FDA Briefing Document

September 13-14, 2018
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Modified Risk Tobacco Product Applications (MRTPAs)
MR0000068-MR0000073
R.J. Reynolds Tobacco Company

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 R.J. Reynolds Tobacco Company's Modified Risk Tobacco Product Applications (MRTPAs) for six Camel Snus products to TPSAC in order to gain TPSAC's insights and recommendations. This briefing package may not include all issues relevant to FDA's decision on the applications 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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Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Matthew R. Holman, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for September 13-14, 2018 discussion of R.J. Reynolds Tobacco Company MRTPAs for its six Camel Snus products (FDA Submission Tracking Numbers MR0000068, MR0000069, MR0000070, MR0000071, MR0000072, & MR0000073)

Introduction

We would like to thank the TPSAC members in advance for their efforts to provide recommendations to FDA on the Modified Risk Tobacco Product Applications (MRTPAs) submitted by R.J. Reynolds Tobacco Company (RJRT).

On March 30, 2017, FDA received MRTPAs from RJRT, which state that RJRT is seeking orders under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for each of its six Camel Snus products: Camel Snus Frost, Camel Snus Frost Large, Camel Snus Winterchill, Camel Snus Robust, Camel Snus Mellow, and Camel Snus Mint. See Appendix A for additional information on the statutory requirements for Modified Risk Tobacco Products (MRTPs).

Figure 1. Camel Snus products (Source: Section 3.1.3 of the MRTPAs)

The applicant describes its six Camel Snus products as portioned, pouched products that use a blend of heat-treated/flavored tobaccos, are pouched in a porous fleece material, and are packaged in metal tins (Figure 1). Each metal tin contains 15 pouches (Section 3.1.2 of the MRTPAs). The applicant states that the products are intended to be placed under the lip and that there is typically no expectoration (spitting). The consumer disposes of the pouch when he/she is finished using the product (Section 3.4 of the MRTPAs).

FDA evaluates all information and statements on the proposed label, labeling, and advertising submitted by the applicant as part of the agency's scientific review. This review includes an evaluation of the proposed label, labeling, and advertising for modified risk claims even if those claims were not specifically identified by the applicant in its request for authorization.

RJRT submitted three different advertising executions for each of its six Camel Snus products.

As part of its evaluation of the MRTPAs, FDA is reviewing the following modified risk information identified across these three advertising executions. Modified risk information is bolded:

1. **Smokers who switch completely from cigarettes to Camel Snus can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.**[1]
2. **Smokers who SWITCH COMPLETELY from cigarettes to Camel Snus can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.**[1]
3. **Smokers who SWITCH COMPLETELY from cigarettes to Camel Snus can greatly reduce their risk of lung cancer and respiratory disease.**[1]
4. **Smokers who use Camel SNUS instead of cigarettes can significantly reduce their health risks from smoking.**
5. **Scientific studies have shown that Camel SNUS contains fewer carcinogens than cigarette smoke.**
6. **Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarette smoke.**
7. **No smoke means...**
   - No hassle
   - No lingering smoke smell
   - More freedom
   - **Fewer carcinogens**
   - **Less risk for you** and those around you
8. **Switching to SNUS means ...**
   - **Less of the harmful chemicals found in cigarette smoke**
   - **Less risk for you** and those around you
   - No lingering smoke smell
   - Hassle-free tobacco
9. **Swap the smoke for** more freedom and **less risk.**
10. **No smoke. Less risk. Choose SNUS.**
11. **NO SMOKE = LESS RISK**

The focus of the TPSAC meeting, as described below, will be the evidence related to the modified risk information, consumer understanding and perceptions of the modified risk information, and use of the proposed modified risk tobacco products.

[1] These statements have been identified as "key claims" by the applicant.

Draft Topics for TPSAC Discussion

FDA is reviewing the scientific information submitted in the MRTPAs to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met. The evidence submitted by the applicant includes data from chemical analyses of the products; nonclinical studies of the products' toxicological properties; clinical studies of biomarkers of exposure and potential harm; actual use studies; studies of understanding, perception, and behavioral intentions; epidemiological evidence; and other scientific information. FDA is also reviewing public comments submitted in accordance with Section 911(e).

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

Evidence related to modified risk information

The proposed advertising submitted in the MRTPAs contains multiple modified risk statements. The modified risk information is primarily centered around reduction in harmful constituents and reduced disease risk. FDA will present the product chemistry, nonclinical and clinical studies, and epidemiological evidence used to assess the scientific accuracy of the statements. TPSAC will be asked to discuss the evidence and the substantiation—i.e., the scientific accuracy—of these statements.

Consumer understanding and perceptions of the label, labeling, and advertising

The applicant submitted three versions of three-page print advertisements for the six Camel Snus products, which include modified risk information. The submitted product labels did not include modified risk information. Online studies were conducted to test consumer understanding and perceptions of the modified risk information in the ads. FDA will present the ads submitted along with results from the consumer studies and will ask TPSAC to discuss potential concerns about consumer perceptions and understanding based on presentation of the modified risk information in the proposed ads (e.g., variety of statements).

Likelihood of use of the proposed MRTPs

FDA will present data from several observational studies to describe characteristics of users who report Camel Snus as their usual brand, patterns of use, and transitions from cigarette smoking to snus use. In addition, FDA will present the likelihood of use studies conducted by the applicant to assess the likelihood that cigarette users will switch to the six Camel Snus products when presented with modified risk information. TPSAC will be asked to discuss the potential use behaviors with respect to the proposed modified risk tobacco products.

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

Preliminary FDA Review Findings

I. Evidence Related to Modified Risk Information

A. Product Chemistry

Product Ingredients

The six Camel Snus products that are subject to these MRTPAs (Camel Snus Frost [MR0000068], Camel Snus Frost Large [MR0000069], Camel Snus Mellow [MR0000070], Camel Snus Mint [MR0000071], Camel Snus Robust [MR0000072], and Camel Snus Winterchill [MR0000073]) are portioned snus smokeless tobacco products. All six Camel Snus products contain the same pouch length (37.5 mm), tobacco particle size, pH, moisture, and pouch quantity per package (15 pouches per tin). Three of the Camel Snus products (Camel Snus Frost, Camel Snus Mellow, and Camel Snus Mint) contain 600 mg pouches and the other three Camel Snus products (Camel Snus Frost Large, Camel Snus Robust, and Camel Snus Winterchill) contain 1000 mg, with differences in the pouch width, tobacco weight, pouch fleece weight, and package weight.

All six of the Camel Snus products contain a tobacco blend different from combusted cigarettes, which typically include an American tobacco blend of tobacco leaf (e.g., flue cured, burley, oriental tobacco leaf), expanded tobacco, and reconstituted tobacco. Differences in tobacco blends may affect the harmful and potentially harmful constituents (HPHCs) present in the six Camel Snus products compared to cigarette smoke; however, the applicant did not provide sufficient information or scientific evidence to compare the tobacco blends of the six Camel Snus products to cigarette or other smokeless tobacco products. The applicant states that the six products differ from moist snuff smokeless tobacco products because they do not contain fermented tobacco or undergo a fermentation process that is common in the manufacturing process of moist snuff tobacco products. Instead, the six products undergo a heat treatment process that the applicant states may lower microbial activity and HPHC quantities in the finished products.

sweetener

Ingredients added to the tobacco blend for the six Camel Snus products--such as ~~sugars~~, flavors, and humectant ingredients—are similar to those added to cigarettes. However, ingredient quantities vary between cigarettes and the six products due to the differences in product design and use. For all six products, in addition to tobacco, the basic formulation consists of casings[2] containing salts, pH adjusters, sweeteners, flavorings, humectants, and pouch materials (Section 3.2 of the MRTPAs). All the casings, except the flavor casing, contain the same ingredients but vary in quantities. (b) (4)
(b) (4)

(b) (4) Chen et al. (2010) reported that commercial smokeless tobacco products contain menthol levels up to 4.3 mg/g, (b) (4)
(b) (4) . In comparison, mentholated cigarettes contain menthol ranging from 2.9 to 19.6 mg/cigarette (Ai et al., 2015). Use of the different tobacco products may result in different delivery of menthol and, therefore, differences in perception and taste. The casing that imparts characterizing flavor to each Camel Snus product contains unique flavor

[2] Casings are additives applied to tobacco during processing.

ingredients. The toxicological implications of ingredients are further discussed in Section I.B of this document (Nonclinical Evidence of Potential Disease Risk).

Harmful and Potentially Harmful Constituents (HPHCs)

Based on the scientific literature, mainstream cigarette smoke contains over 7,000 chemical compounds, including 70 carcinogens. Smokeless tobacco products contain approximately 4,000 chemical compounds, including 29 carcinogens present in the tobacco filler (Rodgman & Perfetti, 2009). The HPHCs that are considered carcinogens are classified as such by the International Agency for Research on Cancer (IARC). The combustion involved in cigarette use contributes to a higher number of HPHCs in cigarettes than in smokeless tobacco, including carcinogens. For example, aromatic amines, volatile hydrocarbons, carbonyls, carbon monoxide, hydrogen cyanide, hydrazine, phenols, heterocyclic aromatic amines, and epoxides found in cigarettes may not be present in smokeless tobacco.

The FDA has identified 93 HPHCs, which are published in the Federal Register (77 FR 20034). These HPHCs are chemical constituents in a tobacco product or in tobacco smoke that are, or potentially are, inhaled, ingested, or absorbed into the body, including as an aerosol (vapor) or any other emission; and cause or have the potential to cause direct or indirect harm to users or non-users of tobacco products (including with respect to five disease outcomes: cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction). Sixty-five HPHCs have been shown to be present in tobacco and 91 have been shown to be present in mainstream cigarette smoke.

The applicant provided HPHC levels in the six Camel Snus products, cigarette tobacco products, and comparator smokeless tobacco products (Section 6.1.5 of the MRTPAs); these were limited to the nine chemical constituents listed in the abbreviated list of HPHCs for smokeless tobacco products in the FDA Draft Guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under section 904(a)(3) of the FD&C Act.[3] The applicant also provided HPHC levels for six additional polycyclic aromatic hydrocarbons (PAHs), which are listed in the Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List (77 FR 20034 studies detailing HPHC levels in smokeless tobacco, cigarettes, and Camel Snus [Sections 7.1.2 and 7.1.3 of the MRTPAs]).

RJRT submitted three studies detailing HPHCs in smokeless tobacco, cigarettes, and Camel Snus (Sections 7.1.2 and 7.1.3 of the MRTPAs). The first study analyzed pH, moisture and HPHC levels (nicotine, metals [cadmium, arsenic], acrylamide, free nicotine, tobacco-specific nitrosamines (TSNAs) [NAB, NAT, NNN, NNK], carbonyls [formaldehyde, acetaldehyde, crotonaldehyde], and PAHs [benzo[a]pyrene (B[a]P), Benzo(a)anthracene (B[a]A), Benzo(b/j)fluoranthene (B[b/j]F), Benzo(k)fluoranthene (B[k]F), Dibenzo(a, h)anthracene (D[a,h]A), Indeno(1,2,3-cd)pyrene (I[1,2,3-cd]P), naphthalene]) in 43 commercial U.S. smokeless tobacco products (e.g., Camel Snus products that are subject of the MRTPAs, moist snuff, dry snuff, loose leaf tobacco) in 2014 and 2015 selected based on market share data. The second study reported the same HPHCs in 45 commercial U.S. cigarette products in 2014 and 2015 selected based on market share data. The third study analyzed the Camel Snus products that are the subject of the MRTPAs sampled quarterly from the manufacturing site (American Snuff Company) between January 2013 and December 2015. Chemicals tested included:

[3] This draft guidance is available for public comment. Once finalized, it will represent the agency's current thinking on the topics therein.

anabasine, nicotine, nornicotine, free nicotine, metals (arsenic, cadmium), B(a)P, carbonyls (acetaldehyde, crotonaldehyde, formaldehyde), and TSNAs (NAB, NAT, NNK, NNN).

An additional two studies, performed by a third-party testing laboratory (Labstat International ULC), were also submitted (Section 7.1.2 of the MRTPAs). The first study analyzed tar, carbon monoxide, pH, moisture, HPHCs (e.g., nicotine, metals [cadmium, arsenic], pH, moisture, free nicotine, TSNAs [NNN, NNK], B(a)P, carbonyls [formaldehyde, acetaldehyde, crotonaldehyde]) of seven commercial U.S. snus products including Camel Snus, four commercial Swedish snus products, and two commercial U.S. cigarette products. The second study analyzed minor alkaloids (e.g., nicotine, nornicotine, anabasine, anatabine, myosmine) and moisture from the six Camel Snus products that are the subject of the MRTPAs, three commercial U.S. dry snuff products, and three commercial U.S. moist snuff products (Section 7.1.1 of the MRTPAs). The main findings from these five studies are summarized in Table 1 and Table 2.

Table 1. HPHC yields, pH, and moisture in the six Camel Snus products that are the subject of the MRTPAs and selected tobacco products based on market share (Data Source: Section 7.1.1-7.1.3 of the MRTPAs)

Constituent	Mean[a] of Camel Snus Products		Cigarettes Mainstream Smoke Mean (SD[d]), unit/cigarette		Smokeless Tobacco Products, unit/g (WWB)			
	unit/g (WWB[b])	unit/ pouch[c]	ISO Smoking Regimen	CI Smoking Regimen	Moist Snuff Mean (SD)	Loose Leaf Mean (SD)	Dry Snuff Mean (SD)	Swedish Snus Mean[e] (SD)
Acetaldehyde (µg)	1.55 (0.44)	0.94, 1.54	615 (158)	1673 (208)	4.61 (8.38)	3.29 (1.54)	2.33 (0.67)	16.19 (8.55)
Arsenic (ng)	76.9 (12.5)	46.6, 76.0	3.0 (1.2)	9.0 (2.7)	108.5 (25.78)	123.0 (48.3)	178.2 (39.9)	115.6 (13.8)
B(a)P (ng)	1.0 (0.2)	0.6, 1.1	9.0 (2.5)	19.7 (4.9)	72.0 (35.0)	4.11 (0.8)	103.0 (76.5)	1.1 (0.3)
Benzo(a)anthracene (ng)	< LOQ[f]	< LOQ	17.6 (5.1)	37.2 (8.3)	83.1 (36.4)	27.1 (1.3)	247 (158)	NP[g]
Benzo(b/j)fluoranthene (ng)	< LOQ	< LOQ	9.5 (2.6)	21.0 (5.2)	39.1 (9.9)	36.0 (1.8)	97.0 (60.3)	NP
Benzo(k)fluoranthene (ng)	< LOQ	< LOQ	2.3 (0.4)	4.4 (1.1)	49.8 (9.9)	< LOQ	31.6 (11.6)	NP
Dibenzo(a, h)anthracene (ng)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	NP
Indeno(1,2,3-cd)pyrene (ng)	4.3 (1.3)	2.8, 5.1	4.5 (1.3)	9.8 (2.3)	7.2 (2.8)	< LOQ	21.3 (12.9)	NP
Naphthalene (ng)	< LOQ	< LOQ	405 (246)	886 (989)	< LOQ	< LOQ	< LOQ	NP
Cadmium (ng)	402 (29)	241, 402	42.2 (16.5)	116 (29)	510 (0.084)	551 (310)	1284 (197)	272 (67)
Crotonaldehyde (µg)	0.69 (0.10)	0.411[h]	13.0 (4.6)	49.0 (7.3)	< LOQ	0.70 (0.03)	< LOQ	< LOQ
Formaldehyde (µg)	1.21 (0.53)	0.76, 0.97	23.8 (10.2)	92.2 (22.7)	1.83 (0.93)	0.88 (0.03)	3.43 (2.28)	2.30 (0.82)
NNK (ng)	332 (123)	200, 330	68.1 (31.2)	152 (58)	482 (480)	459 (270)	15184 (32532)	138 (67)

Constituent	Mean[a] of Camel Snus Products		Cigarettes Mainstream Smoke Mean (SD[d]), unit/cigarette		Smokeless Tobacco Products, unit/g (WWB)			
	unit/g (WWB[b])	unit/ pouch[c]	ISO Smoking Regimen	CI Smoking Regimen	Moist Snuff Mean (SD)	Loose Leaf Mean (SD)	Dry Snuff Mean (SD)	Swedish Snus Mean[e] (SD)
NNN (ng)	1136 (215)	698, 1108	90.1 (40.4)	197 (74)	1710 (1197)	1698 (1010)	13760 (13542)	426 (115)
Nicotine (mg)	9.8 (1.1)	5.95, 9.61	0.91 (0.35)	2.16 (0.6)	12.04 (1.62)	6.47 (1.74)	23.05 (5.48)	11.6 (3.5)
Moisture (%)	33.42 (0.91)	33.39, 33.46	NA	NA	54.2 (1.94)	26.0 (1.9)	6.08 (1.52)	42.67 (9.85)
pH	7.71 (0.12)	7.70, 7.71	NA	NA	7.64 (0.37)	5.77 (0.28)	6.14 (0.24)	7.62 (0.06)
% Unionized (Free) Nicotine	3.24 (0.76)	19.63, 33.39	NA	NA	3.84 (1.83)	0.05 (0.03)	0.34 (0.14)	5.35 (3.09)
Free Nicotine (mg)	33.04 (6.19)	1.96, 3.22	NA	NA	32.75 (17.03)	0.72 (0.62)	1.53 (0.67)	NP

Data source: RDM JMR 2016 235 (Analytical Testing of Camel Snus Products), RDM JAB 2016 281 (Summary of 2014 and 2015 Smokeless Market Surveys), RDM JAB 2016 306 (Summary of 2014 and 2015 Cigarette Market Surveys), and LSI 2014 113 (Determination of Smokeless Tobacco HPHC Values for Camel Snus and Other Tobacco Products – M195-GLP).

