June 26, 2024
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Renewal Modified Risk Tobacco Product Applications (MRTPAs)
MR0000256
Swedish Match USA, Inc.

Office of Science
Center for Tobacco Products
Food and Drug Administration

DISCLAIMER STATEMENT

The attached briefing document contains information prepared by the Food and Drug Administration (FDA) for the members of the Tobacco Products Scientific Advisory Committee (TPSAC). The FDA background package includes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are referring Swedish Match USA, Inc.'s Renewal Modified Risk Tobacco Product Applications (MRTPAs) for eight General Snus products to TPSAC to gain TPSAC's insights and recommendations. This briefing package may not include all issues relevant to FDA's decision on the application and instead is intended to focus on issues identified by FDA for discussion by TPSAC. FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting. The information in these materials does not represent agency position or policy. The information is being provided to TPSAC to facilitate its evaluation of the issues and questions referred to the Committee.

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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Matthew Farrelly, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for June 26, 2024 discussion of Swedish Match USA, Inc. renewal MRTPAs for eight General Snus tobacco products (FDA Submission Tracking Number MR0000256)

Introduction

We would like to thank the TPSAC members in advance for providing recommendations to FDA on the renewal modified risk tobacco product applications (MRTPAs) submitted by Swedish Match USA, Inc. ("Swedish Match").

On October 22, 2019, FDA issued Swedish Match a modified risk granted order (MRGO) for the following eight smokeless tobacco products: General Loose, General Dry Mint Portion Original Mini, General Portion Original Large, General Classic Blend Portion White Large – 12ct., General Mint Portion White Large, General Nordic Mint Portion White Large – 12ct., General Portion White Large, and General Wintergreen Portion White Large (hereafter referred to as "General Snus products"). FDA authorized the marketing of the eight General Snus products with the following claim:

Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.

The MRGO is a risk modification order, meaning the applicant demonstrated that, as actually used by consumers, the eight General Snus products sold or distributed with the modified risk claim will significantly reduce harm and the risk of tobacco-related disease to people who use tobacco and benefit the health of the population as a whole, taking into account both people who use tobacco products and people who do not currently use tobacco products. To arrive at this decision, FDA conducted thorough scientific review of the available scientific evidence, including but not limited to long-term epidemiological studies and perceptions and intentions data. See Appendix A for additional information on the statutory requirements for Modified Risk Tobacco Products (MRTPs).

The risk modification order expires October 22, 2024. On July 17, 2023, FDA received renewal MRTPAs from Swedish Match for the eight General Snus products. The applicant has requested a renewal of their risk modification order under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to continue to market the products specified with the same modified risk claim.

Postmarket Surveillance and Studies Requirements

Under Section 911(i)(1) of the FD&C Act, FDA must require postmarket surveillance and studies (PMSS) for any product for which an applicant received an order under 911(g)(1) in order to: "…determine the impact of the order issuance on consumer perception, behavior, and health, to enable the FDA to review the accuracy of the determinations upon which the order was based, and to provide information that the FDA determines is otherwise necessary regarding the use or health risks involving the tobacco product." FDA communicated the PMSS requirements to the applicant in the MRGO letter. Under Section 911(i), the applicant is required to submit PMSS protocols for approval. The applicant did so, and FDA reviewed and approved the PMSS protocols before the studies began. The applicant submitted reports, as required under 911(i), outlining its progress on PMSS activities each year as part of its annual reports.

Swedish Match's PMSS requirements included the following:

1. Monitoring use of the eight General Snus products that were authorized to be marketed with the MRTP claim in terms of uptake, dual use, and complete switching.
2. An assessment of consumers' perceptions of the products and understanding of the claim, particularly that, to reduce their risk of disease relative to smoking, they must use General Snus exclusively.
3. Surveillance of MRTP sales and distribution, adverse experiences, and new research findings.

Swedish Match conducted the longitudinal "General Snus Patterns of Use Study" to fulfill PMSS requirements. FDA received three annual reports and two amendments that included study updates, as well as the other PMSS requirements, surveillance of MRTP sales and distribution, adverse experiences, and new research findings.

Marketing and Sales Post-Modified Risk Granted Order

After the MRGO was granted on October 22, 2019, the applicant's marketing was limited in scope, budget, and impressions (i.e., the number of times the intended audience(s) had an opportunity to view the advertisements). The applicant's marketing consisted of a branded website, trade print advertisements (i.e., advertising targeted to retailers and distributers), Facebook-only social media posts, paid digital advertising, earned media (i.e., unpaid media publicity that the applicant did not commission or pay for, such as news articles about the product), and point-of-sale advertisements using the modified risk claim**.** See Figure 1 for a sample print advertisement with the modified risk claim.

Sales of General Snus are declining. Liber et al. (2023) found that sales of General Snus decreased over 2017-2021. As part of its PMSS requirements, the applicant submitted unit and dollar wholesale distribution data. The applicant's data show that during 2019-2023, both wholesale unit and dollar sales decreased. Wholesale units (by cans) decreased from 4.94M cans to 3.47M cans between Q4 2019 -- Q3 2020 and Q4 2022 – Q3 2023, and wholesale dollar sales decreased from 17.52M to 14.96M during the same period. FDA conducted an internal analysis of General Snus sales data using NielsenIQ Retail Measurement Service (RMS) Total US xAOC+Convenience data between 2019 and 2023. Sales of General Snus products with MRGOs were evaluated on a quarterly basis. General Snus products in NielsenIQ RMS data were matched by the UPC codes provided in the MRTPA renewal package; that analysis found

that sales of General Snus products in NielsenIQ RMS data have fallen from $6.6M in the quarter the General Snus MRGO was issued (Q4 2019) to $4.9M in Q4 2023.[1]

Figure 1. Sample print advertisement with modified risk claim

Contents of Renewal MRTPA

The applicant submitted information about the modified risk claim and relative health risks of General Snus (i.e., claim substantiation) by cross-referencing scientific evidence in the original premarket tobacco product application (PMTA) and MRTPA and literature submitted as part of its PMSS requirements to support continued claim substantiation. The applicant submitted information about use behaviors, and consumer understanding and perceptions of the modified risk claim by cross-referencing results from its PMSS activities.

Draft Topics for TPSAC Discussion

FDA is reviewing the scientific information submitted in the renewal MRTPA and other scientific information identified by the Agency from other sources to determine whether the standard for issuing

[1] Disclaimer: The author's own analyses, calculations and conclusions informed in part by the NielsenIQ Retail Measurement Service (RMS) data through NielsenIQ's RMS for the tobacco product category smokeless tobacco for the time period 2019 through 2023 for Total US Expanded All Outlets Combined (xAOC) and convenience stores are those of the FDA and do not reflect the views of NielsenIQ. NielsenIQ is not responsible for, had no role in, and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches used in connection with this report. NielsenIQ RMS data consist of weekly purchase and pricing data generated from participating retail store point-of-sale systems in all U.S. markets. See https://NielsenIQ.com/global/en/ for more information.

the MRGO continues to be met. FDA will also review public comments submitted in accordance with Section 911(e).

FDA intends to raise the following matters for discussion with TPSAC:

Use of the MRTP

FDA will present data from several studies, including nationally representative estimates of snus use, as well as data from the applicant's General Snus Patterns of Use Study to describe characteristics of people who use snus, patterns of tobacco use among people who use General Snus, and transitions away from combusted cigarette (CC) smoking among General Snus users. TPSAC will be asked to discuss the use behaviors with respect to the MRTPs.

Consumer understanding and perceptions of the modified risk claim

FDA will present results from the applicant's General Snus Patterns of Use Study and will ask TPSAC to discuss the evidence related to consumer understanding and perceptions of the modified risk claim.

The following sections provide a summary and assessment of the evidence provided in the MRTPA relevant to the foregoing topics.

Preliminary FDA Review Findings

I. RELATIVE HEALTH RISKS

A. Individual Health Risks

FDA conducted a review of individual health risk studies (published between 2019 and 2023) regarding mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. As part of its PMSS requirements, the applicant submitted new literature published since the MRGO. FDA also conducted a literature review to capture additional relevant studies since the MRGO. Overall, we analyzed a total of ten studies that were published since the MRGO (See Appendix A, Tables 1 and 2 for study details). Of these studies, we excluded two that did not focus on outcomes relevant to the modified risk claim and one systematic review that overlapped with the other studies selected.

- *Mouth Cancer*: A pooled study showed that current snus use was not associated with oral cancer when compared to never-snus use (Araghi et al., 2021).
- *Stroke and Ischemic Stroke*: A prospective cohort study of Swedish adults that controlled for age, sex, education, alcohol consumption, walking/bicycling, and exercise found no association between snus use and risk of total stroke (including ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and undefined type of stroke) among the whole sample; however, among people who had never smoked CC, current snus use was associated with higher total stroke and ischemic stroke risk compared to never tobacco use (adjusted Hazard Ratio (aHR) 1.53, 95% CI: 1.02-2.32 and aHR 1.65, 95% CI: 1.06-2.57, respectively) (Titova et al., 2021).
- *Cardiovascular Disease Morbidity and Mortality*: A meta-analysis by Lee et al. (2022) found no significant increase in the risk of ischemic heart disease (IHD) or acute myocardial infarction (AMI). Additionally, a prospective cohort study conducted by Yuan et al. (2022) revealed that

while CC smoking was associated peripheral artery disease (PAD) (HR-4.01, 95% CI=3.17-5.08), snus use was not (HR=0.88, 95% CI=0.66-1.17). Specifically, the risk of PAD was higher among people who currently smoke CC and people who had quit smoking for both more than and less than 10 years compared to those who never smoked. A pooled study found that among people who have never smoked CC, exclusive current snus use compared to never tobacco use was associated with increased cardiovascular disease mortality (aHR 1.27, 95% CI: 1.15-1.41) (Byhamre et al., 2021).

