivalent groups. *R package (version 2.5. 2021)*.

Chesnaye, N. C., Stel, V. S., Tripepi, G., Dekker, F. W., Fu, E. L., Zoccali, C., & Jager, K. J. (2022). An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J*, *15*(1), 14-20. https://doi.org/10.1093/ckj/sfab158

Choi, K., & Forster, J. L. (2014). Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. *Am J Prev Med*, *46*(2), 175-178. https://doi.org/10.1016/j.amepre.2013.10.007

Cibella, F., Campagna, D., Caponnetto, P., Amaradio, M. D., Caruso, M., Russo, C., Cockcroft, D. W., & Polosa, R. (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)*, *130*(21), 1929-1937. https://doi.org/10.1042/cs20160268

Dobbie, F., Hiscock, R., Leonardi-Bee, J., Murray, S., Shahab, L., Aveyard, P., Coleman, T., McEwen, A., McRobbie, H., Purves, R., & Bauld, L. (2015). Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS): a prospective cohort study. *Health Technol Assess*, *19*(95), 1-156. https://doi.org/10.3310/hta19950

Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. (2014). Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*, *11*(4), 4356-4373. https://doi.org/10.3390/ijerph110404356

FDA. (2012). *Guidance for Industry: Modified Risk Tobacco Product Applications* https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UC M297751.pdf

FDA. (2020, 7/7/2020). *FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information* https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information

FDA. (2022, 11/30/2023). *Modified Risk Granted Orders – Exposure Modification* https://www.fda.gov/media/156829/download?attachment

Getsios, D., Marton, J. P., Revankar, N., Ward, A. J., Willke, R. J., Rublee, D., Ishak, K. J., & Xenakis, J. G. (2013). Smoking cessation treatment and outcomes patterns simulation: a new framework for evaluating the potential health and economic impact of smoking cessation interventions. Pharmacoeconomics, 31(9), 767-780. https://doi.org/10.1007/s40273-013-0070-5

Grana, R. A., Popova, L., & Ling, P. M. (2014). A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Intern Med*, *174*(5), 812-813. https://doi.org/10.1001/jamainternmed.2014.187

Halpern, S. D., Harhay, M. O., Saulsgiver, K., Brophy, C., Troxel, A. B., & Volpp, K. G. (2018). A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. *N Engl J Med*, *378*(24), 2302-2310. https://doi.org/10.1056/NEJMsa1715757

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., Rickert, W., & Robinson, J. (1989). Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict*, *84*(7), 791-799. https://doi.org/10.1111/j.1360-0443.1989.tb03059.x

Kasza, K. A., Tang, Z., Seo, Y. S., Benson, A. F., Creamer, M. R., Edwards, K. C., Everard, C., Chang, J. T., Cheng, Y. C., Das, B., Oniyide, O., Tashakkori, N. A., Weidner, A. S., Xiao, H., Stanton, C., Kimmel, H. L., Compton, W., & Hyland, A. (2024). Divergence in Cigarette Discontinuation Rates by Use of Electronic Nicotine Delivery

Systems (ENDS): Longitudinal Findings From the United States PATH Study Waves 1-6. Nicotine Tob Res. https://doi.org/10.1093/ntr/ntae027

Kotz, D., Brown, J., & West, R. (2013). Predictive validity of the Motivation To Stop Scale (MTSS): a single-item measure of motivation to stop smoking. *Drug Alcohol Depend*, *128*(1-2), 15-19. https://doi.org/10.1016/j.drugalcdep.2012.07.012

Leas, E. C., Pierce, J. P., Benmarhnia, T., White, M. M., Noble, M. L., Trinidad, D. R., & Strong, D. R. (2018). Effectiveness of Pharmaceutical Smoking Cessation Aids in a Nationally Representative Cohort of American Smokers. *J Natl Cancer Inst*, *110*(6), 581-587. https://doi.org/10.1093/jnci/djx240

Li, L., & Greene, T. (2013). A weighting analogue to pair matching in propensity score analysis. *Int J Biostat*, *9*(2), 215-234. https://doi.org/10.1515/ijb-2012-0030

Mantey, D. S., Cooper, M. R., Loukas, A., & Perry, C. L. (2017). E-cigarette Use and Cigarette Smoking Cessation among Texas College Students. *Am J Health Behav*, *41*(6), 750-759. https://doi.org/10.5993/ajhb.41.6.9

Markoulidakis, A., Taiyari, K., Holmans, P., Pallmann, P., Busse, M., Godley, M. D., & Griffin, B. A. (2023). A tutorial comparing different covariate balancing methods with an application evaluating the causal effects of substance use treatment programs for adolescents. *Health Serv Outcomes Res Methodol*, *23*(2), 115-148. https://doi.org/10.1007/s10742-022-00280-0

McKeganey, N., Miler, J. A., & Haseen, F. (2018). The Value of Providing Smokers with Free E-Cigarettes: Smoking Reduction and Cessation Associated with the Three-Month Provision to Smokers of a Refillable Tank-Style E-Cigarette. *Int J Environ Res Public Health*, *15*(9). https://doi.org/10.3390/ijerph15091914

McRobbie, H., Phillips, A., Goniewicz, M. L., Smith, K. M., Knight-West, O., Przulj, D., & Hajek, P. (2015). Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. *Cancer Prev Res (Phila)*, *8*(9), 873-878. https://doi.org/10.1158/1940-6207.Capr-15-0058