[a] This mean is the average of the six Camel Snus products that are the subject of the MRTPAs.

[b] WWB: Wet weight basis ("as-is" basis).

[c] Mean of Camel Snus HPHCs in unit per unit of use calculated as: Mean of 600 mg pouch products (i.e., Camel Snus Frost, Mellow, and Mint), Mean of 1000 mg pouch products (i.e., Camel Snus Frost Large, Robust, Winterchill).

[d] SD: Standard deviation.

[e] The LSI 2014 113 report provided the measured values in "dry weight" basis (DWB). The constituent levels were calculated in WWB using the following equation: WWB = DWB x (1 – average moisture %).

[f] < LOQ: Below limit of quantification; for values reported < LOQ, the data was omitted in determining the mean values.

[g] NP: Not provided.

[h] Crotonaldehyde values for 1000mg pouch products were < LOQ.

Table 2. Differences in HPHC yields, pH, and moisture in the six Camel Snus products that are the subject of the MRTPAs and selected tobacco products based on market share (Data Source: Section 7.1.1-7.1.3 of the MRTPAs)

Constituent	Mean of the Camel Snus Products[a]		Average Difference (%) by Unit of Use[d]		Difference (%) by unit/g of Tobacco Product[e]			
	unit/g (WWB[b])	unit/pouch[c]	Cigarette Smoke (ISO)	Cigarette Smoke (CI)	Moist Snuff	Loose Leaf	Dry Snuff	Swedish Snus
Acetaldehyde (µg)	1.55 (0.44)	0.94, 1.54	↓ 99	↓ 99	↓ 66	↓ 53	↓ 33	↓ 90
Arsenic (ng)	76.9 (12.5)	46.6, 76.0	↑ 1904	↑ 579	↓ 29	↓ 38	↓ 57	↓ 34
B(a)P (ng)	1.0 (0.2)	0.6, 1.1	↓ 91	↓ 96	↓ 99	↓ 74	↓ 99	↓ 9
B(a)A (ng)	< LOQ[f]	< LOQ	ND[g]	ND	ND	ND	ND	ND
B(b/j)F (ng)	< LOQ	< LOQ	ND	ND	ND	ND	ND	ND
B(k)F	< LOQ	< LOQ	ND	ND	ND	ND	ND	ND
D(a, h)A	< LOQ	< LOQ	ND	ND	ND	ND	ND	ND
I(1,2,3-cd)P	4.3 (1.3)	2.8, 5.1	↓ 6	↓ 56	↓ 32	ND	↓ 77	ND
Naphthalene	< LOQ	< LOQ	ND	ND	ND	ND	ND	ND
Cadmium (ng)	402 (29)	241, 402	↑ 659	↑ 177	↓ 21	↓ 27	↓ 69	↑ 48
Crotonaldehyde (µg)	0.69 (0.10)	0.411[h]	↓ 97	↓ 99	ND	↓ 3	ND	ND
Formaldehyde (µg)	1.21 (0.53)	0.76, 0.97	↓ 97	↓ 99	↓ 34	↑ 37	↓ 65	↓ 47
NNK (ng)	332 (123)	200, 330	↑ 286	↑ 73	↓ 31	↓ 28	↓ 98	↑ 140
NNN (ng)	1136 (215)	698, 1108	↑ 895	↑ 354	↓ 34	↓ 33	↓ 92	↑ 167
Nicotine (ng)	9.8 (1.1)	5.95, 9.61	↑ 746	↑ 256	↓ 19	↑ 51	↓ 58	↓ 16
Moisture (%)	33.42 (0.91)	33.39, 33.46	NA	NA	↓ 38	↑ 29	↑ 450	↓ 22
pH	7.71 (0.12)	7.70, 7.71	NA	NA	↑ 1	↑ 34	↑ 26	↑ 1
Free Nicotine (mg)	3.24 (0.76)	19.63, 33.39	NA	NA	↓ 16	↑ 6380	↑ 853	↓ 39

[a] This mean is the average of the six Camel Snus products that are the subject of the MRTPAs.
[b] WWB: Wet weight basis ("as-is" basis).
[c] Mean of Camel Snus HPHCs in unit per unit of use calculated as: Mean of 600 mg pouch products (i.e., Camel Snus Frost, Mellow, and Mint), Mean of 1000 mg pouch products (i.e., Camel Snus Frost Large, Robust, Winterchill).
[d] Percent Difference = [Proposed MRTP– Comparator Product]/Comparator Product x 100. Difference for cigarette smoke reflects the percent differences from ISO and CI smoking regimens.
[e] Percent Difference = [Proposed MRTP (in unit/g as-is basis) – Comparator Product (in unit/g as-is basis)]/Comparator Product (in unit/g as-is basis) x 100.
[f] < LOQ: Below limit of quantification; for values reported < LOQ, the data was omitted in determining the mean values.
[g] ND: Not determined.

The published scientific studies found that levels of HPHCs in Camel Snus products (i.e., Frost, Mellow, Robust, Winterchill) were comparable to those reported in the MRTPAs; however, the levels reported have large variability. Briefly, the main findings from these studies reported that NNN levels in Camel Snus products ranged from 684-1790 ng/g (Borgerding et al., 2012; Hatsukami et al., 2007, 2015; Stepanov et al., 2008, 2012, 2013, 2014). Amman et al. (2015) summarized the levels of NNN in Camel Snus Frost reported from 2006 to 2015, indicating that the levels of NNN varied over the years, with up to 95% higher levels reported in 2015 compared to levels reported in 2009. Ammann et al. also reported that NNN levels ranged from 0.59-4.93 µg/g in moist snuff, 5.55-11.19 µg/g in dry snuff, and 0.73-4.27 µg/g in chewing tobacco.

On June 11, 2018, FDA's Southeast Tobacco Laboratory (STL) conducted HPHC testing of the six Camel Snus products in order to verify chemical and physical data submitted in the MRTPAs. This independent testing performed by STL found that levels of nicotine, moisture, and pH were comparable to the levels reported by the applicant. Some differences exist between the applicant's analytical methods and the methods used by a third-party laboratory (i.e. Labstat), which may contribute to the differences in results for all other HPHCs.

The six Camel Snus products compared to mainstream cigarette smoke

The six Camel Snus smokeless tobacco products and cigarettes are portioned products; therefore, FDA compared the levels of the 15 HPHCs tested by the applicant on a per unit of use basis (i.e., per cigarette for the cigarettes and per pouch [same as per portion] for the portioned snus). According to the three studies included in the MRTPAs performed by the applicant (i.e., RDM JAB 2016 306, RDM JAB 2016 281, and RDM JMR 2016 235 in Section 7.1 of the MRTPAs), the six Camel Snus products contain quantifiable levels of 10 of the 15 tested HPHCs, while the levels of five PAHs (B(a)A, [B(b/j)F, B(k)F, D(a,h)A, and naphthalene) are below the limit of quantification (LOQ). The MRTPAs provide evidence that mainstream cigarette smoke contains the same ten HPHCs reported in the six products as well as the four PAHs at levels above LOQ, not including D[a,h]A. Also, the six products contain lower levels of acetaldehyde (<99%), B[a]P (91-96%), I[1,2,3-cd]P (6-56%), crotonaldehyde (97-99%), and formaldehyde (97-99%) than the levels in mainstream cigarette smoke. However, the six products contain higher levels of the following HPHCs than mainstream cigarette smoke (see Table 1 and Table 2).

- Arsenic: 579-1904% higher than mainstream cigarette smoke
- Cadmium: 177-659% higher than mainstream cigarette smoke
- NNK: 73-286% higher than mainstream cigarette smoke
- NNN: 354-895% higher than mainstream cigarette smoke
- Nicotine: 256-746% higher than mainstream cigarette smoke

The HPHC levels reported in the MRTPAs for mainstream cigarette smoke are similar to the levels reported in an FDA/CDC study, which included 50 top selling U.S. cigarettes (Pazo et al., 2016). It must be noted that the six Camel Snus products and cigarette products are drastically different in product design and use (oral versus smoking); users may not be getting the levels of HPHCs for each type of product as indicated above because actual exposure levels are influenced by factors such as user behavior (e.g., the amount of product used per day), the route of administration (oral ingestion versus inhalation), the rate of absorption, and metabolism (Digard et al., 2013). The higher levels of certain HPHCs in the six Camel Snus products (Sections 6.1.5 and 7.1 of the MRTPAs) compared to cigarette products is further discussed in Section II.B of this document (Nonclinical Evidence of Potential Disease Risk).

The six Camel Snus products compared to smokeless tobacco products

The MRTPAs also include a market study of HPHC yields in different smokeless tobacco products, including moist snuff, dry snuff, loose leaf, and Swedish snus. Based on the information provided in the MRTPAs, the six Camel Snus products contain 16-99% lower levels of all HPHCs tested compared to that in moist snuff tobacco products; 3-74% lower levels of certain HPHCs (i.e., acetaldehyde, arsenic, B[a]P, cadmium, crotonaldehyde, NNN, NNK) compared to loose leaf tobacco products; 33-99% lower levels of certain HPHCs (i.e., acetaldehyde, arsenic, B[a]P, cadmium, crotonaldehyde, formaldehyde, NNN, NNK, nicotine) compared to dry snuff tobacco products; and 9-90% lower levels of certain HPHCs (i.e., arsenic, B[a]P, cadmium, formaldehyde, nicotine, free nicotine) compared to Swedish snus tobacco products.

However, the mean quantity of HPHCs in the six Camel Snus products contain higher levels of the following:

- The six Camel Snus products contain higher levels of formaldehyde (37%), nicotine (51%), and free nicotine (6380%) compared to loose leaf/chewing tobacco products
- The six Camel Snus products contain higher levels of free nicotine (853%) compared to dry snuff tobacco products
- The six Camel Snus products contain higher levels of cadmium (48%), NNK (140%), and NNN (167%) compared to Swedish snus tobacco products

The applicant reported that the six Camel Snus products are manufactured using the same processes and procedures as Swedish snus. In Sweden, snus manufacturing is regulated by the Swedish National Food Agency Directive, which sets limits for certain constituents, such as TSNAs and B[a]P (Rutqvist, 2011). The voluntary quality standard for Swedish snus, GothiaTek®, has become an industry standard for all smokeless tobacco products in Europe (Rutqvist, 2011). In comparison to the levels set by the GothiaTek® standard, the levels of NNN and NNK (1.436 - 1.476 µg/g) in the six Camel Snus products are higher than the GothiaTek® standard limit (0.95 µg/g) (Table 3). See Section I.B for information on how these constituent levels may affect disease risk.

Table 3. GothiaTek® standard limits compared to 95% confidence interval levels of constituents in Camel Snus (Data Source: Section 7.1.2 of the MRTPAs)

Constituent (Unit, as-is basis)	GothiaTek® Standard Limit[a]	Levels in the six Camel Snus products (95% Confidence interval)
Nitrite (µg/g)	3.5	NP[b]
NNK (µg/g)	[redacted]	0.32 - 0.343
NNN (µg/g)	[redacted]	1.116 - 1.156
NNN+NNK (µg/g)	0.95	1.436 - 1.476
NDMA (ng/g)	2.5	NP
B(a)P (ng/g)	1.25	1.03 - 1.07
AflatoxinB1+B2+G1+G2 (ng/g)	2.5	NP
Ochratoxin (ng/g)	10	NP
Formaldehyde (µg/g)	7.5	1.11 - 1.302
Crotonaldehyde (µg/g)	0.75	0.636 - 0.735
Cadmium (µg/g)	0.5	0.399 - 0.404
Lead (µg/g)	1	NP
Arsenic (µg/g)	0.25	0.076 - 0.078
Nickel (µg/g)	2.25	NP
Chromium (µg/g)	1.5	NP
Mercury (µg/g)	0.02	NP
Acetaldehyde (µg/g)	25	1.489 - 1.614

[a] Information obtained from Swedish Match (2018)
[b] NP: Not provided

Summary and Conclusions

Scientific studies have reported that 4,000 chemical compounds are found in smokeless tobacco, compared to over 7,000 chemical compounds in mainstream cigarette smoke (Rodgman & Perfetti, 2009). FDA has established a list of 93 HPHCs present in tobacco products and tobacco smoke (77 FR 20034), classifying HPHCs as carcinogens, respiratory toxicants, cardiovascular toxicants, reproductive or developmental toxicants, and/or addictive. Scientific studies report that 65 of the 93 HPHCs have been

shown to be present in smokeless tobacco and 91 of the 93 HPHCs have been shown to be present in mainstream cigarette smoke. Furthermore, 79 of the 93 HPHCs are classified as carcinogens. Of the 79 carcinogens on the HPHC list, 51 carcinogens have been shown to be present in tobacco and 77 carcinogens have been shown to be present in cigarette smoke.

Scientific studies specifically involving the six Camel Snus products that are the subject of the MRTPAs are limited to constituents in tobacco and demonstrate that the HPHCs and carcinogens present in the six Camel Snus products are also present in mainstream cigarette smoke. Additional HPHCs have not been tested potentially because Camel Snus is a smokeless tobacco product that is not combusted and is not expected to contain HPHCs that are formed during the combustion of tobacco. The MRTPAs include evidence that the six Camel Snus products contain the following eight carcinogens: acetaldehyde, formaldehyde, crotonaldehyde, B[a]P, I(1,2,3-cd)P, arsenic, cadmium, NNN, and NNK. The applicant also reported that levels of carcinogenic certain PAHs (i.e., B(a)A, I(1,2,3-cd)P, [B(b/j)F, B(k)F, and naphthalene) are below the LOQ in all six products. The MRTPAs provide evidence that shows that the same eight carcinogens (i.e., acetaldehyde, arsenic, B[a]P, cadmium, are also present in mainstream cigarette smoke, as well as evidence indicating the presence of PAHs with levels higher than the LOQ. Moreover, the scientific studies summarized above report that the following carcinogenic HPHCs are present in the Camel Snus Frost, Mellow, Robust, and Winterchill products: TSNAs (NNN and NNK), metals (arsenic, cadmium, chromium, lead, nickel), and certain PAHs (B[a]P, B[a]A, B[b/j]F, b[f]K, D[a,h]AI[1,2,3,cd]P, naphthalene). The applicant did not provide results for the analysis of additional carcinogens in the six products that are the subject of the MRTPAs.