- *Lung Cancer, Emphysema, and Chronic Bronchitis*: We did not find newly published studies addressing risks of lung cancer, emphysema, and chronic bronchitis.

Overall, the literature published since the MRGO is generally consistent with the body of literature reviewed during the original MRTPA and provides additional evidence that the risks of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis due to Swedish snus use are lower than the risk from CC smoking. While the evidence of the association between Swedish snus use and fatal stroke and post-stroke mortality has been mixed, the results in Titova et al. (2021) based on a single cohort are consistent with prior findings that the level of risk is below the well-established stroke risk of CC smoking. Similarly, the risk of cardiovascular mortality associated with snus use reported by Byhamre et al. (2021) is still lower than that for CC smoking. For example, data from the Contemporary Cohort[2] (2000–2010) among men[3] ages 55-74 indicate that people who smoke CC have elevated risks of stroke (Risk Ratio (RR) 1.92, 95% CI: 1.66-2.21) and cardiovascular mortality (RR 2.50, 95% CI: 2.34-2.66) (Thun et al., 2013). Therefore, the risks of stroke and cardiovascular disease mortality in people who exclusively use snus are lower relative to people who smoke CC, as FDA's prior evaluation concluded, and the scientific evidence published since the original MRGO continues to support the modified risk claim as scientifically accurate.

B. Adverse Experiences

The applicant did not report any serious or unexpected adverse experiences (AEs) for the General Snus products since the issuance of the MRGO. FDA's Tobacco Product Surveillance Team conducted a search for AE reports in the Safety Reporting Portal (SRP) on November 20, 2023. The search did not reveal any AEs involving the General Snus products since the issuance of the MRGO.

C. Summary and Conclusions

The General Snus products have not changed since the issuance of the MRGO, and the modified risk claim is also the same. The product formulation as well as manufacturing practices have not changed; thus, levels of harmful and potentially harmful constituents (HPHCs) remain the same. The published literature and adverse experience reporting since the issuance of the MRGO do not raise concerns that there are any changes to FDA's previous conclusions regarding claim substantiation.

[2] The contemporary cohort consisted of cohorts from five studies. Participants were enrolled in the Nurses' Health Study (NHS) in 1976, the Health Professionals Follow-up Study (HPFS) in 1986, the CPS II Nutrition Cohort in 1992, the National Institutes of Health–American Association of Retired Persons (NIH–AARP) Diet and Health Study in 1995–1996, or the Women's Health Initiative (WHI) in 1993–1998.

[3] Sweden has the highest prevalence of current snus use, particularly among men, with 22% of men using it. However, among women, snus use is rare, at only 4% (Byhamre et al., 2020).

II. PATTERNS OF USE AND IMPACTS TO THE POPULATION

This section examines observational studies and the applicant's General Snus Patterns of Use Study to describe patterns of use of General Snus and its impact on the population. The section includes summaries of published literature, analyses conducted by the applicant, and summaries of FDA's own analyses.

A. U.S. Prevalence of Snus Use

Among adults in the United States, the prevalence of snus use is low. The applicant cites results from the Population Assessment of Tobacco and Health (PATH) Wave 1 study (fielded September 2013 – December 2014), where Cheng et al. (2017) reports that 0.4% of U.S. adults reported currently using pouched snus. Based on population estimates from an internal analysis of PATH Study Wave 7 (fielded January 2022 – April 2023), 0.7% of adults (unweighted n = 29,780) reported currently using snus every day, some days, or on at least one of the past 30 days. FDA notes that these PATH data include all brands of snus, and General Snus would represent only a fraction of these estimates.

B. General Snus Patterns of Use Study

The applicant's PMSS requirements included monitoring use of the eight General Snus products in terms of uptake, dual use, and complete switching. In response to the PMSS requirement, the applicant conducted the General Snus Patterns of Use Study, a prospective study spanning two years (and four data collection time points). The study examined self-reported past 30-day tobacco and nicotine product (TNP[4]) use among people who currently use General Snus. The applicant's four primary study objectives were:

1. Compare TNP patterns of use (every day and some days) for 10 TNPs and General Snus, between all four waves
2. Compare consumption patterns (number of days per month used, number of pouches/CC used on days used) of CC and General Snus over the last 30 days (baseline) with consumption patterns in Waves 2 through 4
3. Characterize people in terms of prior TNP use and demographics and compare this to people who newly use smokeless TNP as reported in the PATH Study
4. Compare the tendencies to quit CC or use General Snus in an incremental fashion, in a supplemental fashion, or in complete substitution of CC (i.e., compare CC used per day baseline to follow-up waves among dual users of General Snus and CC)

The applicant eliminated objective 3 mid-way through the study due to low sample size of "new users" (page 89, "121323 Swedish Match MR0000256 WAVE AMENDMENT1.pdf").

Methods

[4] In the General Snus Patterns of Use Study, the applicant defines TNP use as using the following products: CC, e-cigarette, moist snuff, chewing tobacco, snus, General Snus pouches, nicotine pouches, nicotine replacement therapy, all cigars (cigar, cigarillo, filtered cigar filled with tobacco), pipe tobacco, hookah or waterpipe.

The applicant recruited General Snus purchasers through invitation stickers placed on product packaging. The invitation sticker presented a website to access the baseline survey through a unique and secure link. General Snus products with invitation stickers were available at approximately 10,600 retail stores across all locations where General Snus was sold from July 25, 2020 to August 7, 2020. The applicant also recruited, via email, people who opted in/registered to receive communications from General Snus. Study participants received $40.00 for each completed survey and an additional $50 bonus if they completed all three follow-up surveys.

Participants completed a baseline survey (Wave 1, July 25, 2020 to August 17, 2020) and were asked to participate in follow-up surveys at six months (Wave 2, February 2, 2021 to March 6, 2021), one year (Wave 3, August 5, 2021 to September 7, 2021), and two years (Wave 4, August 4, 2022 to September 5, 2022) from baseline. Participants who completed the baseline survey were allowed to participate in any of the subsequent waves, regardless of participation in prior follow-up waves (i.e., participants could miss a wave and then return for a later wave questionnaire).

The applicant provided descriptive statistics for each study wave according to the statistical analysis plan submitted in the study protocol. In a final report, the applicant provided a small number of statistical, cross-sectional comparisons across waves. FDA conducted internal analyses of the applicant's data to replicate and further understand the applicant's findings.

Eligibility Criteria

To be eligible for the study, individuals must have reported current use of a General Snus product at baseline, defined as using it at least once within the past 30 days prior to study initiation and using it every day or on some days prior to study initiation. They also had to be U.S. residents, ages 21 years and older, who reported being able to read and speak English. Lastly, they had to agree to participate in four surveys over a 24-month period and provide consent and personal contact information.

Exclusion Criteria

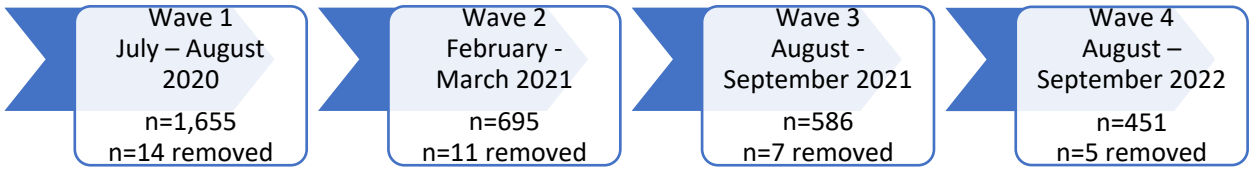
The applicant excluded individuals who selected "don't know" or "decline to answer" to survey questions about their gender or geographic region; who participated in consumer research on TNP in the two weeks prior to accessing the baseline survey; and who were employed in market research, marketing, advertising, TNP manufacturing, or as a physician.

Study Retention

The General Snus Patterns of Use study experienced higher-than-expected drop-out rates over the two-year study duration. *A priori*, the applicant estimated a 40% dropout rate per year, resulting in an estimated sample of n=1,200 participants in Wave 2, n=900 participants in Wave 3, and n=540 participants in Wave 4; however, the actual attrition rate was higher (see Figure 2 for sample size by study wave). Overall, only 281 participants completed all study waves, indicating a 17.0% full-study retention rate. The applicant removed additional responses from each wave due to data cleaning.