Mushtaq, N., & Beebe, L. A. (2017). Psychometric Properties of Fagerström Test for Nicotine Dependence for Smokeless Tobacco Users (FTND-ST). *Nicotine Tob Res*, *19*(9), 1095-1101. https://doi.org/10.1093/ntr/ntx076

Nides, M. A., Leischow, S. J., Bhatter, M., & Simmons, M. (2014). Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav*, *38*(2), 265-274. https://doi.org/10.5993/ajhb.38.2.12

Norton, K. J., June, K. M., & O'Connor, R. J. (2014). Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. *Tob Induc Dis*, *12*(1), 17. https://doi.org/10.1186/1617-9625-12-17

O'Connor, R. J., Hyland, A., Giovino, G. A., Fong, G. T., & Cummings, K. M. (2005). Smoker awareness of and beliefs about supposedly less-harmful tobacco products. *Am J Prev Med*, *29*(2), 85-90. https://doi.org/10.1016/j.amepre.2005.04.013

O'Connor, R. J., Norton, K. J., Bansal-Travers, M., Mahoney, M. C., Cummings, K. M., & Borland, R. (2011). US smokers' reactions to a brief trial of oral nicotine products. *Harm Reduct J*, *8*, 1. https://doi.org/10.1186/1477-7517-8-1

Pacifici, R., Pichini, S., Graziano, S., Pellegrini, M., Massaro, G., & Beatrice, F. (2015). Successful Nicotine Intake in Medical Assisted Use of E-Cigarettes: A Pilot Study. *Int J Environ Res Public Health*, *12*(7), 7638-7646. https://doi.org/10.3390/ijerph120707638

Perneger TV. What's wrong with Bonferroni adjustments. BMJ. 1998 Apr 18;316(7139):1236-8. doi: 10.1136/bmj.316.7139.1236. PMID: 9553006; PMCID: PMC1112991.

Piper, M. E., Baker, T. B., Benowitz, N. L., Smith, S. S., & Jorenby, D. E. (2020). E-cigarette Dependence Measures in Dual Users: Reliability and Relations With Dependence Criteria and E-cigarette Cessation. *Nicotine Tob Res*, *22*(5), 756-763. https://doi.org/10.1093/ntr/ntz040

Polosa, R., Caponnetto, P., Maglia, M., Morjaria, J. B., & Russo, C. (2014). Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health*, *14*, 1159. https://doi.org/10.1186/1471-2458-14-1159

Polosa, R., Morjaria, J. B., Caponnetto, P., Caruso, M., Campagna, D., Amaradio, M. D., Ciampi, G., Russo, C., & Fisichella, A. (2016). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov Med*, *21*(114), 99-108.

Pulvers, K., Emami, A. S., Nollen, N. L., Romero, D. R., Strong, D. R., Benowitz, N. L., & Ahluwalia, J. S. (2018). Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes. *Nicotine Tob Res*, *20*(2), 206-214. https://doi.org/10.1093/ntr/ntw333

Pulvers, K., Hayes, R. B., Scheuermann, T. S., Romero, D. R., Emami, A. S., Resnicow, K., Olendzki, E., Person, S. D., & Ahluwalia, J. S. (2015). Tobacco Use, Quitting Behavior, and Health Characteristics Among Current Electronic Cigarette Users in a

National Tri-Ethnic Adult Stable Smoker Sample. *Nicotine Tob Res*, *17*(9), 1085-1095. https://doi.org/10.1093/ntr/ntu241

Ridgeway, G., McCaffrey, D. F., Morral, A. R., Cefalu, M., Burgette, L. F., Pane, J. D., & Griffin, B. A. (2022). *Toolkit for weighting and analysis of nonequivalent groups: a tutorial for the R TWANG package*. Rand Santa Monica, Calif.

Robins, J. M., Rotnitzky, A., & Zhao, L. P. (1995). Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *Journal of the American statistical Association*, *90*(429), 106-121.

Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, *70*(1), 41-55.

Sharma, M. K., Suman, L. N., Srivastava, K., Suma, N., & Vishwakarma, A. (2021). Psychometric properties of Fagerstrom Test of Nicotine Dependence: A systematic review. *Ind Psychiatry J*, *30*(2), 207-216. https://doi.org/10.4103/ipj.ipj_51_21

Timberlake, D. S., Huh, J., & Lakon, C. M. (2009). Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. *Nicotine Tob Res*, *11*(4), 455-462. https://doi.org/10.1093/ntr/ntp008

U.S. Department of Health and Human Services [DHHS]. (2020). Chapter 4: The health benefits of smoking cessation. In U. S. P. H. S. O. o. t. S. G. N. C. f. C. D. P. a. H. P. U. O. o. S. a. Health. & W. (DC): (Eds.), *Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. https://www.ncbi.nlm.nih.gov/books/NBK555590/

World Health Organization [WHO]. (1998). The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med*(46), 1569-1585.

Xu, C., Li, Z., Xue, Y., Zhang, L., & Wang, M. (2019). An R package for model fitting, model selection and the simulation for longitudinal data with dropout missingness. *Commun Stat Simul Comput*, *48*(9), 2812-2829. https://doi.org/10.1080/03610918.2018.1468457