The applicant provided analytical data for the following carcinogenic HPHCs, measured in the six Camel Snus products and smoke generated from the comparator cigarette products: cadmium, acetaldehyde, arsenic, benzo[a]pyrene (B[a]P), crotonaldehyde, formaldehyde, NNN and NNK. A comparative evaluation of HPHC levels reported by the applicant for the six Camel Snus products, comparator cigarette products, and mainstream smoke HPHC data from fifty U.S. domestic cigarette brands (Pazo et al., 2016) indicates decreases in the levels of four HPHCs -- acetaldehyde (↓ >99%), formaldehyde (↓ 97%-99%), crotonaldehyde (↓ 97%-99%) and B[a]P (↓ 91%-96%) -- measured by the applicant in the six Camel Snus products compared to cigarettes. However, the data also indicate that arsenic (↑ 579%–1904%), cadmium (↑ 177%–659%), NNN (↑ 354%–895%), NNK (↑ 73%–286%), and nicotine (↑ 256%-746%) levels are significantly higher in the six Camel Snus products compared to cigarette smoke. NNK and NNN are potent carcinogens in laboratory animals (IARC, 2007a). NNK induces adenoma and adenocarcinoma of the lung, nasal cavity, and liver of mice, rats, and hamsters (Balbo et al., 2014; Hecht et al., 1980, 1983; Hoffman et al., 1984). NNN and NNK are also human carcinogens.

B. Nonclinical Evidence of Disease Risk

This section summarizes the HPHCs measured in the six Camel Snus products and the comparator tobacco products, biomarkers of exposure (urine mutagenicity and buccal micronucleated cells), the nonclinical studies used by the applicant to evaluate in vitro genotoxicity and cytotoxicity, and the in vivo toxicity and carcinogenicity studies provided by the applicant for the evaluation of the six Camel Snus products and the comparator tobacco products. Additional details on each of the nonclinical studies can be found in the appendices provided by the applicant (Sections 7.1, 7.2, 7.3, and 7.4 of the MRTPAs).

HPHCs

The analytical HPHC measurement data provided by the applicant indicated decreases in the levels of the following HPHCs in the six Camel Snus products compared to cigarettes: acetaldehyde, benzo(a)pyrene, crotonaldehyde, and formaldehyde. However, the HPHC data reported by the applicant for the six Camel Snus products and the comparator cigarette products (Section 7.1 of the MRTPAs) indicated statistically significant increases in several other HPHCs in these Camel Snus products compared to cigarette smoke (Table 4). The six Camel Snus products also contained elevated levels of cadmium, formaldehyde, nicotine, NNK, and NNN compared to certain other smokeless tobacco comparator products, as noted in Table 4.

Table 4: Estimated HPHC increases in Camel Snus products (MR0000068-MR0000073) compared to other tobacco products (Data Source: Section 7.1 of the MRTPAs)

HPHC	Associated Adverse Health Effects (FDA, 2012)[a]	Increase in Mean HPHC Levels (As-Is Basis) in the six Camel Snus products as Compared to the Comparator Product[b]			
		Cigarette smoke	Loose leaf	Dry snuff	Swedish snus
Arsenic	CA, CT, RDT	579 – 1904%	--	--	--
Cadmium	CA, RT, RDT	177-659%	--	--	48%
Formaldehyde	CA, RT	--	37%	--	--
Nicotine	AD, RDT	256 - 746%	51%	--	--
Free Nicotine	AD, RDT	--	6380%	853%	--
NNK	CA	73 - 286%	--	--	140%
NNN	CA	354 - 895%	--	--	167%

[a]Carcinogen (CA), Cardiovascular Toxicant (CT), Respiratory Toxicant (RT), Reproductive or Developmental Toxicant (RDT), Addictive (AD).
[b]Only significant increases in HPHC levels are noted.

TSNAs, including NNN and NNK, are some of the most potent carcinogens present in tobacco products. NNN and NNK have been known to cause oral cancer in smokeless tobacco users who are nonsmokers. NNN is considered the primary driver of oral cancer in smokeless tobacco users. Oral exposure to NNN resulted in tumors at multiple sites (e.g., oral cavity, lung, trachea) in rats and mice (Balbo et al., 2013; Castonguay et al., 1984; Hecht et al., 1983; Hoffmann et al., 1975, 1984; Stoner et al., 1998;). NNN and NNK induced oral tumors when applied as a mixture to the oral cavity (Hecht et al., 1986). A recent study by Balbo et al. (2014) showed that all animals receiving NNK via oral exposure developed lung tumors, indicating that NNK was a systemic lung carcinogen, under the conditions of this study. In addition, arsenic is a carcinogen that also exhibits cardiovascular and reproductive or developmental toxicity, cadmium is a carcinogen and a reproductive or developmental toxicant, and nicotine is addictive and causes reproductive or developmental toxicity (FDA, 2012). NNK, NNN, and cadmium levels are higher in the six Camel Snus products than cigarette smoke and Swedish Snus in the U.S. market. The information provided in the MRTPAs suggests that the six Camel Snus products contain TSNA levels comparable to U.S. moist snuff tobacco products.

Although certain HPHCs are lower in the six Camel Snus products than cigarettes (e.g., acetaldehyde, benzo(a)pyrene), loose leaf and dry snuff (e.g., NNK, NNN, and cadmium), and Swedish Snus (e.g., arsenic, benzo(a)pyrene, formaldehyde), the higher levels of HPHCs in the six Camel Snus products compared to the other tobacco products listed in Table 4 may result in increased user exposures to carcinogens and other toxicants that may subsequently increase the risk for cancer, heart disease and reproductive or developmental effects.

The cancer-causing potential of a chemical mixture is dependent on many factors including, but not limited to, the levels and toxicity of the individual components, how the person or target population is exposed, and the length and intensity of exposure. Exposure to smokeless tobacco such as the six Camel Snus products and cigarette smoke occurs via different routes (oral vs. inhalation). Consequently, there may be differences in HPHC bioavailability and target tissues for carcinogenic effects associated with user exposures to carcinogens from each of these products. Given the oral route of exposure and the fact that smokeless tobacco products are not combusted, it is possible that the carcinogenic potential of the six Camel Snus products is lower than that of cigarette smoke. However, the HPHC data submitted by the applicant did not demonstrate potential for reduced exposure from the six Camel Snus products as compared to cigarette smoke.

Ingredients

All six Camel Snus products being evaluated in these MRTPAs have distinct flavors. Flavored smokeless tobacco products made up at least 54% of the smokeless tobacco market share between 2005 and 2011 (Delnevo et al., 2014). The six Camel Snus products contain ingredients that may act as permeation enhancers, impact HPHC absorption, and consequently enhance HPHC bioavailability in users, thus increasing the overall health risks associated with exposure to these products compared to other smokeless tobacco products that do not have the same flavor ingredients.

The applicant did not provide sufficient ingredient information for the comparator smokeless tobacco products and the comparator cigarettes. This information would be helpful for any one-to-one health risk comparison between the six Camel Snus and cigarettes or other smokeless tobacco products.

Biomarkers

The applicant studied approximately 150 biomarkers from human biosamples in the clinical studies submitted in these MRTPAs (Section 7.4 of the MRTPAs). The applicant did not provide a scientific justification for the biomarkers studied, nor identify which individual biomarkers of exposure and potential harm support each of its requested modified risk claims. In general, the biomarker data are reported by the applicant for the six Camel Snus products as a single comparator group, making it difficult to assess which data are specific to each of the six products. In addition, the applicant did not provide sufficient information about the analytical methods used for measuring the biomarkers.

In the study report CSD0804 (Caraway & Chen, 2013), the applicant evaluated mouth-level exposures to several tobacco constituents including nicotine, TSNAs, B[a]P, and metals in U.S. consumers of Camel Snus Frost, Camel Snus Spice and Camel Snus Original. In this study, 53 adult Camel Snus consumers used their usual brands ad libitum for seven days; the smokeless pouches were collected after each use. Mouth-level exposures were determined by calculating the difference in HPHC levels between the tobacco in the used and unused Camel Snus pouches. The study concluded that only a small fraction (up to 40%) of the HPHC levels present in the tobacco was released during use. The study had several limitations, including a small study population (Camel Snus Frost, n=25; Camel Snus Original, n=12; Camel Snus Spice, n=16) and high variability in the estimated mouth-level exposures to the HPHCs measured. The study was conducted across four geographical locations (Dallas, TX; Kansas City, MO; Orlando, FL; and Raleigh, NC) and baseline levels of constituents in the unused product were calculated as the average values from products purchased for the study across all study sites, without considering regional differences in product constituent levels.

The applicant discusses the utility of urine mutagenicity (studies CSD0901, CSD0904, HSD0702, and CSD0914 in Section 7.4 of the MRTPAs) as a biomarker of internal exposure to genotoxic chemicals from the use of the Camel Snus products described in these MRTPAs. Of the four studies that provide urine mutagenicity data, results from studies CSD0904 and CSD0901 are summarized here; more detailed information on the biomarker studies is provided in Section I.C of this document (Clinical Evidence of Potential Disease Risk). In study CSD0904, the applicant claims that urinary mutagenicity was significantly lower in the Camel Snus Frost, Mellow, and Winterchill, moist snuff, and dual user cohorts compared to the cigarette smoker cohort. In study CSD0901, the applicant reported that a reduction in urine mutagenicity was observed on Day 5 of the study in dual users of cigarettes and Camel Snus products, users of other smokeless tobacco products, and the tobacco abstinent group as compared to the baseline mutagenicity measurements recorded in the subjects at study initiation. The applicant also considers micronucleated buccal cells (i.e., % micronucleated buccal cells data in study cohorts) to be a biomarker for genotoxicity.

The applicant provided biomarker data for (a) exclusive users of Camel Snus products, (b) dual users of Camel Snus products with combusted cigarettes, (c) dual users of Camel Snus products with other non-cigarette tobacco products, (d) poly-users, defined as users of Camel Snus products and two or more other tobacco products (e.g., combusted cigarettes and e-cigarettes), and (e) non-users of any tobacco products. However, the applicant did not provide any biomarker data for potential users, who switch completely from combusted cigarettes to the six Camel Snus products that are the subject of the MRTPAs, thus making it difficult to interpret the biological significance of biomarker levels in these tobacco user populations.

At this time, there is no single biomarker that predicts the risk of disease in people who use tobacco products (NAS, 2012). A more detailed evaluation of the biomarker data is provided in Section II of this document.

In Vitro Studies

The applicant submitted study reports for in vitro genotoxicity and cytotoxicity assays (Section 7.2 of the MRTPAs; refer to Table 5) using Health Canada (test method 501, 502, and 503) and Organization for Economic Co-operation and Development (OECD 471 and 487) methods for the six Camel Snus products and the comparator combusted and smokeless tobacco products. The applicant performed the sister chromatid exchange (SCE) assay as per the “Labstat Method TBA-504”. The protocol for “Labstat Method TBA-504” could not be found in these MRTP applications, nor could it be found online. The in vitro genotoxicity study results indicated that the Camel Snus products listed in these MRTPAs as well as the comparator cigarettes and smokeless tobacco products were genotoxic in vitro, under the conditions of the studies.

Table 5: In vitro studies discussed in MR0000068-MR0000073 (Data Source: Section 7.2 of the MRTPAs)

Assay Name	Assay Endpoint	Camel Snus (CS) Products Tested	Comparator Tobacco Products Tested	
			Cigarette Products	Smokeless Tobacco Products
Ames mutagenicity assay	Genotoxicity	CS Frost, CS Frost large, CS Mint, CS Mellow, CS Robust, and CS Winterchill	2R4F and 3R4F Kentucky reference cigarettes, Marlboro Gold King Size Box and Newport Menthol King Size Box	2S3 and CRP1 reference moist snuff, Camel Fresh Strips, Camel Mellow Sticks, Copenhagen Long Cut Moist Snuff, Ariva Wintergreen, Camel Fresh Orbs, General Original Snus (U.S. & Sweden), Catch Dry Eucalyptus Mini Snus (Sweden), Granit Snus (Sweden), Skruf Stark Snus (Sweden)
Sister chromatid exchange (SCE) assay	Genotoxicity	CS Frost	2R4F Kentucky reference cigarette	2S3 reference moist snuff, Copenhagen Long Cut Moist Snuff, Camel Fresh Strips, Camel Mellow Sticks, Ariva Wintergreen, and Camel Fresh Orbs
Micronucleus (MN) assay	Genotoxicity	CS Frost	2R4F Kentucky reference cigarette	2S3 reference moist snuff, Copenhagen Long Cut Moist Snuff, Camel Fresh Strips, Camel Mellow Sticks, Ariva Wintergreen, and Camel Fresh Orbs
Neutral red uptake (NRU) assay	Cytotoxicity	CS Frost, CS Frost large, CS Mint, CS Mellow, CS Robust, and CS Winterchill	2R4F and 3R4F Kentucky reference cigarettes, Marlboro Gold King Size Box and Newport Menthol King Size Box	2S3 and CRP1 reference moist snuff, Copenhagen Long Cut Moist Snuff, Camel Fresh Strips, Camel Mellow Sticks, Ariva Wintergreen, Camel Fresh Orbs, General Original Snus (U.S. & Sweden), Catch Dry Eucalyptus Mini Snus (Sweden), Granit Snus (Sweden), Skruf Stark Snus (Sweden)

The cigarette products used in the above-listed in vitro assays were smoked in accordance with either the ISO smoking regimen alone or under both ISO and CI regimens, and total particulate matter (TPM) was extracted for testing. All smokeless tobacco products were extracted either in dimethyl sulfoxide (DMSO; studies M97 Ames, M100 MN, M125 SCE, M100 NRU) or complete artificial saliva (CAS; M194A Ames, M194B NRU). Smokeless tobacco product samples were compared on a "DMSO-extracted smokeless tobacco" basis, "DMSO-extracted moisture-corrected smokeless tobacco" basis, and "DMSO-extracted nicotine" basis. The "DMSO-extracted nicotine" basis was used to compare the in vitro study results between smokeless tobacco and cigarette products. The Ames assay was conducted with *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of S9 metabolic activation (OECD 1997, Health Canada 2004).

Results from the in vitro genotoxicity assays indicate that the six Camel Snus products as well as the comparator cigarettes and smokeless tobacco products are genotoxic in vitro. The SCE and MN assays were only conducted with Camel Snus Frost. These results provide limited data on the in vitro genotoxic potential of the other Camel Snus products in the MRTPAs, as measured by these assays. The in vitro studies used higher concentrations of cigarette smoke TPM extract to test for in vitro genotoxicity and cytotoxicity compared to extracts from smokeless tobacco products, including the six Camel Snus products. The applicant analyzed the results from these assays by using a quantitative linear regression slope approach to compare the relative genotoxic potential of the six Camel Snus products to other smokeless tobacco products and cigarette smoke. However, this method of data analysis and interpretation is not supported by the current OECD, Health Canada, or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for in vitro genotoxicity evaluation and the applicant did not provide a scientific justification for this analysis.

The neutral red uptake (NRU) cytotoxicity assay results indicate that cigarette smoke is more cytotoxic than the six Camel Snus products. However, this study has several limitations, including but not limited to, lack of reproducibility of results (the NRU assay was replicated three times, but cytotoxicity was observed only one time for the smokeless tobacco products) and inadequate assay validation data and use of a cell type (CHO cells) that is not directly relevant to the adverse health effects described in the MRTPA claims.