Differential loss to follow-up by tobacco use status could impact the study's ability to observe transitions in tobacco use and result in biased study results. As a result, FDA conducted an attrition analysis of the applicant's data to evaluate potential demographic or tobacco use differences in participants who dropped out versus participants who were retained at each study wave. Results are presented in the "FDA's Attrition Analysis" section.

Figure 2. General Snus Patterns of Use Study sample Information across waves



FDA's Study Evaluation Approach

To fully evaluate the applicant's study results, FDA relied on the published literature and population estimates of use and analyzed applicant-provided data to replicate findings or to further investigate questionable findings. FDA compared demographic and tobacco use characteristics of baseline participants in the General Snus Patterns of Use Study with characteristics typically seen among people who use CC and smokeless tobacco products to provide the context needed to evaluate the generalizability of the study population and the study results.

The applicant used an unconventional approach to understanding behavior on quitting and intention to quit that relied upon multiple measures. People who currently (past 30-day) used CC were asked, "Have you completely quit smoking cigarettes in the past 29 days?" Those who responded "No" were asked, "Are you currently trying to quit smoking cigarettes?" Those who responded "No" to that question were then asked about their intention to quit CC using the Motivation to Stop Scale (MTSS); this question included seven response options and a "don't know" option. The response categories were: (1) "I don't want to stop smoking"; (2) "I think I should stop smoking but don't really want to"; (3) "I want to stop smoking but haven't thought about when"; (4) "I really want to stop smoking but I don't know when I will"; (5) "I want to stop smoking and hope to soon"; (6) "I really want to stop smoking and intend to in the next 3 months"; (7) "I really want to stop smoking and intend to in the next month." FDA analyzed the data from these measures to categorize people who dual use General Snus and CC into categories describing their readiness to quit. The readiness to quit categories included: attempting to quit in the past 29 days; currently trying to quit CC; not currently trying to quit CC but high intention to quit in the future; not currently trying to quit CC but low intention to quit in the future; not currently trying to quit CC with known future quit intention. High quit intention included responses of 4-7, low intention included responses of 1-3, and unknown intention included "don't know" on the MTSS.

FDA discusses past 30-day other tobacco product use among people who use General Snus, as well as complete switching and smoking cessation over the course of the study. We considered the significant loss to follow-up observed and the implications of study attrition on our evaluation of the applicant's results.

Findings

Sample Characteristics

Table 1 presents participant demographic and tobacco use characteristics at baseline and Wave 4 to describe the sample. At baseline, participants had a mean age of 36.1, were predominantly White and male, and were more likely to have some college, an Associate's or Bachelor's degree, have a household income of $50,000-99,999 per year, and reside in the South and Midwest. Regarding tobacco use behaviors, baseline participants predominantly used more than 200 General Snus pouches in their lifetime. Among those who currently smoked CC, baseline participants predominantly smoked more than 100 CC in their lifetime and started smoking over 36 months ago. Among people who used CC at baseline (n=299), more than 60% reported a readiness to quit by a quit attempt in the past 29 days (16.4%), currently trying to quit (36.8%), or having high intention to quit in the future (8.4%). Baseline participant characteristics were mostly similar between baseline to Wave 4 participants; however, compared to the total baseline participants, those who completed Wave 4 were more likely to have reported an income >$100,000 (33.7% vs. 28.0%) and an educational attainment of post-graduate degree (13.1% vs. 11.8%). In terms of tobacco use characteristics, those who completed Wave 4 were more likely to have had used >200 lifetime number of General Snus pouches (82.3% vs. 75.0%).

FDA notes that participant demographics in the current study are more similar to those of people who report using smokeless tobacco than those who report using CC.

Table 1. Demographics and Tobacco Use by People who Used General Snus at Baseline and Wave 4, Based on FDA Analysis of Applicant Data

		Total baseline participants (n=1,655)		Baseline values for participants who completed Wave 4 (n=451)
	n	mean (std) or % (95% CI)	n	mean (std) or % (95% CI)
Mean age (years)	1,655	36.1 (10.4)	451	37.5 (10.5)
Gender				
Male	1,517	91.7 (90.2, 92.9)	423	93.8 (91.2, 95.8)
Female	138	8.3 (7.1, 9.8)	28	6.2 (4.2, 8.8)
Race/ethnicity				
Non-Hispanic White	1,471	88.9 (87.3, 90.4)	406	90.0 (86.9, 92.6)
Black/African American	24	1.5 (0.9, 2.2)	5	1.1 (0.4, 2.6)
Hispanic	42	2.5 (1.8, 3.4)	11	2.4 (1.2, 4.3)
Non-Hispanic Other	100	6.0 (4.9, 7.3)	27	6.0 (4.0, 8.6)

Don't know/Decline to answer	18	1.1 (0.6, 1.7)	2	0.4 (0.1, 1.6)
Geographic region				
West	199	12.0 (10.5, 13.7)	60	13.3 (10.3, 16.8)
South	467	28.2 (26.1, 30.5)	138	30.6 (26.4, 35.1)
Midwest	567	34.3 (32.0, 36.6)	157	34.8 (30.4, 39.4)
Northwest	422	25.5 (23.4, 27.7)	96	21.3 (17.6, 25.4)
Education attainment				
<High school/High school/GED	261	15.8 (14.0, 17.6)	54	12.0 (9.1, 15.3)
Some college/Associate degree	621	37.5 (35.2, 39.9)	170	37.7 (33.2, 42.3)
Bachelor's	571	34.5 (32.2, 36.8)	167	37.0 (32.6, 41.7)
Post-graduate	195	11.8 (10.3, 13.4)	59	13.1 (10.1, 16.5)
Missing	7	0.4 (0.2, 0.9)	1	0.2 (0.0, 1.2)
Household income				
<$50,000	508	30.7 (28.5, 33.0)	116	25.7 (21.7, 30.0)
$50,000 - $99,999	621	37.5 (35.2, 39.9)	166	36.8 (32.3, 41.4)
$100,000+	463	28.0 (25.8, 30.2)	152	33.7 (29.3, 38.3)
Missing	63	3.8 (2.9, 4.8)	17	3.8 (2.2, 6.0)
Lifetime number of General Snus pouches used				
200+	1,242	75.0 (72.9, 77.1)	371	82.3 (78.4, 85.7)
1-199	313	18.9 (17.1, 20.9)	56	12.4 (9.5, 15.8)
Don't know	100	6.0 (4.9, 7.3)	24	5.3 (3.4, 7.8)
Smoking status				
Currently uses CC[a]	299	18.1 (16.2, 20.0)	63	14.0 (10.9, 17.5)
Formerly[b] used CC	613	37.0 (34.7, 39.4)	178	39.5 (34.9, 44.1)
Never[c] used CC	741	44.8 (42.4, 47.2)	210	46.6 (41.9, 51.3)
Lifetime number of CC smoked (among current users of CC)				
100+ CC	257	86.0 (81.5, 89.7)	55	87.3 (76.5, 94.4)
1-99 CC	34	11.4 (8.0, 15.5)	7	11.1 (4.6, 21.6)
Don't know	8	2.7 (1.2, 5.2)	1	1.6 (0.0, 8.5)
First started CC (among current users of CC)				
>36 months ago	272	91.0 (87.1, 94.0)	59	93.7 (84.5, 98.2)
0-36 months ago	27	9.0 (6.0, 12.9)	4	6.3 (1.8, 15.5)
Readiness to quit among people currently using CC				
Any quit attempt in past 29 days	49	16.4 (12.4, 21.1)	11	17.5 (9.1, 29.1)
Currently trying to quit CC[d]	110	36.8 (31.3, 42.5)	25	39.7 (27.6, 52.8)

Not currently trying to quit CC, but high intention to quit in the future[e]	25	8.4 (5.5, 12.1)	6	9.5 (3.6, 19.6)
Not currently trying to quit CC, low intention to quit in the future[e]	106	35.5 (30.0, 41.2)	17	27.0 (16.6, 39.7)
Not currently trying to quit CC, unknown intention[e]	9	3.0 (1.4, 5.6)	4	6.3 (1.8, 15.5)

CC = combusted cigarettes.

a. Currently uses CC includes 49 participants who reported making a quit attempt sometime in the past 29 days.
b. Formerly used CC is defined as participants who answered "Yes" to the question: "Have you ever used any of the following tobacco or nicotine product fairly regularly" for cigarettes and answered "Not at all" to the question "In the past 30 days, how often did you use the following tobacco or nicotine products" for CC. FDA generated these values.
c. Never used CC defined as participants who answered "No" and "Not at all" to the questions: "Have you ever used any of the following tobacco or nicotine product fairly regularly?" for cigarettes and "In the past 30 days, how often did you use the following tobacco or nicotine products?" CC. FDA generated these values.
d. Currently trying to quit smoking cigarettes was asked only among those who did not report making a quit attempt sometime in the past 29 days.
e. Intention to quit smoking CC was asked only among those who did not report currently trying to quit CC. FDA generated these values. FDA defined high quit intention as Motivation to Stop Smoking scores from 4-7, with (4) "I really want to stop smoking but don't know when I will" and (7) "I really want to stop smoking and intend to in the next month." We defined low quit intention as Motivation to Stop Smoking scores from 1-3 with (1) "I don't want to stop smoking" and (3) "I want to stop smoking but haven't thought about when." We classified those who responded "don't know" as having unknown intention.

Tobacco Product Use Patterns

Table 2 presents cross-sectional patterns of tobacco use data at Waves 1 and 4 using values provided by the applicant and values derived by FDA.

As described above, due to study eligibility criteria, all participants currently used General Snus at baseline. The majority of participants at baseline used General Snus every day (82.1%). The applicant did not provide the proportion of people who used General Snus at baseline who formerly or never smoked CC. FDA generated formerly smoked CC and never smoked CC values (see Table 1 notes).

Table 2. Patterns of Tobacco Use Among People who Use General Snus, Waves 1 and 4 (cross-sectional)

	W1 (Baseline) ***n*=1,655**		**W4** ***n*=451**	
	n	**% (95% CI)**	***n***	**% (95% CI)**
Any General Snus Use				
Every day	1,358	82.1 (80.1, 83.9)	273	60.5 (55.9, 65.1)
Some days	297	17.9 (16.1, 19.9)	121	26.8 (22.8, 31.2)
Exclusive General Snus Use	428	25.9 (23.8, 28.0)	100	22.2 (18.4, 26.3)

Dual use with CC overall[a]				
Every day	120	7.3 (6.0, 8.6)	16	3.5 (2.0, 5.7)
Some days	179	10.8 (9.4, 12.4)	37	8.2 (5.8, 11.1)
Dual use with CC only	70	4.2 (3.3, 5.3)	11	2.4 (1.2, 4.3)
Polyuse with CC and any other TNP	229	13.8 (12.2, 15.6)	42	9.3 (6.8, 12.4)
Dual use with any non-cigarette tobacco product	928	56.1 (53.6, 58.5)	241	53.4 (48.7, 58.1)
Dual use with nicotine pouches overall[b]				
Every day	97	5.9 (4.8, 7.1)	59	13.1 (10.1, 16.5)
Some days	451	27.3 (25.1, 29.5)	107	23.7 (19.9, 27.9)
Dual use with moist snuff[c] overall				
Every day	185	11.2 (9.7, 12.8)	53	11.8 (8.9, 15.1)
Some days	364	22.0 (20.0, 24.1)	75	16.6 (13.3, 20.4)

CC = combusted cigarettes.

a. The applicant defined people who "dual use" as participants who reported General Snus use and CC, regardless of other TNPs; therefore, this value is for dual use of CC and snus regardless of other tobacco product use.
b. The applicant defined people who "dual use" as participants who reported General Snus use and nicotine pouches, regardless of other TNPs; therefore, this value is for dual use of nicotine pouches and snus regardless of other tobacco product use.
c. The applicant defined people who "dual use" as participants who reported General Snus use and moist snuff, regardless of other TNPs; therefore, this value is for dual use of moist snuff and snus regardless of other tobacco product use.

Dual/Poly Use of General Snus*, CC, and Other Tobacco Products*

At baseline, 25.9% of participants reported exclusive use of General Snus. The applicant defined dual use as participants who reported using General Snus and CC *regardless* of other tobacco product use. FDA examined these data to further characterize dual/poly use in the sample. At baseline, 18.1% of participants reported use of General Snus and CC, with 4.2% reporting use of General Snus and CC only and 13.8% reporting use of General Snus, CC, and any other tobacco product (see Table 2). More than half of the baseline sample reported using General Snus with another non-cigarette tobacco product (56.1%). Approximately 33.2% of the baseline respondents reported use of nicotine pouches and 33.2% reported use of moist snuff (groups are not mutually exclusive).

Among Wave 4 participants, approximately 3.5% (n=16) reported smoking CC every day and 8.2% (n=37) reported smoking CC on some days in the past 30 days. Between baseline and Wave 4, the applicant reported no significant change in the number of days smoked per month or the number of CC smoked per day (p=0.22) among people who smoked CC at baseline who returned for Wave 4. FDA notes that the applicant did not account for missing data when assessing percent change in frequency of smoking over time. The applicant reports that the prevalence of past 30-day CC smoking at Wave 4 did not significantly differ from baseline prevalence (p=0.62). The applicant also reports a significantly increased proportion of people who used nicotine pouches between baseline and Wave 4 (p<0.0001); however, the applicant observed no difference in moist snuff use (p=0.79).

Complete Substitution and CC Cessation

Tam et al. (2015) found that approximately 5% of people who dual use CC and smokeless tobacco report completely switching to a smokeless tobacco product over time. The applicant defined complete substitution as people who used General Snus and CC at baseline but quit CC and only used General Snus at Waves 2, 3, or 4. Participants who completely substituted General Snus for CC may also use other tobacco products. CC cessation includes those who completely substituted General Snus for CC plus those who quit both products.

The applicant provided estimates of complete substitution using the total participants who remained in the study for each follow-up wave (including people who did not smoke CC at baseline) as the denominator. Using this approach, among all participants who completed Waves 2 (n=695), 3 (n=586), and 4 (n=451), 4.2%, 4.9%, and 5.5% of people who used General Snus reported completely substituting General Snus in place of CC, respectively. Similarly, among participants who completed all waves of the General Snus Patterns of Use Study (n=281), 4.6% reported completely substituting General Snus for CC at Wave 4.

FDA does not agree with the applicant's approach of including people who did not smoke CC at baseline in the denominator, so we independently analyzed the applicant's data to calculate complete substitution and CC cessation using people who report CC use at baseline (n=299) as the denominator (note: 299 includes 49 individuals who reported making a quit attempt sometime in the past 29 days at baseline, as they have not demonstrated sustained cessation behavior). As displayed in Table 3, the proportion of participants who reported completely substituting CC with General Snus was 9.7% in Wave 2, 9.7% in Wave 3, and 8.3% in Wave 4. Notably, 9% (n=27) reported CC cessation at Wave 4. In addition, among participants who quit CC, five used General Snus exclusively, 20 used General Snus plus another non-cigarette tobacco product, and two quit both General Snus and CC. This reflects a conservative estimate of complete switching and CC cessation because it assumes that all the people who use CC at baseline who were lost to follow-up remained people who use CC. An alternative approach would be to assume that the people who use CC were missing at random and calculate these estimates among people who use CC who returned for waves 2, 3, or 4. However, as described below, participants were not missing at random. Instead, those lost to follow-up were more likely to have a low intention to quit CC (see "FDA Attrition Analysis" section for more detail).

Table 3. Waves 2-4 Complete Substitution and CC Cessation Among People Who Dual-Used General Snus and CC at Baseline (n=299)

	Participants who Completed Wave 2		**Participants who Completed Wave 3**		**Participants who Completed Wave 4**	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Complete Substitution[a] of General Snus for CC	29	9.7 (6.6, 13.6)	29	9.7 (6.6, 13.6)	25	8.4 (5.5, 12.1)

CC Cessation[b]	32	10.7 (7.4, 14.8)	31	10.4 (7.2, 14.4)	27	9.0 (6.0, 12.9)

CC = combusted cigarettes.

a. The applicant defined complete substitution as participants who used General Snus and CC at baseline but quit CC smoking and only used General Snus at Waves 2, 3, or 4. Participants who completely substituted General Snus for CC may also use other tobacco products.
b. The applicant defined CC cessation as participants who completely substituted General Snus for CC plus those who quit both products.

FDA's Attrition Analysis[5]

The General Snus Patterns of Use Study experienced the highest dropout percentage between Wave 1 and Wave 2, resulting in a reduced sample size of 695 (42%) participants in Wave 2. As noted previously, by Wave 4, only 451 (27%) of the original study population (n=1,655) remained in the cohort. FDA found that attrition at Wave 2 was higher among participants who were younger, female, possessed lower levels of education, and had a lower household income (all $p < 0.05$). Similarly, at Wave 4, FDA found that attrition was higher among participants who were younger and had a lower household income (all $p<0.05$). Overall, participants who were older, male, possessed higher levels of education, and had a higher household income were more likely to be retained in the study.

Regarding tobacco use behaviors, FDA found that attrition at Wave 2 was higher among participants who used General Snus non-daily; had used less than 200 General Snus pouches in their lifetime; and smoked CC (either daily or some-day), regardless of whether they used other tobacco/nicotine products. Likewise, FDA found that retention at Wave 2 was higher among participants who used General Snus daily; had used 200 or more General Snus pouches in their lifetime; and did not smoke CC regardless of whether they used other tobacco/nicotine products. Quit intentions understandably appear to have played a role in study attrition. People who smoke CC who reported greater intention to quit smoking were more likely to return at Wave 2 compared to participants who did not return (all $p < 0.05$). At Wave 4, attrition was higher among participants who used General Snus non-daily and had used less than 200 General Snus pouches in their lifetime (all $p < 0.05$). Among those who smoked CC, there were differences in readiness to quit between baseline and those who returned at Wave 4. FDA notes that a greater proportion of those who reported trying to quit CC returned for Wave 4 (39.7% at Wave 4 versus 36.8% at baseline), and among those not currently trying to quit, those who reported high intention to quit CC at baseline were more likely to return two years later (9.5% at Wave 4 versus 8.4% at baseline). These findings suggest that observed tobacco use transitions may not accurately represent the actual likelihood of transition when the data appears to not be missing at random (i.e., associated with tobacco use).