In Vivo Studies

The applicant submitted sub-acute, sub-chronic, and chronic toxicity in vivo studies conducted in Wistar Hannover (Han) rats and Swiss Webster mice exposed to either Camel Snus native tobacco blend (TB), an aqueous extract of the tobacco blend (TE), or nicotine tartrate (NT, positive control) by ad libitum consumption of the NTP-2000 powdered feed (negative control (C); Table 6). The applicant also submitted a two-year carcinogenicity study in Wistar Hans rats in support of the MRTPAs (Table 6). The in vivo studies were performed consistent with FDA's Good Laboratory Practice (GLP) regulations (21 CFR Part 58) for the conduct of nonclinical laboratory studies. The applicant referenced peer-reviewed literature to present a comparative assessment of the in vivo toxicity and carcinogenicity of cigarettes vs. smokeless tobacco.

Table 6: In vivo studies discussed in MR0000068-MR0000073 (Data Source: Section 7.3 of the MRTPAs)

Study	Purpose	Doses Used	Conclusions
14-day dose range-finding study	To find appropriate dose ranges for long-term in vivo studies	Rats: TB and TE—0.2-40 mg nicotine/kg/day; NT - 2-40 mg kg/day Mice: TB and TE—0.2-40 mg (Phase I) and 40-400 mg nicotine/kg/day (Phase II); NT - 40-400 mg/kg/day	- Dose range for the follow-up studies: Rats: up to 20 mg nicotine/kg/day Mice: up to 200 mg nicotine/kg/day - Selection was based on maximum tolerated dose (MTD), as defined by a 10% decrease in the body weight gain compared to control group.
28-day sub-acute study	To evaluate the short-term toxicity of Camel Snus TB and TE as compared to the control (NT and C) groups	Rats: TB and TE—0.2-20 mg nicotine/kg/day; NT - 20 mg/kg/day Mice: TB and TE—2-200 mg nicotine/kg/day; NT - 200 mg/kg/day	- Significant reduction in body weight and feed intake was noted at intermediate and high doses. - Clinical chemistry results did not reveal any significant changes due to the treatment or dose-related trends.

			- Dose range for the follow-up studies: Rats: up to 6 mg nicotine/kg/day Mice: up to 120 mg nicotine/kg/day
90-day sub-chronic study	To evaluate the sub-chronic toxicity of Camel Snus TB and TE as compared to the control (NT and C) groups	Rats: TB and TE—0.3-6 mg nicotine/kg/day; NT - 6 mg/kg/day Mice: TB and TE—6-120 mg nicotine/kg/day; NT - 120 mg/kg/day	- Significant reduction in body weight and feed intake were noted at high doses. - The C_{max} for nicotine was higher than ~30 ng/ml, exceeding levels typically observed in smokeless tobacco smokers, for both the high and intermediate doses. - No adverse effects related to organ weight, gross pathology, and microscopic pathology results were observed in TB/TE groups compared to the control (C) group. - Dose range for the follow-up study: Rats: up to 5 mg nicotine/kg/day
1-year chronic toxicity and 2-year carcinogenicity study	To evaluate the chronic toxicity and carcinogenic potential of Camel Snus TB and TE as compared to the control (C) group	Rats: TB and TE— 0.2, 2, and 5 mg nicotine/kg/day	- No treatment related effects on mortality were observed. - Significant reduction in body weight and feed intake were noted at high doses. - Malignant carcinomas of the uterus in females, and malignant mesothelioma of the epididymis in males were observed. The applicant claims these were "*typical of spontaneous changes and consistent with background changes previously reported in untreated Wistar Han rats.*"

The in vivo toxicity and carcinogenicity studies reported have the following shortcomings and therefore have limited value for the evaluation of these MRTPAs:

- All the toxicity and carcinogenicity studies were conducted with the Camel Snus native tobacco blend or an aqueous extract of the tobacco blend. The applicant claims that "*All Camel Snus styles are manufactured with an identical tobacco blend, so the findings of this series of in vivo studies that investigate that blend and an aqueous extract of that blend are relevant to all six styles (Frost, Frost Large, Mellow, Robust, Winterchill)*" (p. 17, Section 6.1.4. of the MRTPAs). Neither the Camel Snus native tobacco blend nor the aqueous extract of the tobacco blend contain the various ingredients, flavors, and additives that formulate the distinctive Camel Snus products (MR0000068-MR0000073). All of these products have ingredients that may act as permeation enhancers and therefore may enhance the uptake of HPHCs and potentially affect toxicities.
- Significant reduction in body weight and feed intake was noted at intermediate and high doses. This could be due to decreased diet palatability in the higher dose groups or toxicity of the

higher doses. Regardless of the reason for the decreased food consumption, it can impact the exposure levels in the animals in these dose groups.

- A detailed pathology analysis was only conducted in the negative and positive control groups and in the highest concentration treatment groups. Both male and female control groups exhibited high incidences of histopathological effects that limited interpretation of treatment-related effects. It is unclear whether these histopathological changes observed in the negative control groups are consistent with historical data, and the applicant did not provide any historical data to address this issue. Several possibly biologically significant increases were observed for lung inflammation (E6M and E6F) and prostate inflammation (B6M) in the high-dose groups.
- As the in vivo studies were conducted with the tobacco blend and tobacco blend extract, and not the six Camel Snus products, and since no parallel studies were conducted with conventional cigarettes, no comparative conclusions on health effects between consumption of the six Camel Snus products and conventional cigarette use can be made from these data in the MRTPAs.

Summary and Conclusions

Toxicology-related substantive issues identified in MR0000068-MR0000073 include:

- The HPHC data provided indicates that the HPHCs, arsenic, cadmium, NNK, NNN, and nicotine, are substantially increased in the six Camel Snus products compared to the comparator cigarette smoke.
- The applicant studied approximately 150 biomarkers in these MRTPAs. However, the applicant did not provide a scientific justification for the biomarkers studied or identify which individual biomarkers of exposure and potential harm support each of the requested modified risk claims. The biomarkers of exposure submitted by the applicant include biomarkers for HPHCs such as nicotine, TSNAs, and PAHs. The biomarker data are reported for the six Camel Snus products as a single comparator group, making it difficult to assess which data are specific to each of the six products.
- All Camel Snus products in these MRTPAs are flavored and contain ingredients that may act as permeation enhancers and impact HPHC absorption in users.
- The in vitro genotoxicity assay results indicate that the six Camel Snus products, other comparator smokeless tobacco products, and cigarette smoke are genotoxic to mammalian cells.
- The in vivo toxicity and carcinogenicity studies reported in these MRTPAs contain several shortcomings, including the use of only the native tobacco blend and an extract of the blend for all in vivo assays and significant reduction in feed intake and body weight at high doses. Therefore, these data in the present form have limited utility for the evaluation of the MRTPAs.

C. Clinical Evidence of Disease Risk

Overview of Clinical Studies

RJRT submitted eight U.S. clinical studies (Section 7.4 of the MRTPAs), which are summarized in Appendix B. The studies enrolled literate, English-speaking, generally healthy adult non-pregnant/non-lactating chronic tobacco users and nonusers and employed a variety of designs and product exposures. Study Camel Snus products included three of the proposed MRTPs (Camel Snus 600mg in Frost and

Mellow flavors; Camel Snus 1000mg in Winterchill flavor for few participants in study 04_CSD0904_PMS) and others (not included in the MRTPAs) including Camel Snus 400mg pouches in Frost, Spice and Original flavors. Seven out of the eight submitted studies involved more than one Camel Snus product and allowed participants to choose the specific product(s) they used. Three studies (01_HSD0702_QOL; 03_CSD0901_SSSO; 07_CSD1010_SS) asked participants to switch from cigarette smoking to using Camel Snus over periods of five days up to 52 weeks; three studies (04_CSD0904_PMS; 06_CSD0914_SUL; 08_CSD1101_STM) involved one or a series of laboratory visits to compare differences in biomarkers, health effects and behaviors; and one study (05_CSD0905_SL) aimed to reduce cigarette smoking by introducing dual use with Camel Snus over a period of three weeks.

Several studies submitted in Section 7.4 of the MRTPAs focused on health effects, adverse experiences (AEs), biomarkers of exposure (BOE), and biomarkers of potential harm (BOPH) data. Here we summarize four studies that provided data most relevant to the clinical evaluation of the MRTPAs: 01_HSD0702_QOL, 03_CSD0901_SSSO, 04_CSD0904_PMS, and 07_CSD1010_SS.

Study 01_HSD0702_QOL primarily evaluated the feasibility of measuring changes in respiratory symptoms and biomarkers after switching from cigarette smoking to one of three assigned products (including Camel Snus 400mg pouches in Frost, Spice, and Original flavors) ad libitum for 24 weeks. RJRT concluded that there were no clinically significant changes in spirometry, electrocardiogram (EKG) results, vital signs or oral exams that were related to Camel Snus and no definite improvements in physical health self-report ratings (Standard Form [SF]-36). AEs possibly related and unresolved at study end included buccal tenderness since day 168, increased sputum since day 13 and dry cough requiring drug treatment since day 74. RJRT did not submit bridging information for relevance of this study's findings from a 400mg Camel Snus product to the 600 mg or 1000 mg Camel Snus products that are the subjects of the MRTPAs.

Study 04_CSD0904_PMS was a cross-sectional cohort study that primarily evaluated biomarkers (discussed below) and functional capacity (standard spirometry indices before and after a six-minute walk test [6MWT]) in five cohorts of tobacco product natural adopters and one cohort of non-tobacco users. A single oral examination, an EKG and several vital sign collections were included. There were very minimal changes in spirometry from pre-to post-6MWT. RJRT concluded that the 6MWT may not be a sensitive measure for differentiating among generally healthy consumers of different types of tobacco products.

Study 07_CSD1010_SS was a 52-week switching (from combusted cigarettes) and tobacco product cessation study in which one of the two groups of Camel Snus users (600mg Frost or Mellow) received relative risk information on the day before switching. The study had a low completion rate (33%) and many protocol violations involving product accountability and inaccurate dispensing. Most Camel Snus-exposed subjects were dual users (Camel Snus 71%; Camel Snus + info 67%). Oral AEs in Camel Snus users exceeded those in nicotine replacement therapy (NRT) lozenge users, and included leukoplakia, oral ulceration, mucosal irritation and gum disorders. The following were unresolved, possibly related AEs at study end: three in the Camel Snus + info group (moderate gingivitis since day 21 requiring product cessation, leukoplakia since day 83, pharyngitis since day 83); and one in the Camel Snus group (pharyngitis since day 84). There were no clinically significant mean changes in vital signs, height or weight. None of the isolated or sustained blood pressure elevations during the experimental phase were reported as AEs.

Biomarkers of Exposure (BOE)

In three clinical studies (01_HSD0702_QOL, 03_CSD0901_SSSO, and 04_CSD0904_PMS; Section 7.4 of the MRTPAs), RJRT studied approximately 40 BOE such as thiocyanate, carboxyhemoglobin (COHb), and other biomarkers representing aromatic amines (AAs), mercapturic acid metabolites of select combustion by-products (MAMs), polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), and urine mutagenicity (UM). RJRT considered a reduction in BOE to be consistent with potentially reduced risk of adverse health effects from use of the six proposed MRTP Camel Snus products compared with cigarette smoking, including cancers (Section 2.9.1.2.12 of the MRTPAs).

Study 01_HSD0702_QOL used Camel Snus 400 mg pouches (Frost, Spice, and Original flavors) and provided data from 24 BOE (Clinical Study Report [CSR], Section 11, Table 11-16 [b,d-g], pp. 211, 213-216), but lacked bridging information for relevance to the proposed MRTPs. RJRT reported 4/4 AAs, 6/7 MAMs, 2/2 UM, 4/6 PAHs, 1/1 TSNA, and COHb were lower after 24 weeks of Camel Snus use compared to baseline concentrations from usual brand cigarette smoking. Study 03_CSD0901_SSSO had a primary objective of determining multiple BOE (CSR Table 14.2.3-1, p. 417) and comparing within and between cohorts during baseline usual brand cigarette smoking and after five days of intervention. RJRT concluded that the cohorts who used Camel Snus products (exclusive and dual users) had generally lower concentrations of several BOE: AAs (exclusive and dual users - 4/4), MAMs (exclusive users - 8/8; dual users - 7/8), PAHs (exclusive and dual users - 8/9), TSNAs (exclusive and dual users – 3/4) and UM (exclusive and dual users - 1/1) at Day 5. Thiocyanate and COHb were significantly reduced at Day 5 compared to baseline for exclusive and dual user cohorts. BOE for exclusive Camel Snus users were generally lower compared to the cohort of dual users at Day 5: AAs (4/4), MAMs (8/8), PAHs (7/9), TSNAs (1/4), and UM (0/1). Thiocyanate and COHb were also significantly reduced at Day 5.

Study 04_CSD0904_PMS had a primary objective of determining multiple BOE (CSR, Table 5, p. 78; Table 7, pp. 96-101 of the MRTPAs). A secondary objective was to analyze differences in BOE between the six enrolled cohorts. Camel Snus users reported being natural product adopters of Camel Snus 600 mg Frost and Mellow and Camel Snus 1000 mg Winterchill (n=2-5) flavored products. Data were pooled for all Camel Snus products. RJRT concluded that the cohorts who smoked cigarettes (exclusive and dual use) had generally higher concentrations of most BOE compared to exclusive Camel Snus users (CSR p. 131 of the MRTPAs; AAs: exclusive and dual users – 3/4; MAMs: exclusive and dual users - 6/6; PAHs: exclusive users - 6/9 and dual users - 5/9; and UM: exclusive and dual users - 1/1). Although COHb was significantly reduced in both cohorts, thiocyanate was significantly reduced in exclusive Camel Snus users, but not in dual users compared to cigarette smokers. In addition, RJRT concluded that TSNAs were generally not different between the cohorts who smoked (exclusive and dual users) and exclusive Camel Snus users, but that all three cohorts had lower BOE than other moist snuff users (CSR p. 130). Exclusive cigarette smokers and dual users of cigarettes and Camel Snus were largely not different, except for the reduction of 1/1 UM biomarker, suggesting that prolonged ad libitum dual use of Camel Snus (600 mg products) and cigarettes does not significantly lower tobacco constituent exposure in users, as it did in the confined five-day study. As discussed below in the Biomarkers of Potential Harm section, several specific study design and analysis issues for Study 04_CSD0904_PMS weaken the interpretation of RJRT's findings.

Three peer-reviewed publications provided by the applicant (Section 2.9.1.2.2 of the MRTPAs) assessed NNN and/or NNAL (TSNAs) as BOE after Camel Snus use. After five days of confinement, NNAL-T was not significantly different compared to usual brand smoking (Blank & Eissenberg, 2010; 400 mg pouches Original, Frost and Spice flavors); NNAL (but not NNN) decreased in a four-week smoking cessation trial

(Kotlyar et al., 2011; 400 mg pouches Original, Frost, and Spice flavors); and NNAL and NNN levels were not significantly different from baseline at Week 4 during a 12-week smoking cessation trial (Hatsukami et al., 2016; 1000 mg pouches Robust and Winterchill flavors, but switched to 600 mg pouches Frost and Mellow flavors, if adverse events occurred).

Biomarkers of Potential Harm (BOPH)

Within these MRTPAs, RJRT considers biomarkers of effect, which it defines as early biological effects and alterations in morphology, structure, and function (Section 6.1.2.1 and Figure 6.1.2-1 of the MRTPAs), to be synonymous with biomarkers of potential harm (BOPH). In two clinical studies (01_HSD0702_QOL; 04_CSD0904_PMS), RJRT studied a large number of BOPH that it regarded as being indicative of inflammation, oxidative stress and other physiologic processes. RJRT deemed a reduction in BOPH to be consistent with potentially reduced risk of adverse health effects from the use of the six Camel Snus products compared with cigarette smoking, including cancers, pulmonary disease and cardiovascular disease (Section 2.9.1.2.12 of the MRTPAs).