[5] All p-values mentioned in the "FDA's Attrition Analysis" section were not adjusted for multiple tests. Caution should be used when interpreting the Type I error rate associated with these tests.

C. Youth

Literature citing the National Youth Tobacco Survey (NYTS) data show generally low use of snus among U.S. youth. The applicant cites results from the 2022 NYTS finding that 1% of students reported ever use of snus and 0.5% indicated use of snus at least once in the past 30 days. An additional study provided by the applicant examining NYTS data from 2011–2020 found that the prevalence of ever snus use among youth declined from 5.2% in 2011 to 2.4% in 2020, with an average annual percent reduction of 4.8% (Dai & Leventhal, 2023). Results from an internal analysis of 2023 NYTS data indicate that 0.8% of middle and high school students reported current snus use. Furthermore, population estimates from an internal FDA analysis of PATH Study Wave 7 (fielded January 2022 – April 2023) found that among youth (unweighted n=10,632), 0.08% reported using snus in the past 30 days. The percentage using General Snus specifically would be even lower.

D. Tobacco Related Health Disparities

Tobacco-related health disparities affect those who have systematically experienced greater obstacles to good health based on group membership due to the inequitable distribution of social, political, economic, and environmental resources (U.S. Department of Health and Human Services, 1998; U.S. National Cancer Institute, 2017; U.S. Department of Health and Human Services, 2021). People who experience tobacco-related health disparities tend to be racial/ethnic minorities, sexual and gender minorities, have lower levels of educational attainment and income, or suffer from severe mental disorders or substance use problems (U.S. National Cancer Institute, 2017). Additionally, current tobacco use is more common among individuals who have less than a Bachelor's degree and a low income level, as well as those who identify as lesbian, gay, or bisexual; current use of combustible tobacco products is higher among Black or African-American non-Hispanic adults and other race non-Hispanic adults than among White non-Hispanic adults (Cornelius et al., 2023). In contrast, participants in the General Snus Patterns of Use Study were predominantly White, in their late 30s, male, had some college or an Associate or Bachelor's degree, had a household income of $50,000-$99,999 per year, and resided in the South and Midwest regions (see Table 1).

E. Summary and Conclusions

NYTS and PATH data indicate generally low prevalence of snus use among U.S. youth and adults, with General Snus representing only a fraction of these small estimates. Sales data from the applicant and Nielsen data indicate declining sales of General Snus. The applicant conducted its General Snus Patterns of Use Study to provide some insight on the characteristics of people who use General Snus. Due to the small number of people who use General Snus in the U.S., study participants were recruited through product packaging at the point of purchase. As a result, based on the applicant's study design, all participants used General Snus at baseline. In the General Snus Patterns of Use Study, the majority of baseline participants who used General Snus reported co-use: 18% reported also using CC (4.2% use cigarettes only and 13.8% used CC and other tobacco products), and 56.2% reported also using a non-cigarette tobacco product. Among study participants who were dual users of General Snus and CC at baseline (n=299), 9.0% reported quitting CC by Wave 4 and 8.4% reported completely substituting CC with General Snus.

FDA's attrition analysis results show differential attrition (i.e., participants who used CC every day and have a lower readiness to quit smoking were more likely to leave the study, and participants who used

more General Snus products in their lifetime and had a higher readiness to quit were more likely to remain in the study). However, the applicant's study is descriptive in nature and does not test hypotheses by estimating an association between General Snus use and smoking cessation or complete substitution. FDA notes that 7.5% of all people who smoke CC successfully quit for 6 months or more in the past year in the U.S. (Creamer et al., 2019), and therefore results for smoking cessation within the study fall within an anticipated range.

III. CONSUMER UNDERSTANDING AND PERCEPTIONS

This section describes consumer perceptions of snus and assesses the applicant's General Snus Patterns of Use Study conducted to evaluate risk perceptions of General Snus products and understanding of the modified risk claim.

A. U.S. Consumers' Perceptions of Snus Risk

According to literature that the applicant and FDA identified, between 45.8% and 81.7% of U.S. adults incorrectly believe that using snus is equally or more harmful than smoking CC (Kaufman et al., 2014; Regan, Dube, & Arrazola, 2012; Denlinger-Apte, et al., 2021; Wackowski, Ray, & Stapleton, 2019; Wackowski & Delnevo, 2016; Popova & Ling, 2013). This misperception as documented in the literature has not changed since the original MRGO. Findings from Norway, where use of Swedish snus is widespread, indicate a similar misperception that the risk of daily snus use is relatively equivalent to the risk from daily cigarette smoking (Lund & Scheffels, 2014; Lund & Vedoy, 2019; Nilsen et al., 2020), and these perceptions have not changed over the past two decades (Lund & Vedoy, 2019).

Risk perceptions of snus vary depending on the disease specified. However, even when assessing risk perceptions for specific diseases, most participants have incorrect beliefs. For example, people believe that smokeless tobacco products, including snus, are equally or more likely to cause oral cancer compared to CC (Choi et al., 2012; Lund & Scheffels, 2014; Pepper et al., 2015; Pillitteri et al., 2020). Most adults also incorrectly believe that snus and CC are equally likely to cause heart disease (Pepper et al, 2015; Lund & Scheffels, 2014).

Risk perceptions of snus also vary depending on tobacco use status. People who use snus have more accurate relative risk perceptions of snus compared to CC (i.e., they are more likely to perceive snus as less harmful than CC) than the general public (Lund & Vedoy, 2019; Kaufman et al., 2014; Wackowski & Delnevo, 2016). People who smoke CC or who use tobacco also tend to have more accurate relative risk perceptions of snus compared to CC (Kaufman 2014), though one study did not find this difference (Wackowski & Delnevo, 2016), and generally most adult tobacco users perceive snus as equally or more harmful than CC (Kaufman et al., 2014).

Some of the differences across studies in snus risk perceptions may reflect differences in measurement approaches. When direct relative risk measures are used (e.g., "Compared to cigarettes, using snus is [less/equally/more harmful]"), a smaller proportion of participants rate snus as less harmful than CC compared to when indirect relative risk measures are used (i.e., comparisons of responses to two separate questions that assess perceived absolute risk of snus and CC) (Popova & Ling, 2013). Whether the measure asks about snus specifically or smokeless tobacco generally also likely affects risk perceptions. In a nationally representative sample of young adults, a significantly higher proportion of

participants believed snus was less risky than CC compared to the relative risk for smokeless tobacco (Wackowski & Delnevo, 2016). However, a greater proportion of participants were unsure about snus compared to smokeless tobacco (Wackowski & Delnevo, 2016).

B. General Snus Patterns of Use Study

FDA's PMSS requirements state that the applicant must assess consumers' understanding of the modified risk claim and perceptions of the products. In particular, the applicant's PMSS must assess the extent to which people who use General Snus understand that, to reduce their risk of disease relative to smoking as described in the modified risk information, they must use General Snus exclusively. The applicant conducted the General Snus Patterns of Use Study among U.S. adults ages 21 and older who currently use General Snus. The key objectives related to consumer understanding were to assess the following in people who use General Snus:

1. Absolute risk perceptions of developing mouth cancer, heart disease, and lung cancer from using only General Snus daily, smoking only CC daily, dual-using General Snus and CC daily, and never having used any TNPs.
2. Understanding of the risk reduction as stated in the modified risk claim.

Measures

Participants were not shown the modified risk claim at any time during the study. They answered the same questions at each wave. All items specifically assessed General Snus as opposed to generally assessing all smokeless tobacco products. One relative risk perception question was asked; all other risk perception questions assessed absolute perceived risk. FDA used participants' responses to the absolute risk questions to evaluate relative risk using an indirect approach.

<u>Perceptions of Absolute Health Risks from Using General Snus</u>

The General Snus Patterns of Use Study assessed participants' perceived absolute risk of a person developing mouth cancer, heart disease, and lung cancer if they engaged in four tobacco use patterns: (1) exclusive daily use of General Snus, (2) exclusive daily use of CC, (3) daily dual use of General Snus and CC, and (4) never having used any tobacco or nicotine product. The study assessed perceptions of the likelihood that a person "would suffer from the following health conditions" in a series of grids such that participants focused on one tobacco use pattern at a time and viewed the risk perception items for heart disease, lung cancer, and mouth cancer together (see Figure 3). The order in which the health conditions were listed was randomized. Each item used a five-point Likert-type scale ranging from 1 ("very low chance") to 5 ("very high chance"). Participants could also select "don't know."

Figure 3. Exclusive daily use of General Snus absolute risk items

B3. In your opinion, what is the chance that a person who **only uses *General* Snus® every day** would suffer from the following health conditions during his/her lifetime?