Study 01_HSD0702_QOL involved a 400mg pouch size of Camel Snus (Frost, Original, or Spice) and provided data from BOPH (CSR, Table 11-18(f), pp 237-238; Table 11-19(f), pp. 248-249; Table 11-22, pp. 258-259; Table 11-23, pp. 260-263 of the MRTPAs), but lacked bridging information to the proposed MRTPs. Study 04_CSD0904_PMS had the primary objective of obtaining levels of multiple BOPH listed in the CSR Table 6 (pp. 84-91 of the MRTPAs) and Table 8 (p. 103 of the MRTPAs). The applicant's secondary objective was to analyze differences in the BOPH measures between the six enrolled cohorts. After statistical analyses, RJRT concluded that the cohorts who smoked cigarettes (exclusive and dual users) had generally higher concentrations of select biomarkers of oxidative stress and inflammation. RJRT reported statistically significant differences for three of the BOPH of inflammation: isoprostane iPF2α-III, intracellular adhesion molecule 1 (ICAM-1), and white blood cells (WBC) (Final CSR, Section 13.1 of the MRTPAs). RJRT found that all three were lower in the exclusive Camel Snus cohort than in the smoking cohorts and higher in the exclusive Camel Snus cohort than in the non-tobacco cohort.

A number of issues with the design and analysis of study 04_CSD0904_PMS do not support RJRT's conclusions. This study as designed, conducted, and analyzed does not support statistical inference, i.e., it is not clear that the results are representative of the general population. Participants' self-selection ("natural adopters") into type of product use may bias the results in ways that cannot be overcome by analytical strategies. FDA review of study 04_CSD0904_PMS, identified that 8% of subjects in the "exclusive Camel Snus" group were self-reported current dual/poly tobacco users and that four BOPH, including WBC, were analyzed from the blood draw only at the screening visit, whereas the rest were drawn only during a 24-hour confinement after an overnight abstinence (~14 to 30 days later). In addition, several subjects reported taking medications (e.g., anti-inflammatory, lipid lowering) that may impact the BOPH results. Finally, making hundreds of comparisons without adjusting for multiplicity allows for the occurrence of multiple false positives, while an underpowered study also promotes the occurrence of false negative results.

Summary and Conclusions

In the studies provided by RJRT, BOE were reported as generally lower in exclusive Camel Snus users compared to exclusive cigarette smokers. In natural product adopters, BOE were lower in exclusive Camel Snus compared to dual users. However, no data were provided for three MRTPA products (Camel Snus Robust 1000mg, Camel Snus Frost Large 1000mg, and Camel Snus Mint 600mg), only a few participants in one study (04_CSD0904_PMS) used Camel Snus Winterchill 1000mg, and RJRT did not

provide bridging information to the proposed MRTP Camel Snus products. Data were not analyzed by pouch size, flavor, or actual use pattern, and potentially important variables (e.g., dwell time for pouches) were not included in the analyses.

The submitted clinical studies did not demonstrate that smokers who switch completely from cigarettes to the six Camel Snus products reduce their overall health risks from smoking or their specific risks of lung cancer, oral cancer, respiratory disease, and heart disease, nor were they designed to do this. RJRT did not define the target population of "smokers who switch completely." Of the eight studies submitted, two (01_HSD0702_QOL; 04_CSD0904_PMS) had primary outcomes evaluating respiratory symptoms and functional capacity but none had primary outcomes for oral cancer, lung cancer, or heart disease. Data were analyzed by assignment which did not always reflect actual use or inclusion criteria. There are no validated BOPH for tobacco-related diseases, and two studies that evaluated BOPH (01_HSD0702_QOL; 04_CSD0904_PMS) lacked either bridging information to the proposed MRTPs or appropriate study design and statistical analyses.

D. Epidemiological Evidence of Disease Risk

This section summarizes the long-term epidemiological evidence on smokeless tobacco use, cigarette smoking, and risks for selected tobacco-related diseases that relate to the proposed modified risk tobacco products.

General Disease Burden

Cigarette Smoking

Among U.S. adults in 2015, more than one in seven (15.1%) were current cigarette smokers and one in five (21.9%) were former smokers (NCHS, 2016; Phillips et al., 2017). Smoking prevalence has declined over time; in 1997, one-quarter (24.7%) of adults were current smokers, whereas in 1965 nearly one in two adults (42%) were current smokers (NCHS, 2016; US DHHS, 2014). More than 30 diseases are causally linked to smoking, including twelve forms of cancer and more than 20 chronic conditions affecting the cardiovascular and respiratory systems, immune function and reproductive health (US DHHS, 2014). Secondhand tobacco smoke exposure has been causally linked to cancer, cardiovascular and respiratory diseases and has adverse consequences on infant and child health (US DSSH, 2014).

From 2005 to 2009, an estimated 440,000 deaths annually were attributable to active cigarette smoking and approximately 40,000 additional deaths were due to secondhand smoke (US DHHS, 2014). The Centers for Disease Control and Prevention (CDC) estimates that annually in the U.S. active smoking causes 131,000 deaths due to lung cancer, 161,000 deaths due to cardiovascular and metabolic diseases, and 113,000 deaths due to pulmonary diseases, including COPD (US DHHS, 2014). In addition, in 2009 U.S. adults lived with an estimated 14 million smoking-related conditions (Rostron et al., 2014).

Smokeless Tobacco Use

In 2015, approximately one in 40 (2.3%) U.S. adults were current users of any smokeless tobacco product, with prevalence higher among males (4.4%) than females (0.2%) (Phillips et al., 2017). From 2002 to 2014, prevalence of past 30-day smokeless tobacco use increased slightly for adults aged 18-25 years (4.8% to 5.6%) and remained stable for adults aged $\geq$26 years (3.2% to 3.0%) (SAMHSA, 2015).

Multiple authoritative reviews by scientific and public health agencies have evaluated evidence for smokeless tobacco use as a cause of disease. Table 7 summarizes these findings. A report on smokeless tobacco published by the National Cancer Institute (NCI) and CDC estimated that in 2008 approximately 1,600 new cases of oral cancer, 500 new cases of pancreatic cancer and 200 new cases of esophageal cancer in the U.S. were attributable to use of all forms of smokeless tobacco use (NCI/CDC, 2014).

Table 7. Conclusions of authoritative reviews on smokeless tobacco use and disease risk (Data Source: Adapted from Section 6.1 of the MRTPAs and review of pertinent evidence by FDA)

Scientific or Public Health Entity	Conclusion for Smokeless Tobacco and Disease
U.S. Surgeon General (US DHHS, 1986)	• "The scientific evidence is strong that the use of snuff can cause cancer in humans. The association between smokeless tobacco use and cancer is strongest for cancers of the oral cavity." • "Smokeless tobacco use is responsible for the development of a portion of oral leukoplakias."
International Agency for Research on Cancer (IARC, 2007a)	• "There is sufficient evidence in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity and pancreas."
Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2008)	• "STP [smokeless tobacco products] are carcinogenic to humans and the pancreas has been identified as a main target organ. All STP cause localised oral lesions and a high risk for development of oral cancer has been shown for various STP but the evidence for oral cancer in users of Swedish moist snuff (snus) is less clear." • "There is inadequate evidence that STP cause lung cancer." • "There is some evidence for an increased risk of fatal myocardial infarction among STP users."
International Agency for Research on Cancer (IARC, 2012)	• "There is sufficient evidence in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas."
National Cancer Institute/Centers for Disease Control and Prevention (NCI/CDC, 2014)	• "There is sufficient evidence that ST products cause addiction; precancerous oral lesions; cancer of the oral cavity, esophagus, and pancreas; and adverse reproductive and developmental effects including stillbirth, preterm birth, and low birth weight." • "The evidence suggests that some, but not all, ST products are associated with increased risk of fatal ischemic heart disease, fatal stroke, and type 2 diabetes." • "There is insufficient evidence to assess whether ST products are associated with increased risks of lung cancer, cervical cancer, and hypertension."

Overview of Evaluation of the Epidemiological Evidence

We summarize epidemiological evidence on smokeless tobacco use, cigarette smoking, and risk for selected tobacco-related diseases to assess the MRTPAs. A wide variety of smokeless tobacco products are used around the world, with varying product characteristics, use patterns and health effects (NCI/CDC, 2014). In Section 6.1.1 of the MRTPAs, RJRT presents epidemiological evidence for U.S. smokeless tobacco use and for Scandinavian snus use. The applicant explains:

> "Within each outcome, evidence is presented separately for studies conducted in U.S. populations and Scandinavian populations, because U.S. and Scandinavian smokeless tobacco products are not identical. However, given that Camel Snus is a Swedish style snus product in regards to tobacco type, formulation, portion size, production methods, and comparative chemistry, the epidemiology regarding the health effects of snus for Swedish cohorts is considered relevant for evaluating the health risks to US users of Camel Snus." (Section 4.1 of the Ramboll/Environ literature review, page 6)

Data on tobacco product HPHC yields indicates that cadmium, a toxic metal, and NNN and NNK, potent TSNAs, in the six Camel Snus products exceed those of Swedish snus products sold in the U.S. and are in the range of, or somewhat lower than, levels for other U.S. moist snuff and loose leaf tobacco products and are much lower than the levels for dry snuff products (see Table 2). Exposure to toxic metals is linked to cardiovascular disease, while TSNAs contribute to multiple forms of cancer (see Table 4; IARC, 2007a; Solenkova et al. 2014). For selected health outcomes including cancers and circulatory diseases, we highlight the evidence from U.S. studies of smokeless tobacco use, while data are presented for both U.S. and Swedish studies (Table 8). Evidence from both regions provides generally similar conclusions when compared to the health risks associated with cigarette smoking. Nicotine is present in all forms of smokeless tobacco and HPHC testing indicates that nicotine and free nicotine in Camel Snus products are somewhat lower than the levels in Swedish snus sold in the U.S. and other moist snuff and are higher than the levels in loose leaf and dry snuff (Table 2). Nicotine exposure is understood to contribute to risk of adverse pregnancy outcomes and type 2 diabetes; thus, for these outcomes, we report on evidence from U.S. and Swedish studies (see Table 4; US DHHS, 2014). Our evaluation focuses on estimates of smokeless tobacco use and disease risk from more recent published meta-analyses rather than individual study estimates, since we generally consider summary relative risk estimates to be more robust. While most of the evidence we present was submitted by the applicant in Section 6.1.1 of the MRTPAs and supporting reports, we identify where we include additional peer-reviewed studies, omitted from the applicant's literature review or published after that review was conducted. The estimates from these more recent studies are generally consistent with the summary risk estimates produced from the meta-analyses.

There are several general considerations regarding the epidemiological evidence presented below. The information on disease risks pertains to smokeless tobacco products generally—including products referred to in the literature as chewing tobacco, snuff, dip, or spit; the applicant did not present, nor are we are aware of, long-term epidemiological studies pertaining to the six Camel Snus products specifically. In addition, much of the available U.S. evidence on smokeless tobacco and disease risk relies on three cohorts: First National Health and Nutrition Examination Survey (NHANES-I) Epidemiologic Followup Study (NHEFS) (Accortt et al., 2002), the Cancer Prevention Study (CPS)-I, and CPS-II (Henley et al. 2005; 2007) (see Appendix C for study summaries). Among studies that reported multiple risk estimates, we generally prioritized estimates pertaining to current (or ever) exclusive smokeless tobacco users (i.e., never smokers) and estimates that adjust for the greatest numbers of potential confounders. Finally, other than adverse pregnancy outcomes, the available literature generally focuses on the health effects that were studied in male smokeless tobacco users.

To our knowledge, Henley et al. (2007) is the only study that examined disease risk among adults who became exclusive smokeless tobacco users at the time of or after quitting exclusive smoking. In Henley et al. (2007), disease risks from CPS-II participants were directly compared to risks for two groups: (1) exclusive former smokers (i.e., quit all tobacco products) and (2) those who never used tobacco. However, Henley et al. (2007) did not compare risks among switchers to risks among continuing smokers, which would have provided additional, relevant evidence to evaluate the MRTPAs.

In the sections below, we summarize epidemiological evidence on tobacco use and risk of lung cancer, respiratory disease, oral cancer and heart disease, the four disease-specific endpoints identified by the applicant in the MRTPAs. (Appendix D describes health conditions included in the studies that evaluated these four endpoints.) For each endpoint, disease risk information is presented for:

- smokeless tobacco users compared to non- or never users
- cigarette smokers compared to never smokers
- former smokers who switched to smokeless tobacco use compared to former smokers who quit all tobacco and compared to never tobacco users

Finally, we present evidence on selected other disease-specific endpoints and tobacco product use patterns that relate to additional modified risk information identified across the three advertising executions.

Selected Health Risks Among Smokeless Tobacco Users Compared to Non-Users of Tobacco

In its applications, RJRT reports on published systematic reviews and meta-analyses that examined smokeless tobacco use and risk of lung cancer (Section 6.1.1.3.1 of the MRTPAs), oral cancer (Section 6.1.1.3.4 of the MRTPAs), and heart disease (Section 6.1.1.3.3 of the MRTPAs) in both U.S. and Nordic populations (Boffetta et al., 2008; Boffetta & Straif, 2009; Lee, 2007; Lee & Hamling, 2009a). Table 8 summarizes findings from these four meta-analyses. No meta-analyses for respiratory diseases were identified (Section 6.1.1.3.2 of the MRTPAs).

Lung cancer

Boffetta et al. (2008) reported an elevated but non-significant association for lung cancer mortality among exclusive ever U.S. smokeless tobacco users (RR=1.8, 95%CI=0.9-3.5, n=3 studies) compared to never users of tobacco. Results reported by Lee and Hamling (2009a), restricted to studies of smokeless tobacco users who never smoked, were consistent (RR=1.79 95%CI=0.91-3.51, n=3). A more recent U.S. cohort study not included in either meta-analysis nor cited in the applications examined cancer risk and tobacco use in the Agricultural Health Study (AHS), a prospective cohort of 90,000 pesticide applicators and their spouses followed from 1993-97 to 2011 (Andreotti et al., 2017). Ever exclusive use of smokeless tobacco was associated with increased lung cancer incidence (HR=2.21, 95%CI=1.11-4.42) compared to never users of tobacco, although few lung cancer cases occurred among smokeless tobacco users (n=10), exposure was measured as exclusive ever smokeless use (not current use), and tobacco use status and confounders were assessed at baseline only (Andreotti et al., 2017).

Oral cancer

Boffetta et al. (2008) reported an increased risk of oral cancer among ever U.S. smokeless tobacco users (RR=2.6, 95%CI=1.3-5.2, n=9) compared to non-users (never or non-current users) of tobacco. It was previously noted that two of the estimates included in the Boffetta et al. summary relative risk from a study by Stockwell and Lyman (1986) likely did not adjust for smoking and consequently may have produced considerably larger risk estimates than would have been observed with adjustment (Lee & Hamling, 2009b). FDA previously re-analyzed the data omitting the two estimates from Stockwell and Lyman and produced a summary relative risk for the other seven estimates of 2.16 (95%CI=1.08-4.33) (FDA, 2017). Results from Lee and Hamling (2009a) restricted to studies of smokeless tobacco users who never smoked also indicated an increased risk of oropharyngeal cancer (RR=3.33, 95%CI=1.76-6.32, n=5), while summary relative risks for the overall data (RR=2.16, 95%CI=1.55-3.02, n=31) and for studies that adjusted for smoking (RR=1.65, 95%CI=1.22-2.25, n=12) were somewhat lower.