[SELECT ONE FOR EACH ROW; RANDOMIZE ROWS AS IN B1]

		Very Low Chance	Low Chance	Moderate Chance	High Chance	Very High Chance	Don't Know
1	Heart disease	1	2	3	4	5	99
2	Lung cancer	1	2	3	4	5	99
3	Mouth cancer	1	2	3	4	5	99

Perceptions of Relative Health Risks from Using General Snus

The General Snus Patterns of Use Study directly assessed participants' perceived relative risk of General Snus compared to CC with one item. Because the item used verbatim claim language, it reflects recall/comprehension of claim language in addition to perceived relative risk. Participants completed the following sentence (which is the applicant's modified risk claim language verbatim): "Using General Snus instead of cigarettes…," with one of six responses: (1) puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis; (2) does not affect your risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis; (3) puts you at higher risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis; (4) none of the above; (5) don't know; or (6) decline to answer. The study did not directly assess perceived health risks of General Snus relative to nonuse, cessation, and nicotine replacement therapy.

Understanding How to Use General Snus to Reduce Risk

The General Snus Patterns of Use Study assessed participants' understanding that the modified risk claim does not apply to partial switching with one item. The item asked, "If you are going to use General Snus instead of cigarettes to lower your risk of diseases, how many cigarettes, if any, can you smoke per day?" Response options were: zero (0) cigarettes; up to 5 cigarettes; up to 20 cigarettes; as many as you want to smoke; don't know; decline to answer. This item was asked only of the subset of participants who correctly responded that using General Snus instead of CC "puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

The study did not directly assess perceived health risks of exclusive General Snus use relative to dual use of CC and General Snus. Therefore, FDA evaluated perceived risk of exclusive General Snus relative to dual use indirectly by comparing the absolute risk items for exclusively using General Snus every day and daily dual use of General Snus and CC to inform our assessment of participant understanding of how to use the MRTP to reduce risk. Greater perceived risk for dual use relative to exclusive use of General Snus supports that participants understand that they must use General Snus exclusively (i.e., without CC) to reduce their risk.

Findings

Understanding that Using General Snus Presents Less Risk of Various Diseases than Smoking CC

At baseline, participants (N = 1,655) were more likely to be in their late 30s, male, use more than 200 General Snus pouches in their lifetime, smoke more than 100 CC in their lifetime, and have a low intention to quit smoking. Most baseline participants (69.8%) responded correctly that using General Snus instead of CC "puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." The percentage of participants who understood that using General Snus instead of CC "puts you at lower risk" remained high over all waves, ranging from 72.5% to 77.8% across waves 2-4.

There was a statistically significant increase in understanding from baseline to Wave 3 ($p < 0.05$) among the subset of participants who completed both those waves. However, attrition was high in the General Snus Patterns of Use Study and participants who completed Wave 2, Wave 3, and/or Wave 4 were more likely to have responded correctly to this relative risk item at baseline compared to those who dropped out at each wave. Therefore, the longitudinal findings should be interpreted with caution.

These findings, which are based on a sample of people who use General Snus, are consistent with the literature showing that people who use snus have more accurate relative risk perceptions of snus (i.e., they perceive snus as less harmful than CC) compared to the general public, who tend to overestimate the relative and absolute risk of snus (Lund & Vedoy, 2019; Kaufman, et al., 2014; Wackowski & Delnevo, 2016). The findings are also consistent with Tan et al.'s (2024) study that examined participants' harm perceptions after they viewed a de-identified (i.e., product brand and product type were not disclosed) version of General Snus' modified risk claim. This study found that across groups of people who use CC and do not use CC, 64.6-69.2% of participants perceived that the modified risk product would be much less or slightly less harmful to their health than CC. People who use CC were significantly more likely to perceive modified risk products as much less harmful than CC compared to people who never or formerly used CC.

Understanding that Using General Snus Still Presents Risks

Participants generally viewed using General Snus every day as having some, but generally low, health risk, particularly for mouth cancer and heart disease. At baseline, 34.9% of participants perceived a low risk and 34.6% perceived a moderate risk that a person who only uses General Snus every day would suffer from mouth cancer; 39.1% perceived a low risk and 34.1% perceived a moderate risk that a person who only uses General Snus every day would suffer from heart disease. In comparison, 13.1% and 18.1% perceived a very low risk of suffering mouth cancer and heart disease, respectively. These perceptions did not change over the four study waves.

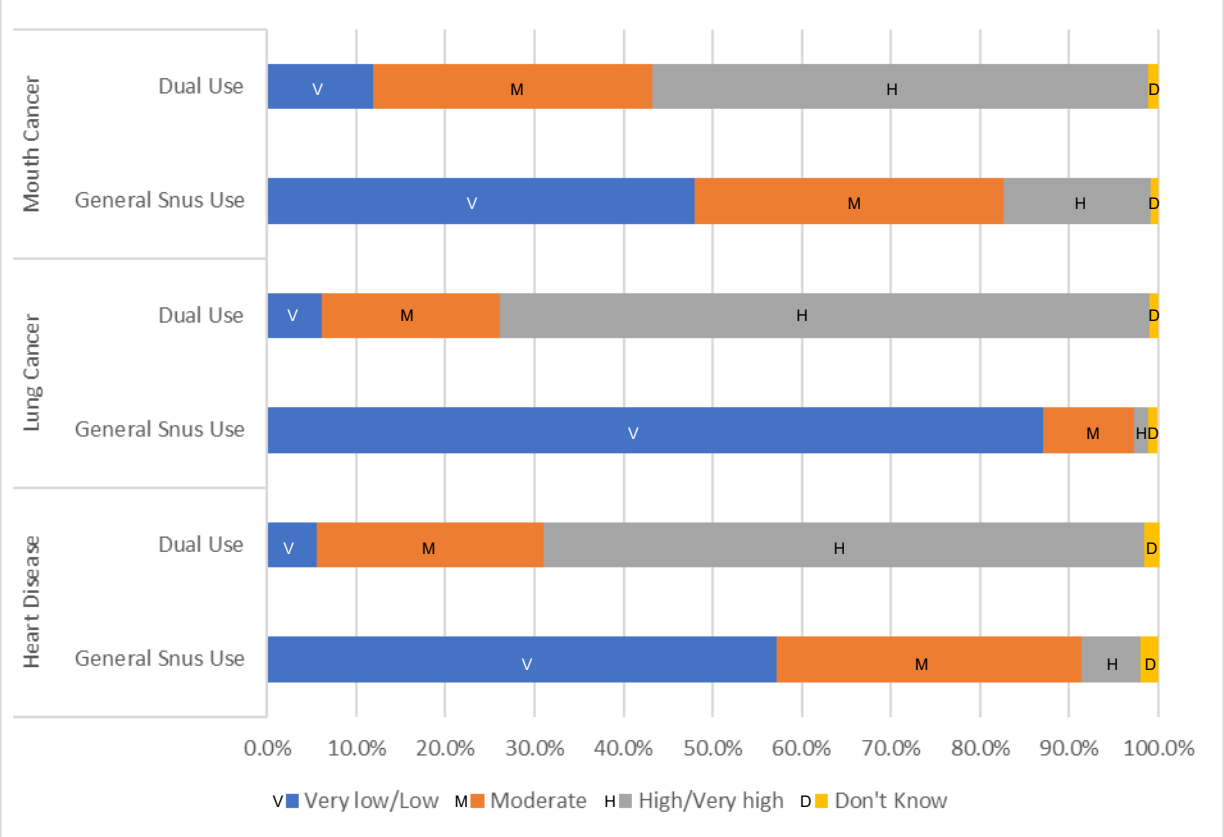
Understanding How to Use General Snus to Reduce Risk

Among the 69.8% of participants (n = 1155) at baseline who were asked how many CC they could smoke per day if they used General Snus instead of CC, 80.3% correctly responded "zero cigarettes," indicating they understood that a person must exclusively use General Snus instead of CC in order to reduce risk.

The percentage of participants who responded correctly remained relatively stable across waves. There was a statistically significant increase in correct understanding from baseline to Wave 2. Among participants who completed both baseline and Wave 2 and selected "lower risks" at both responses (n = 418), 73.0% believed that the modified risk claim only applies to complete switching at both baseline and Wave 2. From baseline to Wave 2, 7.2% changed from the correct response of "zero cigarettes" to a different response at Wave 2; 13.4% changed from other responses at baseline to the correct response of "zero cigarettes" at Wave 2. Together, these results are consistent with findings submitted in the original MRTPA and suggest that people understand that they must exclusively use General Snus instead of CC to reduce their disease risk.

To provide further insight into whether General Snus users understand how to use General Snus to reduce their risk, FDA compared perceived absolute risk of suffering mouth cancer, lung cancer, and heart disease from using General Snus to perceived absolute risk of suffering the same diseases from dual use of CC and General Snus. At baseline and at each subsequent study wave, participants perceived dual use of CC and General Snus as more harmful than exclusive use of General Snus across all three health outcomes (See Figure 4).