A more recent study not included in either meta-analysis relied on data for 11 U.S. case-control studies of head and neck cancers from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, which evaluated associations with U.S. smokeless tobacco use (Wyss et al., 2016). The

studies were conducted between 1981 and 2006 and included in total approximately 6,700 cases and 8,400 controls. In analyses stratified by tumor site, restricted to never smokers, and adjusted for duration of other combustible product use and demographics, Wyss et al. (2016) reported significant elevated associations for oral cavity cancer among ever snuff users who never smoked (OR=3.01, 95%CI=1.63-5.55) and among chewing tobacco users who never smoked (OR=1.81, 95%CI=1.04-3.17) compared to never users of those products, although the numbers of exposed cases were small (n=20 and n=23, respectively). Zhou et al. (2013) identified approximately 1000 cases of head and neck squamous cell carcinoma from medical facilities in Boston, matched to approximately 1,200 controls selected from the Massachusetts town books. Restricting the analysis to oral cavity cancer, Zhou et al. (2013) reported an elevated but non-significant association among ever users of smokeless tobacco for $\geq$10 years (OR=2.88, 95%CI=0.68-12.25) versus never users, adjusting for smoking, alcohol use and demographic characteristics, although the number of exposed cases was small (n=4).

Heart disease

Boffetta and Straif (2009) reported an increased risk of fatal heart disease (myocardial infarction) among exclusive ever U.S. smokeless tobacco users (RR=1.11, 95%CI=1.04-1.19, n=3) compared to never users of tobacco. Lee (2007) reported an elevated but non-significant risk of heart disease among U.S. smokeless tobacco users (RR=1.14, 95%CI=0.96-1.34, n=3). Both studies relied on the same three U.S. cohorts (NHANES-I/NHEFS, CPS-I and CPS-II) although different estimates from the original studies were prioritized by the authors of each meta-analysis. A more recent U.S. cohort study not included in either meta-analysis nor cited in the applications examined mortality risk and smokeless tobacco use in the National Longitudinal Mortality Study (NLMS), which included adults who completed any Tobacco Use Supplement to the Current Population Survey (TUS-CPS) cycle between 1985 and 2011 and were followed through 2011 (Timberlake et al., 2017). Timberlake et al. reported that exclusive current smokeless tobacco users had increased mortality risks for coronary heart disease (hazard ratio (HR)=1.24, 95%CI=1.05-1.46) compared to never tobacco users, although the study could not adjust for other heart disease risk factors including exercise and diet.

Table 8. Selected results from published systematic review/meta-analyses of health effects associated among smokeless tobacco users compared to non-users of tobacco[a] (Data Source: Sections 6.1.1.3.1, 6.1.1.3.3 and 6.1.1.3.4 of the MRTPAs)

	Lung Cancer		Oral Cancer		Heart Disease	
Publication	U.S. Studies RR (95%CI)	Scandinavian Studies RR (95%CI)	U.S. Studies RR (95%CI)	Scandinavian Studies RR (95%CI)	U.S. Studies RR (95%CI)	Scandinavian Studies RR (95%CI)
Lee (2007)[b]	n/a	n/a	n/a	n/a	1.14 (0.96-1.34)	1.06 (0.83-1.37)
Boffetta et al. (2008)	1.8 (0.9-3.5)	0.8 (0.6-1.0)	2.6 (1.3-5.2)	1.0 (0.7-1.3)	n/a	n/a
Lee and Hamling (2009a)	1.22 (0.82-1.83)[d] 1.38 (0.72-2.64)[e] 1.79 (0.91-3.51)[f]	0.71 (0.66-0.76)[d] 0.71 (0.66-0.76)[e] 0.82 (0.52-1.28)[f]	2.16 (1.55-3.02)[d] 1.65 (1.22-2.25)[e] 3.33 (1.76-6.32)[f]	0.97 (0.68-1.37)[d] 0.97 (0.68-1.37)[e] 1.01 (0.71-1.45)[f]	n/a	n/a
Boffetta and Straif (2009)[c]	n/a	n/a	n/a	n/a	1.11 (1.04-1.19)	1.27 (1.07-1.52)

[a] Appendix E provides the citations for the studies used to produce the summary relative risk estimates in the meta-analyses.
[b] Results reported are for the random-effects models reported in Lee (2007); disease endpoint is referred to as "IHD or AMI".
[c] The disease endpoint is referred to as "fatal myocardial infarction" in Boffetta and Straif (2009).
[d] This estimate pertains to the "overall data" results reported in Lee and Hamling (2009a).
[e] This estimate pertains to the "smoking-adjusted" results reported in Lee and Hamling (2009a).
[f] This estimate pertains to the "never smokers" results reported in Lee and Hamling (2009a).
Note: the applicant did not provide, nor are we aware of, published meta-analysis results for smokeless tobacco use and respiratory disease.
RR is relative risk produced as the summary estimate; 95%CI is the 95% confidence interval for the summary estimate; n/a is not available.

Respiratory diseases

Two articles drawing on three U.S. cohorts examined exclusive smokeless tobacco use and fatal respiratory disease (Section 6.1.1.3.2 of the MRTPAs). Accortt et al. (2002) used data from the NHANES-I/NHEFS cohort, while Henley et al. (2005) relied on CPS-I and CPS-II (Appendix C provides study details). Accortt et al. (2002) reported no association between respiratory disease and ever exclusive smokeless tobacco use for males (HR=0.9, 95%CI=0.3-2.5) or females (HR=0.6, 95%CI=0.1-2.3) compared to non-users of tobacco. Similarly, analyses of CPS-II found no association between current exclusive smokeless tobacco use and mortality due to respiratory system diseases (HR=1.11, 95%CI=0.84-1.45), COPD (HR=1.28, 95%CI=0.71-2.32) or influenza/pneumonia (HR=0.85, 95%CI=0.71-2.32), compared to never tobacco users (Henley et al., 2005). Results from CPS-I indicated that current exclusive smokeless tobacco use was associated with increased overall respiratory system disease mortality (HR=1.28, 95%CI=1.03-1.59) and COPD mortality (HR=1.86, 95%CI=1.12-3.06) but not influenza/pneumonia mortality (HR=1.16, 95%CI=0.88-1.51) compared to never tobacco users (Henley et al., 2005).

Selected Health Risks for Cigarette Smoking Compared to Never Smokers

The preceding section presented evidence on selected health risks for smokeless tobacco use compared to non-users of tobacco. Here we briefly report on mortality risk estimates for the same conditions for U.S. smokers compared to never smokers based on findings from the CPS-II referenced in Section 6.1.1.2 of the MRTPAs and presented in the 2014 U.S. Surgeon General's Report (US DHHS, 2014). According to CPS-II, among male current smokers, the relative risk (RR) for lung cancer is 23.26, the RRs for respiratory diseases associated with COPD are 17.10 for bronchitis/emphysema, and 10.58 for chronic airway obstruction, the RR for lip/oral cavity/pharynx cancer is 10.89, and the RR for ischemic heart disease is 2.80 for males aged 35-64 years and 1.51 for males aged ≥65 years (Appendix F).

Selected Health Risks for Switching from Cigarettes to Smokeless Tobacco Use

In Section 6.1.1.5 of the MRTPAs, RJRT presents data on selected mortality risks for male former smokers who switched to U.S. smokeless tobacco products at the time of or after quitting exclusive cigarette smoking (Henley et al., 2007). To our knowledge, Henley et al. (2007) is the only study that examined disease risk associated with sequential product use (i.e., those who first exclusively smoked, and subsequently exclusively used smokeless tobacco). Table 9 summarizes study characteristics of Henley et al. (2007).

Table 9. Summary of study characteristics for Henley et al. (2007) (Data Source: Section 6.1.1.5 of the MRTPAs)

Study Characteristic	Description
Study population	Male participants of Cancer Prevention Study (CPS)-II cohort; included at baseline, those reporting to be: - Former exclusive cigarette smokers (previously smoked cigarettes and no other product) - Current smokeless tobacco users who began using smokeless tobacco at time of or after quitting exclusive smoking (i.e., "switchers") - Never users of any tobacco
Study period	1982-2002; 20 years of follow up
Age at baseline	≥30 years
Study size (approximate)	112,000 former exclusive cigarette smokers (i.e. quit all tobacco use) 4,000 current exclusive smokeless tobacco users who previously smoked cigarettes (i.e., "switchers") 112,000 never users of any tobacco product
Smokeless tobacco type	Smokeless tobacco, chewing tobacco, snuff
Exposure ascertainment	Tobacco use status ascertained from questionnaire completed at baseline. Full cohort was not re-interviewed for potential changes in tobacco use status over time.
Mortality Outcomes (ICD-9)	Referent group: quit all tobacco: Lung cancer (162), oral cancer (140-149), COPD (490-492, 496), coronary heart disease (410-414), stroke (430-438), all causes Referent group: never tobacco users: Lung cancer, COPD, coronary heart disease, stroke
Outcome ascertainment	-From 1982-88, through personal inquiries from volunteers of American Cancer Society and reported deaths verified by death certificate -From 1988-2002, through automated linkage with the National Death Index
Measure	Hazard ratio
Adjustment factors	Age, number of cigarettes formerly smoked per day, number of years smoked cigarettes, age at which participant quit smoking, race, educational level, BMI, exercise level, consumption of: alcohol, fat, fruit/vegetables, aspirin intake, employment type, employment status

Henley et al. (2007) reported on mortality risks among former smokers who had switched to any smokeless tobacco at the time of or after quitting exclusive cigarette smoking (i.e., "switchers") compared to those who quit all tobacco use. After twenty years of follow-up, switchers had higher rates of death than quitters for lung cancer (hazard ratio (HR)=1.46, 95%CI=1.24-1.73), heart disease (HR=1.13, 95%CI=1.00-1.29), oral cancer (HR=2.56, 95%CI=1.15-5.69), stroke (HR=1.24, 95%CI=1.01-1.53) and all causes (HR=1.08, 95%CI=1.15) (Table 10). Henley et al. (2007) also reported on mortality risks among switchers compared to never users of tobacco. Switchers had higher rates of death than never users for lung cancer (HR=5.61), heart disease (HR=1.28), COPD (HR=3.24) and stroke (HR=1.34); results for fatal oral cancer and all-cause mortality were not presented (Table 10). Henley et al. (2007) did not compare risks among switchers to risks among continuing smokers, which would have provided additional relevant evidence to evaluate the MRTPAs.

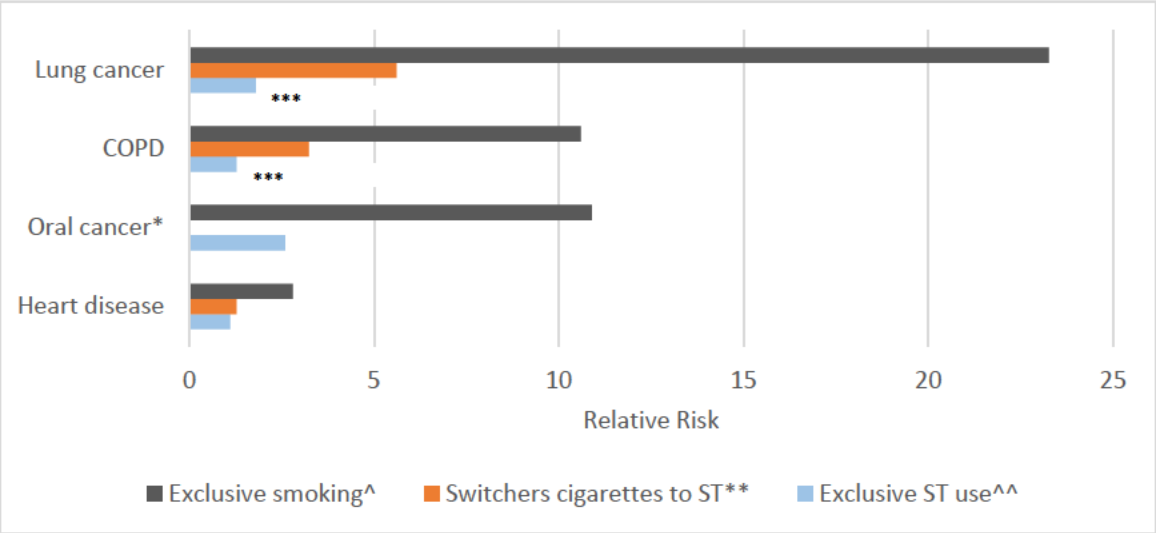
Table 10. Study results for Henley et al. (2007) (Data Source: Section 6.1.1.5 of the MRTPAs)

Disease Outcome (mortality)	Switchers vs Former Smokers (Quit All Tobacco) (HR, 95%CI)	Switchers vs Never Tobacco Users (HR)[a]
Lung cancer	1.46 (1.24-1.73)	5.61
COPD	1.31 (0.96-1.78)	3.24
Oral cancer	2.56 (1.15-5.69)	[b]
Coronary heart disease	1.13 (1.00-1.29)	1.28
Stroke	1.24 (1.01-1.53)	1.34
All-cause mortality	1.08 (1.01-1.15)	[b]

[a] Numerical values for 95% confidence intervals (CIs) were not reported for estimates of switchers versus never tobacco users in Henley et al. 2007, Figure 1; results were statistically significant for each of the four disease endpoints based on the vertical line corresponding to the 95%CI for each HR in Figure 1 not including 1.0.
[b] Results were not reported for risks of fatal oral cancer or all-cause mortality among switchers compared to never tobacco users in Henley et al. (2007).
Note: HR is hazard ratio

Henley et al. (2007) noted that switchers tended to begin smoking at a younger age and quit smoking at a later age compared to those who quit tobacco entirely, although both groups had previously smoked roughly the same number of cigarettes per day (CPD). At baseline, switchers had used smokeless tobacco for nine years on average. Compared to former smokers who quit using tobacco entirely, switchers tended to be less educated and more likely to work in blue-collar employment. While the analyses adjusted for these and other factors, the possibility of residual confounding could not be ruled out in explaining part or all the observed findings. Exposure misclassification may have occurred since tobacco use was only ascertained at baseline. A follow-up study of a subset of cohort members found that smoking relapse at 10 years from the time tobacco use status was reported was generally low, but higher among switchers than those who quit using tobacco entirely, although the study authors considered their estimates to be relatively robust to any potential misclassification.

Figure 2. Disease-specific relative risks for mortality for exclusive smokers, switchers from cigarettes to smokeless tobacco and exclusive smokeless tobacco users, and the common referent group is non-users of tobacco, U.S. males (Source: Section 6.1.1.5 of the MRTPAs)



*Henley et al. (2007) did not provide information on oral cancer morality risks for former smokers who switched to smokeless tobacco products at the time of or after quitting exclusive cigarette smoking as compared to never tobacco users.
^Exclusive current cigarette smoking relative risks (RRs) as compared to never smokers obtained from CPS-II; heart disease relative risk for male current cigarette smokers aged 35-64 years only; this information is reported in Appendix F of this document.
**RRs for former smokers who switched to smokeless tobacco (ST) products at the time of or after quitting exclusive cigarette smoking, as compared to never tobacco users, obtained from Henley et al. (2007); this information is also reported in Table 10 of this document.
^^RRs for exclusive smokeless tobacco use compared to non-users of tobacco for lung cancer obtained from Boffetta et al. (2008); for chronic obstructive pulmonary disease (COPD) obtained from Henley et al. (2005) for CPS-II; for oral cancer obtained from Boffetta et al. (2008); for heart disease from Boffetta and Straif (2009); this information is also reported in Table 8 of this document.
*** RR estimates for lung cancer and COPD among exclusive smokeless tobacco users compared to non- or never users are not statistically significant.
Notes: This figure modifies Figure 6.1.1-1 of Section 6.1.1.5 of the MRTPAs by using alternative estimates, as described above, for disease risks among smokeless tobacco users compared to non-users.

Figure 2 summarizes the disease-specific relative risk estimates among males only that were presented in the previous sections (see Tables 8 and 10, and Appendix F). Estimates are reported by tobacco use status for exclusive cigarette smoking (compared to never smoking), switching from former exclusive smoking to exclusive smokeless tobacco use (compared to never tobacco use) and exclusive smokeless tobacco use (compared to never tobacco use).

<u>Selected Other Health Outcomes and Smokeless Tobacco Use</u>

In this section, we present evidence on selected other disease-specific endpoints and tobacco product use patterns that relate to additional modified risk information identified across the three advertising executions.

Other forms of cancer and other circulatory diseases

In Section 6.1.1.4.1 of the MRTPAs, RJRT presents evidence on additional cancer risks among users of U.S. smokeless tobacco products, Swedish snus, and U.S. smokers, as compared to non-tobacco users, relying on information presented in the Lee and Hamling (2009a) meta-analysis on smokeless tobacco use and tobacco-related cancers. As part of that analysis, Lee and Hamling (2009a) compared the

summary relative risks they estimated for U.S. smokeless tobacco users and Swedish snus users to risks for U.S. male current cigarette smokers based on data from CPS-II. In Table 6.1.1-3 of the MRTPAs, RJRT presented the smoking-adjusted smokeless tobacco summary relative risks. Based on studies of U.S. smokeless tobacco users that adjusted, Lee and Hamling (2009a) reported an elevated association with cancer of the larynx (RR=2.01, 95%CI=1.15-3.15) and not find associations with cancer of the esophagus, pancreas, bladder or kidney. Boffetta et al. (2008) which also examined esophageal and pancreatic cancer risks did not find associations in studies of U.S. smokeless users. Lee and Hamling (2009a) did find in U.S. studies that restricted to never smokers, use of smokeless tobacco elevated the risk of kidney cancer (RR=4.80, 95%CI=1.18-19.56, n=1 study), and overall cancer (RR=1.10, 95%CI=1.01-1.20, n=4). For each cancer endpoint, Lee and Hamling (2009a) found relative risks were higher for exclusive smokers (compared to never users), than for smokeless tobacco users (compared to never users), with the exception of kidney cancer risks in the single study on never smokers.

In Section 6.1.1.4.5 of the MRTPAs, RJRT presents evidence on health risks for cerebrovascular disease (stroke) among U.S. smokeless tobacco users. A systematic review by Boffetta and Straif (2009) reported an increased risk of fatal stroke among U.S. smokeless tobacco users (RR=1.39, 95%CI=1.22-1.60, n=3) compared to non-users. Stroke results reported by Lee (2007) were consistent (RR=1.41, 95%CI=1.17-1.71, n=3). Both studies relied on three U.S cohorts: NHANES-I/NHEFS; CPS-I; CPS-II. As reported in Table 10, mortality risk for stroke among former smokers who had switched to smokeless tobacco (i.e., "switchers"), were significantly increased (RR=1.24, 95%CI=1.01-1.53) compared to former smokers (Henley et al., 2007). Switchers also had higher risks of fatal stroke (RR=1.34) compared to never users (Henley et al., 2007). According to CPS-II, among current smokers, the RR for stroke is 3.27 for males aged 35-64 years and 1.63 for males aged $\geq$65 years compared to never smokers (Appendix F).

Adverse pregnancy outcomes

In Section 6.1.1.6 of the MRTPAs, RJRT presents evidence related to smokeless tobacco use and pregnancy and birth outcomes. The applicant cites a review by Lee (2014) that reported that exclusive Swedish snus users had increased risks for preterm birth, still birth, small for gestational age, and infant apnea, compared with never users. In Section 6.1.1.8.2 of the MRTPAs, RJRT cited a review by Inamdar et al. (2015) that assessed use of smokeless tobacco use during pregnancy in nine studies from many geographic regions, including the U.S., Sweden, Asia and South Africa. Those studies had found associations with smokeless tobacco use and preterm birth, still birth, small for gestational age, and low birth weight (Inamdar et al., 2015).

Type 2 Diabetes

Section 6.1.1 of the MRTPAs did not include evidence related to possible associations between smokeless tobacco use and risk of type 2 diabetes. A recent U.S. cohort study that evaluated tobacco use status and insulin resistance (IR) and type 2 diabetes incidence reported that in cross-sectional analyses at baseline, current smokeless tobacco users had higher levels of biomarkers of IR, specifically glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR), after adjusting for other risk factors; however, associations were not reported for insulin resistance by dose or intensity of smokeless tobacco use (Keith et al., 2016). In addition, an association was reported between type 2 diabetes and former smokeless tobacco use in longitudinal analyses with 10 years of follow-up that adjusted for age, sex and race/ethnicity (HR=3.18, 95%CI=1.72-5.86, n=12 events) but not in models that adjusted for additional confounders (Keith et al., 2016). A pooled meta-analysis of five cohort studies of Swedish snus users reported that current snus use was associated with an increased risk of type 2

diabetes (pooled HR= 1.15, 95%CI=1.00-1.32) compared to never users (Carlsson et al., 2017). Among those with high levels of snus consumption (≥7 boxes/week), the risks were greater (pooled HR: 1.68, 95%CI=1.17-2.41) (Carlsson et al., 2017).

Health Risks Associated with Dual Use of Cigarettes and Smokeless Tobacco

In Section 6.1.1.6 of the MRTPAs, RJRT presents information pertaining to dual use of cigarettes and smokeless tobacco, which they describe as concurrent use of both tobacco products. The applicant cited two U.S. studies that examined dual user risks for lung cancer, all cancer and heart disease (Accortt et al., 2002), and oral cancer (Winn et al. 1981). For lung cancer, mortality risks were similarly elevated (based on confidence interval overlap) for dual users (ever smokeless tobacco and current smokers) and current exclusive smokers (HR=33.9, 95%CI=8.0-143.7 and HR=24.7, 95%CI=8.3-73.5, respectively) where the common referent group was non-tobacco users (Accortt et al., 2002). For all cancer, mortality risks were also similarly elevated for dual users and current exclusive smokers (HR=2.2, 95%CI=1.2-3.7 and HR=1.8, 95%CI=1.1-3.1, respectively) (Accortt et al., 2002). For heart disease, mortality risks were elevated for exclusive smokers (HR=1.5, 95%CI=1.1-2.1), whereas no association was reported for dual users (HR=0.8, 95%CI=0.5-1.5) (Accortt et al., 2002). For oral cancer, among white females, relative risks for dual use of smokeless tobacco and cigarettes were similarly elevated to the risks among exclusive smokers (RR=3.3, 95%CI=1.4-7.8 and RR=2.9, 95%CI=1.8-4.7), where the common reference was never users of either tobacco product (Winn et al., 1981). More recently, in analyses of the Agricultural Health Study by Andreotti et al. (2016) that was described previously, risks for total cancers, smoking-related cancers, gastrointestinal cancers, urinary cancers and head and neck cancers for U.S. smokeless tobacco users who currently smoked were not significantly different as compared to the risks of exclusive smokers, with the exception of lung cancer (HR=0.50, 95%CI=0.27-0.92, n=14 cases). A review of the Swedish literature by Lee (2014) assessed risk of circulatory diseases, cancers, pregnancy-related conditions and chronic inflammatory diseases in dual users, users of only snus or only cigarettes, and never users. Lee (2014) conducted tests for interactions and did not find evidence of significant interactions associated with dual use. However, the findings from Lee (2014) also indicated consistently across different disease endpoints that disease risks for dual users were not significantly different from those of smokers only.

Related to dual use behaviors is the potential for smokers to cut back on cigarettes and use smokeless tobacco but without completely quitting smoking. Health outcomes associated with this use pattern were not addressed in Section 6.1.1 of the MRTPAs. Epidemiological studies evaluating disease risk associated with reductions in smoking intensity have been inconsistent. For example, some studies have observed significant reductions in lung cancer risk associated with >50% reduction in CPD (Godfredsen et al., 2005; Song et al., 2008). However other studies did not observe a change in disease or mortality risk with reduction in smoking intensity (Godtfredsen et al., 2002; Godtfredsen et al., 2003; Hart et al., 2013; Tverdal et al., 2006). The lack of consistent findings may be due, in part, to variations in definitions of smoking reduction, differences in the dose-response relationship by disease endpoint, and the potential for smoking compensation among self-reported reducers across published studies.

Summary and Conclusions

In this section we summarize the applicant's conclusions and assess the evidence presented by the applicant to support the MRTPAs. In Section 6.1.1 of the MRTPAs, RJRT states its conclusions in support of the proposed modified risk claims relating to lung cancer, respiratory disease, oral cancer and heart disease:

> "…results from the studies included in the Ramboll Environ systematic, critical review of the relevant epidemiological literature on the risks of lung and oral cancers, respiratory disease, and cardiovascular diseases, specifically coronary heart disease, among users of snus and other ST products compared with cigarette smokers and never or non-users of tobacco products provide evidence to support the modified risk advertising that switching completely from cigarette smoking to the exclusive use of Camel Snus will significantly reduce the risk for these four health outcomes. The available data provide no consistent support for an increased risk associated with ST use for these health outcomes compared with non- or never-users of tobacco; and studies that indicate an increased risk suffered from methodological flaw and/or reflected use of historic ST products having higher levels of potentially harmful constituents." (Section 6.1.1 of the MRTPAs, page 13).

We evaluated the epidemiological evidence on smokeless tobacco use, cigarette smoking and risks for lung cancer, respiratory disease, oral cancer and heart disease. Since we are not aware of long-term epidemiological studies pertaining to the six Camel Snus products specifically, we relied on studies of smokeless tobacco products generally. In summarizing the risks associated with exclusive smokeless tobacco use, we highlighted estimates from studies of U.S. users that were primarily derived from meta-analyses. The evidence on smokeless tobacco risks from the U.S. literature is generally consistent with the Swedish literature in terms of finding lower risks of disease for conditions including lung cancer and COPD. We do note that there are few published long-term prospective studies of U.S. smokeless tobacco use and disease; NHANES-I/NHEFS, CPS-I and CPS-II provide much of the epidemiological evidence for disease risks among exclusive U.S. smokeless tobacco users. While these three cohorts had relatively large sample sizes of smokeless tobacco users, they still have fewer users than studies of smokers; thus, the smokeless tobacco studies typically have longer follow-up in order for sufficient numbers of disease events to occur. Extended follow-up has the potential to misclassify tobacco exposure and weaken associations between smokeless tobacco use and risk of disease. In addition, the studies may not have fully controlled for confounding at baseline and lacked information on time-varying confounders.

To our knowledge, Henley et al. (2007) is the only study that examined disease risks among those who began using smokeless tobacco at the time of or after quitting exclusive cigarette smoking and directly compared those risks to former smokers who quit tobacco entirely and to never tobacco users. Henley reported that after 20 years of follow-up, switchers had higher risks of death from any cause (HR=1.08, 95%CI=1.01-1.15), lung cancer (HR=1.46, 95%CI=1.24-1.73), coronary heart disease (HR=1.13, 95%CI=1.00-1.29) and stroke (HR=1.24, 95%CI=1.01-1.53) than those who quit using tobacco entirely. Switchers also had higher risks of death due to lung cancer, COPD, coronary heart disease and stroke than never tobacco users. Henley et al. (2007) did not compare risks among switchers to those of continuing smokers, which would have provided additional, relevant evidence to evaluate the MRTPAs. The applicant also presented findings from a meta-analysis by Lee (2013) that produced summary relative risks for heart disease among snus users who formerly smoked; however, the original studies did not necessarily restrict analyses to those who first stopped smoking and then initiated snus use and thus may have measured the effects of dual use. In the review, Lee (2013) also reconstructed disease associations between "switchers" and former smokers or non-tobacco users when risk estimates for those referent groups were not directly estimated in the original study.

This section has reviewed epidemiological evidence for lung cancer, respiratory disease, oral cancer and heart disease risk according to tobacco use status. Many adverse health consequences are caused by

the inhalation of the complex mixture of chemicals and toxicants created by combustible tobacco products. Smokeless tobacco is not combusted and not inhaled and thus generally presents fewer routes of exposure and exposure to fewer numbers of toxicants than tobacco smoke. These factors contribute to observed differences in long-term risks of fatal lung cancer and fatal respiratory diseases, including COPD, between cigarette smokers and smokeless tobacco users, as summarized below.

For smokers who use combustible tobacco products, then quit using them, the potential size and rate of decline in risk following cessation varies by disease. Any potential reductions in disease risk are affected by previous smoking exposure, including time since smoking cessation, age at quitting, and duration of smoking, as well as other individual behavioral, environmental and other risk factors. The Agency for International Research on Cancer (IARC) synthesized available evidence on reversal of disease risk after quitting smoking (IARC, 2007b). For lung cancer, on average, lower risks for quitters were observed in five to nine years compared to continuing smokers, although compared to never smokers, risks for quitters persisted decades after cessation (IARC, 2007b). For respiratory conditions, accelerated loss of lung function generally slowed after quitting smoking and within five years after cessation became similar to the declines observed in never smokers, while COPD mortality rates gradually declined among quitters compared to continuing smokers but remained elevated compared to never smokers, which may reflect effects of quitting due to disease symptoms (IARC 2007b). The findings of the IARC review are less clear for oral cancer and heart disease in the context of the MRTPAs, since these conditions are associated with exclusive use of smokeless tobacco among those who have never smoked. For oral cancer, risks among quitters were similar to never smokers around ten years after cessation, while for heart disease risks among quitters declined by approximately one-third in the initial two to four years after cessation compared to continuing smokers (IARC, 2007b).

With respect to lung cancer, epidemiological evidence suggests that risks are substantially elevated among exclusive cigarette smokers (compared with never users) and risks are elevated but much lower among former smokers who switched to smokeless tobacco at the time of or after quitting exclusive cigarette smoking (i.e., “switchers”) (compared to never tobacco users). Switchers also had higher lung cancer risk than quitters. Although certain nitrosamine levels are comparable or elevated in smokeless tobacco users compared to smokers, lung cancer has not been conclusively linked to exclusive smokeless tobacco use, and in CPS-II, which found an association, the size of the risk is considerably smaller than the risk for smokers. These risks according to tobacco use status are consistent with the mechanistic bases for combustible tobacco use to cause lung cancer and are generally consistent with available information on lung cancer risk reduction after smoking cessation.

For respiratory diseases, specifically COPD, risks are substantially elevated among exclusive cigarette smokers (compared with never users) and risks are increased but much lower among switchers (compared to never tobacco users). Switchers were reported to have COPD risks that were comparable to risks of former smokers who quit tobacco entirely. In addition, there is no consistent evidence that risks of COPD or other respiratory diseases are elevated among exclusive smokeless tobacco users as compared to never tobacco users. These risks according to tobacco use status are consistent with combustible tobacco use as a cause of COPD as well as the available information on reduction in respiratory disease risks following smoking cessation.

For oral cancer, risks are substantially elevated among exclusive cigarette smokers (compared with never users) and risks are increased but lower among smokeless tobacco users (compared to non-users). Information has not been published on the risk of oral cancer among switchers compared to never tobacco users, although oral cancer risk was elevated among switchers compared to those who quit

tobacco entirely. These risks by tobacco use status are consistent with the mechanistic bases for combustible and non-combustible tobacco use to cause oral cancer including through exposure to carcinogens such as potent TSNAs, which are present in smokeless tobacco products and in cigarette smoke and are absorbed in the oropharyngeal tissue of users (Boffetta et al., 2008). While evidence suggests that oral cancer risk declines after smoking cessation, smokeless tobacco use can lead to oral cancer independent of smoking, making the evidence related to risk reversal after smoking cessation more challenging to interpret.