Figure 4. Perceived absolute risk of exclusive daily General Snus use and perceived absolute risk of



C. Summary and Conclusions

In the General Snus Patterns of Use Study, the applicant demonstrates that most study participants, all of whom were General Snus users at baseline, understood that using General Snus instead of smoking CC "puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." However, approximately 20% of participants at baseline did not understand that using General Snus presents less health risk than smoking CC. These proportions did not change markedly over the course of the study, although the high rate of attrition limits the conclusions that can be drawn related to trends over time. Most study participants also understood that using General Snus still presents health risks and they perceived that using General Snus every day carries some risk of developing mouth cancer and heart disease. Lastly, most study participants understood that they could not use General Snus with CC and experience the potential health benefits described in the modified risk claim. As with understanding that using General Snus instead of CC "puts you at lower risk" of various diseases, approximately 20% of participants did not understand that they cannot smoke CC while using General Snus to experience health benefits. These proportions did not change over the course of the study. They align with similar research finding that most people who use CC understood the need to stop smoking completely and use a snus product instead to receive health benefits (Pillitteri, 2020). Further supporting consumer understanding of how to use the MRTP to reduce their risk, study participants accurately perceived dual use of General Snus with CC as more likely to cause mouth cancer, lung cancer, and heart disease than use of General Snus alone. This suggests that participants understand that the reduced risk described in the claim does not apply to dual use of CC and General Snus.

Overall, the new evidence provided by the applicant is consistent with evidence from the original MRTPA and shows that most adult consumers' risk perceptions of General Snus align with current scientific evidence regarding the health risks of using General Snus and most adult consumers understand how to use General Snus to reduce their health risk.

Appendix A: Statutory Requirements for Modified Risk Tobacco Products (MRTPs) and Overview of FDA Review Process

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines "modified risk tobacco product" (MRTP) as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products [Section 911(b)(1)]. With respect to a tobacco product, the term 'sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products' means a tobacco product:

1) the label, labeling, or advertising of which represents, either implicitly or explicitly, that:
    a) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
    b) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
    c) the tobacco product or its smoke does not contain or is free of a substance;
2) the label, labeling, or advertising of which uses the descriptors "light", "mild", "low", or similar descriptors; or
3) the tobacco product manufacturer of which has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [Section 911(b)(2)]

Before an MRTP can be introduced into interstate commerce, an order from FDA under Section 911(g) must be issued and in effect with respect to the tobacco product, and if the proposed modified risk tobacco product is also a new tobacco product, it must comply with the premarket review requirements under Section 910(a)(2).

To request a Section 911(g) order from FDA, a person must file a modified risk tobacco product application (MRTPA) under Section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled "Modified Risk Tobacco Product Applications," which discusses the submission of applications for an MRTP under Section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (https://www.fda.gov/media/83300/download).

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an MRGO from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two conditions for FDA to issue an order.

Risk Modification Order: FDA shall issue an order under Section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

FDA may require, with respect to tobacco products for which risk modification orders are issued, that the product comply with requirements relating to advertising and promotion of the tobacco product (Section 911(h)(5) of the FD&C Act).

Exposure Modification Order: Alternatively, for products that cannot receive a risk modification order from FDA under Section 911(g)(1) of the FD&C Act, FDA may issue an order under Section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under Section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been

demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially-marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

Per Section 911(g)(4), when evaluating the benefit to health of individuals and of the population as a whole under Sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the tobacco product that is subject of the application;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to the tobacco product that is subject of the application;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is subject of the application;
- The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation and approved under chapter V to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and if accepted whether to file it. In general, after filing an application, FDA begins substantive scientific review. This scientific review process involves soliciting and considering public comments on the application as well as recommendations from TPSAC. FDA intends to review and act on a complete MRTPA within 360 days of its filing. It's important to note that an order authorizing an MRTP pertains to a specific product, not an entire category of tobacco products (e.g., all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is valid for a predetermined period specified in the order. To continue marketing an MRTP beyond this period, the applicant must request renewal of the order and FDA would need to determine that the findings continue to be satisfied. Additionally, if at any time FDA determines that it can no longer make the determinations required for an MRTP order, FDA is required to withdraw the order. Prior to withdrawing an MRTP order, the FDA will provide an opportunity for an informal hearing as mandated by law.

Appendix B: Summary of Individual Health Effects studies published since the MRGO (2019–2023)

Table B-1. Selected Study Characteristics and Results of Snus and Cardiovascular Disease from Individual Studies

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
				Exposure	**Outcome**	**HR[7] (95% CI[8])**	
Main author • Titova Publication year • 2021 Country • Sweden Study design • Prospective cohort Study period • July 1, 2009-December 31, 2017	Exposure assessed through self-administered questionnaire at baseline (2008-2009) Snus use classified: • regular (more than 5 portions of snus/week) • current • former[6]	41,162 eligible participants • n=18,027 women • n=23,135 men • mean baseline age of 70 (56–94) years. • Nonusers n=38,862 (94%) • Users n=2,300 (5.6%)	Sample from population-based survey Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER) Two cohorts form basis of SIMPLER (Swedish Mammography Cohort/Cohort of Swedish Men)	Among people who never smoked CC: Current snus use (vs. never use)	Myocardial infarction (exposed cases, n = 21) (ICD[9]-10 I21)	1.36 (0.87-2.11)	Age, Sex, Education, alcohol intake walking/bicycling, exercise
				Among people who never smoked CC: Current snus use (vs. never use)	Heart failure (exposed cases, n =14) (ICD-10 I50 and I11.0)	0.92 (0.54-1.57)	
				Among people who never smoked CC: Current snus use (vs. never use)	Atrial fibrillation (exposed cases, n=43) (ICD-10 I48)	1.29 (0.95-1.75)	
				Among people who never smoked CC: Current snus use (vs. never use)	Total stroke (exposed cases, n = 24) (ICD-10 I62)	**1.53 (1.02-2.32)**	
				Among people who never smoked CC: Current snus use (vs. never use)	Ischemic stroke (exposed cases, n = 21) (ICD-10 I63)	**1.65 (1.06-2.57)**	

[6] People who formerly use snus and people who do not use snus were combined into one group for analysis.
[7] Hazard ratio
[8] Confidence interval
[9] International Classification of Diseases (ICD)

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
				Among people who never smoked CC: Current snus use (vs. never use)	CVD mortality (exposed cases, n=15) (ICD-100 and I99)	1.58 (0.94-2.67)	
Main author • Yuan* Publication year • 2022 Country • Sweden Study design • Prospective cohort Study period • 2007-2019	Exposure assessed through self-administered questionnaire at baseline in 2009. Regular snus use = more than 5 servings per week. Smoked regularly = more than 5 CC per week. Snus • Never • Past • Current CC • Current • Never • Past quitting ≥ 10 years • Past, quitting < 10 years	Sample of 24,085 participants • Men • aged 45 to 79 years • Never snus (n=18,789) • Past snus (n=2,946) • Current snus (n=2,350) Men who have never smoked CC: • 44.3% of the total population (n=10,702) • Men who smoked CC in the past: 42.3% of the total population (n=10,195) • Men who currently smoke CC 8.5% of the total population (n=2,047)	Sample from population-based survey, Cohort of Swedish Men (COSM) study • n=100,303	**Exposure**	**Outcome**	**HR (95% CI)**	Age, BMI[10], education levels, history of hypertension, hypercholesterolemia, diabetes mellitus, tobacco smoking in the analysis of snus dipping, snus dipping in the analysis of tobacco smoking, physical activity, and diet score (continuous)
				Past snus use (vs. never snus use/never CC use)	Peripheral artery disease (exposed cases, n=66)	0.95 (0.73-1.24)	
				Current snus use (vs. never snus use/never CC use)	Peripheral artery disease (exposed cases, n=56)	0.88 (0.66-1.17)	
				Past, quitting ≥ 10 years smoke CC (vs. never snus use/never CC use)	Peripheral artery disease (exposed cases, n=236)	**1.38 (1.14-1.68)**	
				Past, quitting < 10 years smoke CC (vs. never snus use/never CC use)	Peripheral artery disease (exposed cases, n=48)	**2.61 (1.89-3.61)**	

*Literature identified and provided by applicant.
[10] Body mass index (BMI)

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
				Current CC use (vs. never snus use/never CC use)	Peripheral artery disease (exposed cases, n=124)	**4.01 (3.17-5.08)**	
Main author • Antoniewicz* Publication year • 2022 Country • Sweden Study design • Cross-sectional Study period • not provided	Exposure was assessed by self-administered wellness form and medical evaluation: • ECG • dynamic spirometry • blood pressure control • blood tests Endothelial vasodilatory function • venous occlusion plethysmography of brachial artery Arterial stiffness • pulse wave velocity	50 healthy males • n=24 men who use snus chronically • (≥15 years of snus use) • n=26 age-matched controls • (30-65) years. Exclusion • prior CC use > 1 year • hypertension • cardiovascular • metabolic disease • respiratory disease	Sample population includes healthy males. • mean age 44 (18-40 years) • no history of CC use • no history cardiovascular disease. (Prior to measurements, study participants had to abstain from all forms of nicotine, alcohol, and caffeine for 24 hours and from vigorous physical	**Exposure**	**Outcome**	**Mean ± Standard Deviation (p-value)**	Age-matched
				Chronic snus use vs no tobacco use	Arterial stiffness (**Pulse wave velocity [m/s]**)	**6.6±0.8 vs 7.1±0.9 (p = 0.026)**	
				Chronic snus use vs no tobacco use	Arterial stiffness (Augmentation index corrected for heart rate [%])	**0.1±13.2 vs7.3±7.8 (p = 0.023)**	
				Chronic snus use vs no tobacco use	Endothelial independent vasodilation, (reaction to acetylcholine)	**Not Significant**	

* Literature identified and provided by applicant.

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
	• pulse wave analysis	• BMI >30 • allergy or inflammation within 4 weeks prior to the study	activity for 48 hours.)	Chronic snus use vs no tobacco use	Endothelial independent vasodilation, (reaction to glyceryl trinitrate)	(p = 0.042)	
				Chronic snus use vs no tobacco use	Endothelial independent vasodilation, (reaction to bradykinin)	**Not Significant**	
Main author • Byhamre Publication year • 2023 Country • Sweden Study design • Cross-sectional Study period • 1986-2014	Exposure assessed through self-administered questionnaire 1986-2014. To validate the self-reported tobacco habits, plasma concentrations of cotinine (the predominant nicotine metabolite) were measured in a subsample of the	Tobacco users • n=5,930 • Men • (median age 50.0 years) • Never = no history of snus or CC use (n=2,000) • past = past history of snus or CC use (n=1,559) • current, snus = current snus (n=1,109)	The Northern Sweden MONICA study consists of seven population-based surveys (in 1986, 1990, 1994, 1999, 2004, 2009, and 2014. • n= 12,069 • Stratified for age (25 to 64 years in 1986 and 1990; 25 to 74 years in	**Exposure**	**Outcome**	**Mean difference (95% CI)**	Age, calendar year, education, BMI, alcohol consumption, and diagnosis of diabetes.
				Past use of snus or CC (n=1,559) vs Never use of snus and CC (n=2,000)	Non-HDL[11] cholesterol	0.07 (-0.01, 0.15)	
				Current, snus use (n=1,109) vs Never use of snus and CC (n=2,000)	Non-HDL cholesterol	0.08 (-0.01, 0.16)	
				Current cigarette use (n=850) vs Never use of snus and CC (n=2,000)	Non-HDL cholesterol	**0.12 (0.02, 0.21)**	

[11] High-density lipoprotein

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
	1990 survey (n = 321 subjects; 46.4% men)	• CC = current cigarette use (n=850) (including non-daily). • 13.7% were sampled in the 1980s, 43.6% in the 1990s, 30.1% in the 2000s, and 12.6% in the 2010s.	1994 to 2014) and sex. • Participation rate decreased over time, from 81% in 1986 to 63% in 2014.	Past use of snus or CC (n=1,559) vs Never use of snus and CC (n=2,000)	HDL cholesterol (mmol/L)	0.01 (-0.02, 0.03)	
				Current, snus use (n=1109) vs Never use of snus and CC (n=2,000)	HDL cholesterol (mmol/L)	**0.03 (0.00, 0.06)**	
				Current cigarette use (n=850) vs Never use of snus and CC (n=2,000)	HDL cholesterol (mmol/L)	-0.01 (-0.04, 0.02)	
				Current snus use (n=1,109) vs Current cigarette (n=850)	HDL cholesterol (mmol/L)	**0.04 (0.01, 0.08)**	
				Past use of snus or CC (n=1,559) vs Never use of snus and CC (n=2,000)	Triglycerides (mmol/L)	0.05 (-0.02, 0.11)	
				Current, snus use (n=1,109) vs Never use of snus and CC (n=2,000)	Triglycerides (mmol/L)	**0.08 (0.01, 0.16)**	
				Current cigarette use (n=850) vs Never use of snus and CC (n=2,000)	Triglycerides (mmol/L)	**0.26 (0.17, 0.34)**	
				Current snus use (n=1,109) vs Current cigarette (n=850)	Triglycerides (mmol/L)	**-0.17 (-0.26, -0.08)**	

CC = combusted cigarettes.

Table B-2. Selected Study Characteristics and Results of Snus and Various Health Outcomes from Pooled Studies and a Meta-analysis

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
Main author • Araghi* Publication year • 2021 Country • Sweden Study design • Pooled analysis Study period • 1978-2013	Exposure was assessed through self-administered questionnaires (7 studies) or interviews (2 structured phone interview and personal interviews by nurses) conducted at baseline within the included cohort studies.	418,369 male participants • 14,625 excluded • 9 cohort studies • Mean age 40 years (18-99) • 30% ever used Snus • All included current snus use • 7 included former snus use • Never-use n=485 • Ever-use n=143 • Former use n=51 • Current use n=92	Pooled individual data from the Swedish Collaboration on Health Effects of Snus. • 9 cohort studies • 5 were population based. • 2 were occupational cohorts • 1 participants in a charity-walk • 1 twin study	**Exposure**	**Outcome**	**HR / 95% CI**	Age, CC use (never, former, and current) and BMI
				Ever snus use vs Never snus use	Oral cancer (exposed cases, n=143)	0.90 (0.74, 1.09)	
				Former snus use vs Never snus use	Oral cancer (exposed cases, n=51)	1.20 (0.89, 1.61)	
				Current snus use vs Never snus use	Oral cancer (exposed cases, n=92)	0.79 (0.63, 1.00)	
Main author • Byhamre Publication year • 2020 Country • Sweden Study design • Pooled analysis Study period • 1978–2010	Exposure was assessed through self-administered questionnaires (7 studies) and a structured phone interview for 1 study.	169,103 male participants • All studies included current snus use. • 6 studies included former snus use. • Excluded ever	Pooled individual data from the Swedish Collaboration on Health Effects of Snus. • n=383,015 • Men • 8 population based cohorts	**Exposure**	**Outcome**	**aHR / 95% CI**	Age and BMI
				Among men who never smoked CC: Exclusive current snus use vs Never tobacco use	All-cause mortality (exposed cases, n=1,410)	**1.28 (1.20–1.35)**	

* Literature identified and provided by applicant.

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
		regular use of cigarettes n=202,171 • never-users of tobacco n=124,256 • Exclusive current snus users n=39,156 • Exclusive former snus users n=5,691		Among men who never smoked CC: Exclusive former snus use vs Never tobacco use	All-cause mortality (exposed cases, n=246)	**1.15 (1.02–1.31)**	
				Among men who never smoked CC: Exclusive current snus use vs Never tobacco use	Cardiovascular diseases mortality (exposed cases, n=443)	**1.27 (1.15–1.41)**	
				Among men who never smoked CC: Exclusive former snus use vs Never tobacco use	Cardiovascular diseases mortality (exposed cases, n=83)	1.13 (0.91–1.41)	
				Among men who never smoked CC: Exclusive current snus use vs Never tobacco use	Cancer mortality (exposed cases, n=332)	1.12 (1.00–1.26)	

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
				Among men who never smoked CC: Exclusive former snus use vs Never tobacco use	Cancer mortality (exposed cases, n=82)	**1.26 (1.01–1.57)**	
				Among men who never smoked CC: Exclusive current snus use vs Never tobacco use	Other causes, mortality (exposed cases, n=511)	**1.37 (1.24–1.52)**	
				Among men who never smoked CC: Exclusive former snus use vs Never tobacco use	Other causes, mortality (exposed cases, n=69)	1.14 (0.89–1.45)	
Main author • Lee[*12] Publication year • 2022	Exposure was assessed through self-reported data	Studies included in review • Lung cancer n=8	Identification of studies via databases and registries (Medline).	**Exposure**	**Outcome**	**RR / 95% CI**	Age, alcohol, aspirin use, BMI, education, employment, fat, fruit and vegetable intake,

[*] Literature identified and provided by applicant.
[12] Industry funded study.

Study Information	Exposure Assessment	Sample Size	Study Population	Results			Adjustment Factors
Country • North America, Europe, Japan Study design • Review with meta-analysis Study period • 1990-2020		• COPD n=3 • Cardiovascular disease n=16 Reports of included studies Lung cancer n=10 COPD n=4 Cardiovascular disease n=17	• Publications in English • years 1990 to 2020 • provide results relating use of current ST or snus) in people who do not smoke CC to the risk of lung cancer, COPD, IHD/AMI or stroke • based on epidemiological cohort or case-control studies • conducted in North America, Europe or Japan • involving at least 100 cases of the disease of interest.	Current snus use vs never use among people who never smoked CC (Latest)[13]	IHD/AMI (ischemic heart disease/acute myocardial infarction)	1.00 (0.91-1.11)	race and sex where available.
				Current snus use vs non-current use among people who never smoked CC (All)	IHD/AMI (ischemic heart disease/acute myocardial infarction)	1.04 (0.92-1.18)	
				Current snus use vs Never use among people who never smoked CC (Latest)	Stroke	1.05 (0.95-1.17)	
				Current snus use vs non-current use among people who never smoked CC (All)	Stroke	1.06 (0.98-1.14)	

[13] As reported in Lee et al 2022: where the referent is people who do not currently use snus, there are estimates for some studies from multiple publications of the same cohort. For these studies, the estimate "Latest" includes only the result from the latest publication of the same cohort, while the estimate "All" includes all the results. Where the referent is never use of snus, there is only one estimate from each cohort.

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