For heart disease, risks are elevated among exclusive cigarette smokers (compared with never users) and risks are increased but somewhat lower among switchers and among exclusive smokeless tobacco users (compared to never tobacco users). Risks according to the three tobacco use statuses are more similar for heart disease than they are for lung cancer and COPD. Much of what is known about the effects of tobacco use on cardiovascular risks comes from studies of smokers (NCI/CDC, 2014). A review by the American Heart Association concluded that nicotine may contribute to smoking's effects on cardiovascular health, and that other constituents in cigarette smoke that are also present in smokeless tobacco products (such as toxic metals, PAHs, and volatile aldehydes) appear to have important effects (Piano et al., 2010). While evidence suggests that heart disease risk decreases relatively more rapidly following smoking cessation compared to other health outcomes, smokeless tobacco use can lead to heart disease independent of smoking, making the evidence related to risk reversal after quitting smoking more challenging to interpret.

The proposed advertising executions include additional modified risk statements (i.e., statements other than those about lung cancer, oral cancer, respiratory disease, and heart disease). Some of these statements refer to reduced disease risk associated with use of the six Camel Snus products but do not identify specific health endpoints for which risk is reduced. There are health conditions for which the risks of exclusive use of smokeless tobacco products generally are similar to smoking or the magnitude of the risk difference is unclear. Studies included in reviews by Lee (2014) and Inamdar et al. (2015) have reported increased risks for multiple adverse pregnancy outcomes. FDA previously concluded that there is evidence of increased risk among users of Swedish snus during pregnancy of several conditions including preterm birth, still birth, infant apnea, and oral cleft formation (US DHHS, 2016). FDA also concluded that the magnitudes of risks of some adverse pregnancy outcomes between exclusive Swedish snus users and cigarette smokers are comparable (US DHHS, 2016). For type 2 diabetes, the magnitude of difference in risks between users of smokeless tobacco and cigarette smokers is unclear. A recent cohort study of U.S. smokeless tobacco users reported that markers of insulin resistance were elevated in current smokeless tobacco users at baseline and there was some evidence of elevated associations for former smokeless tobacco use and type 2 diabetes in longitudinal analyses (Klein et al., 2016). In pooled cohort analyses conducted in Sweden, any snus use was associated with increased risk of type 2 diabetes and risks among the highest consuming snus users approximated the risks of type 2 diabetes among U.S. smokers (Carlsson et al. 2017; US DHHS, 2014). The mechanisms by which these conditions can occur are understood to be through exposure to nicotine that is present in the tobacco products (US DHHS, 2014).

Furthermore, some of the additional modified risk statements in the advertising executions do not describe the intended consumer behavior to achieve the relative decrease in risk, i.e., complete switching from cigarettes to snus. Of particular concern is the potential for dual use of cigarettes and smokeless tobacco. Section III of this document discusses observational evidence on tobacco use patterns of Camel Snus users, including the frequency dual use, which is common. Evidence from U.S. studies suggests that the health risks for dual users are generally similar to the risks for exclusive

smokers. Furthermore, Lee (2013) reported that for multiple tobacco-related diseases, the risks of dual use of Swedish snus and cigarettes compared to the risks of exclusive smoking were similar. Evidence on risks associated with cutting back on cigarettes without complete cessation, while limited, generally has not indicated a significantly decreased risk of death or disease from smoking reduction compared with continued cigarette smoking unless smokers cut back substantially on their smoking.

II. CONSUMER UNDERSTANDING AND PERCEPTIONS

A. U.S. Consumers' Perceptions of Smokeless Tobacco Risk

Almost all U.S. tobacco users and nonusers perceive smokeless tobacco and snus as harmful. In 2012-2013, 93% of U.S. smokeless tobacco users perceived smokeless tobacco as harmful and 90% perceived it as addictive (Agaku et al., 2016). A study of a representative sample of U.S. adults found that a comparable majority (88%) believe snus is both harmful and addictive (Kaufman et al., 2014). These results are consistent with qualitative research on diverse samples (Couch et al., 2017; Liu et al., 2015; Wray et al., 2012). A study including youth and young adults found that most correctly identified that smokeless tobacco use causes oral cancer (82%) and gum disease (82%) (Adkinson et al., 2014). Respondents were less likely to identify smokeless tobacco use as causing heart disease (47%). Some reported that smokeless tobacco use causes emphysema (36%), although there is no consistent evidence that risks of emphysema are elevated among exclusive smokeless tobacco users. Some also reported that smokeless tobacco use causes lung cancer (37%); lung cancer has not been conclusively linked to exclusive smokeless tobacco use. Tobacco users generally believe that smokeless tobacco and snus are less harmful and addictive than do nonusers (Agaku et al., 2016; Kaufman et al., 2014).

Several nationally representative surveys ask U.S. adults to rate the harm of using snus and smokeless tobacco relative to smoking cigarettes and show that most U.S. adults rate snus (70-81%) and smokeless tobacco (74-90%) as equally or more harmful than cigarettes or other combusted products (Borland et al., 2011; Kiviniemi & Kozlowski, 2015; Richardson et al., 2014; Wackowski & Delnevo, 2016). These studies also find that a minority of U.S. adults (7-12%) rate smokeless tobacco or snus as less harmful than cigarettes or other combusted products, though one study found that a larger proportion (22%) rated snus as less harmful than cigarettes (Popova & Ling, 2013). In these studies, up to one-fifth responded "don't know." Results were similar in a nationally representative study of youth (Persoskie et al., 2017). Qualitative research on U.S. youth and adults found a range of beliefs regarding the harmfulness of snus compared to cigarettes, including beliefs that snus is more, equally, and less harmful (Bahreinifar et al., 2013; Couch et al., 2017; Choi et al., 2012; Liu et al., 2015; Wray et al, 2012). Several studies also found that, compared to nonusers, tobacco users are more likely to believe that smokeless tobacco or snus is less harmful than cigarettes (Borland et al., 2011; Capella et al., 2012; Kaufman et al, 2014; Richardson et al., 2014), though one study did not find this difference (Kiviniemi & Kozlowski, 2015).

Few studies have examined perceptions of harm relative to cigarettes separately for snus and smokeless tobacco. However, two studies found that most people do not believe that either is less harmful than cigarettes. Wackowski and Delnevo (2016) found that 10% percent perceived snus to be less harmful than cigarettes, and 7% perceived smokeless tobacco to be less harmful than cigarettes. Richardson and colleagues (2014) found that 12% perceived snus to be less harmful than cigarettes, and 10% perceived smokeless tobacco to be less harmful than cigarettes.

B. Label, Labeling, and Advertising

With its MRTPAs, RJRT submitted print ads, direct mail, handouts, website, and two email formats (all available in Section 4 of the MRTPAs). RJRT does not propose to include modified risk information on the product labels.

Because the other submitted ads generally contained a subset of the information in the print ads, we describe the print ads in detail. RJRT submitted three versions of three-page ads (called "executions") with modified risk information. RJRT developed the ads in three focus group studies with smokers. RJRT made formatting changes to initial drafts based on subsequent qualitative interview studies and online pretests with tobacco users and nonusers.

Figure 3 is an example of the advertising submitted by the applicant (Appendix G for full-page version; other executions are available in Section 4 of the MRTPAs).

Figure 3. Advertisement Execution 2 (Source: Section 4 of the MRTPAs)

In addition to modified risk information (Table 11), the executions also include general product information ("What is snus?" and "How do I use it?") and additional information, that the applicant refers to as "balancing information," (e.g., that Camel Snus and other tobacco products contain nicotine and are addictive; the recommendation that smokers concerned about the health risks of smoking should quit and talk to a healthcare provider). In its applications, RJRT stated that it developed Execution 1 first and subsequently developed Executions 2 and 3 to reduce the reading level and use formatting (i.e., capitalization, underlining, and/or bolding) to emphasize switching completely, addictive potential, and who should not use the product.

Each execution includes one of what the applicant identifies as "key claims" (Table 11; top 3 rows). Executions 1, 2, and 3's claims have Flesch-Kincaid reading levels of 15.4, 13.9, and 12.2, respectively. Execution 2's claim is identical to Execution 1's except it says "greatly" instead of "significantly." Executions 3's claim is identical to Execution 2's claim, but it excludes "oral cancer" and "heart disease."

Table 11: Overview of modified risk information appearing in each execution of each type of advertising submitted in the application (advertisement, blue email, white email, direct mailer, website) (Data Source: Section 4 of the MRTPAs)

Modified Risk Information	Print ad 1	Print ad 2	Print ad 3	Blue email 1	Blue email 2	Blue email 3	White email 1	White email 2	White email 3	Direct mail 1	Direct mail 2	Direct mail 3	Web Ex 1	Web Ex 2	Web Ex 3	Handout Ex1	Handout Ex2	Handout Ex3
Smokers who **switch completely** from cigarettes to Camel SNUS can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0
Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease.	0	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0	X	0
Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer and respiratory disease.	0	0	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0	x
SWAP THE SMOKE FOR MORE FREEDOM & LESS RISK	X	0	0	X	X	X	X	X	X	X	0	0	X	0	0	X	0	0
NO SMOKE LESS RISK CHOOSE SNUS	0	X	X	0	0	0	0	0	0	0	X	X	0	X	X	0	X	X
-Smokers who use Camel SNUS **instead of** cigarettes can significantly reduce their health risks from smoking.	X	0	0	0	0	0	0	0	0	X	0	0	0	0	0	0	0	0
NO SMOKE = LESS RISK	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Scientific studies have shown that Camel SNUS contains fewer carcinogens than cigarette smoke.	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0	X	0	0
Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarette smoke.	0	X	X	0	X	X	0	X	X	0	X	X	0	X	X	0	X	X
-Less of the harmful chemicals found in cigarette smoke.	0	X	X	0	0	0	0	0	0	0	X	X	0	X	X	0	X	X
-Fewer carcinogens	X	0	0	0	0	0	0	0	0	X	0	0	x	0	0	X	0	0
-Less risk for you and those around you	X	X	X	0	0	0	0	0	0	X	X	X	X	X	X	X	X	X
-However, smokers who use Camel SNUS **instead of** cigarettes can significantly reduce their health risks from smoking.	X	0	0	X	X	X	X	X	X	X	0	0	X	0	0	X	0	0

Note. The statements' formatting (e.g., bolding, underlining) sometimes varies by ad type and execution.
"X" indicates the information was present in the ad submitted, 0 indicates it was absent.

As indicated in Table 11, each execution also includes additional modified risk information (see pp. 6, Memorandum). For example, all ads contain (1) large text either saying "SWAP THE SMOKE FOR MORE FREEDOM AND LESS RISK" or "NO SMOKE LESS RISK CHOOSE SNUS", and (2) a section titled "NO SMOKE=LESS RISK," which includes, for example, a statement that the product contains less of the harmful chemicals found in cigarette smoke.

Each execution also includes a section titled "NO TOBACCO PRODUCT IS SAFE," which contains "balancing information" (e.g., the product is addictive, tobacco products are not for tobacco nonusers, tobacco products are not for minors or pregnant women, the best choice for smokers is to quit). Each execution also advertises the website.

RJRT adapted these three ad executions to be disseminated in six formats: print ads, direct mail, handouts, website, and two email formats (all available in Section 4 of the MRTPAs). The main difference across the six formats is the amount of general product information. The print ads contain the largest amount of text. Generally, the other formats contain a subset of the text from the print ads.

C. Studies of Modified and Relative Risk Information and Consumer Perception

This section provides a summary of published experiments on the effect of modified and relative risk information on consumer perceptions of snus or smokeless tobacco. It also contains a summary of the three online studies the applicant conducted to assess consumer perceptions and understanding after viewing one of the three print ad executions. Additional detail on each study can be found in Section 7.5 of the MRTPAs.

Published experiments assessing effects of modified risk information on smokeless tobacco and snus risk perceptions

The applicant did not conduct experimental studies to assess whether the modified risk claims caused changes in risk perceptions. However, FDA's review of the published peer-reviewed literature identified several experimental studies that suggest that the presentation of modified risk information can decrease risk perceptions of smokeless tobacco and snus compared to cigarettes. One included smokers (Callery et al., 2011), whereas others included smokers and nonsmokers (Capella et al., 2012; Mays et al., 2016; Rodu et al., 2016). These studies randomly assigned participants to see control stimuli (with no modified risk information) or a range of smokeless products (including snus) with the statement "Using ST is less harmful than smoking cigarettes" on the label (Callery et al., 2011); a one-page Camel Snus ad with the statement "Using this product is 90% less dangerous than cigarettes" (Capella et al., 2012); a General Snus ad with the statement "…switching completely from cigarettes to snus may substantially lower health risks" (Mays et al., 2016); and a General Snus package with modified risk information in the warning (Rodu et al., 2016). In one study, compared to the control, viewing modified risk information decreased mean health risk ratings of using snus for smokers, smokeless tobacco users, and never smokers (Rodu et al., 2016). In almost all studies, compared to the control, viewing modified risk information increased participants' likelihood of perceiving smokeless tobacco or snus as less harmful than cigarettes (Callery et al., 2011; Mays et al., 2016). Mean differences were 0.5 points on a 5-point scale (Mays et al., 2016).

Published experiments assessing effects of relative risk information on smokeless tobacco and snus risk perceptions

Two other studies assessed consumer perceptions of snus products after reading information about the reduced risk of smokeless tobacco compared to cigarettes (Wackowski et al., 2015; Wackowski et al., 2017). One interview study randomized 30 smokers to read either an imitation news article describing research showing that smokeless tobacco and snus were lower risk than cigarettes, or articles that did not (Wackowski et al., 2015). Results indicated that while some smokers changed their minds to believe that smokeless tobacco and snus were less harmful than cigarettes, many continued to believe that smokeless tobacco and snus were equally or more harmful than cigarettes.

A follow-up experimental quantitative study randomly assigned smokers to a control condition or to read one of three imitation news stories: one on the reduced health risk of smokeless tobacco and snus compared to cigarettes ("favorable"), one on the health risks of smokeless tobacco and snus ("cautious"), or one that included information from both of these stories ("mixed"; Wackowski et al.,

2017). Compared to participants in the control and "cautious" conditions, those in the "favorable" or "mixed" condition were more likely to perceive smokeless tobacco or snus to be less harmful than cigarettes.

RJRT consumer perception studies

Methods

RJRT conducted three online studies with the purpose of assessing perceptions and understanding of the three print ad executions. Each study included never, former, and current tobacco users (N_{Study1}=8,404, N_{Study2}=4,924, N_{Study3}=4,906). Studies were nearly identical, differing only by whether participants viewed Execution 1, 2, or 3 of the 3-page print advertisement. Within each study, all participants viewed and responded to the same ad execution (i.e., there were no conditions). Thus, studies were not experiments that assessed the *effect* of modified risk information on risk perceptions and understanding; it is unknown whether the data from these studies reflect preexisting perceptions of the product, or how much perceptions may have changed as a result of seeing the modified risk information in the ad execution. Respondents answered questions on their understanding of the ad on the same screen that they viewed the ad, and answered other questions on subsequent pages. Recall that Execution 1 of the print ad was developed first, Execution 2 was developed to simplify Execution 1, and Execution 3 was identical to Execution 2 except that it removed two health effects (heart disease and oral cancer; see Section II.B for more information). Each ad contained photos of the front of the package of 5 flavors of Camel Snus. We focus on three outcomes:

- Absolute risk perceptions: 15 items, for three products (Camel Snus, specific flavor not specified; cigarette smoking; and smokeless tobacco other than Camel Snus) and five health outcomes (lung cancer/oral cancer/respiratory disease/heart disease/generally poorer health). "Please estimate what impact you believe using each type of tobacco has on a person's risk of developing….." Response options ranged from 1 to 7, with 1 labeled "No risk" and 7 labeled "Substantial risk."
- Relative risk perceptions: two items. One item assessed risk compared to nicotine replacement therapy ("Camel Snus [is/is NOT] a safer alternative than products that are used to quit tobacco such as gum, patches, and lozenges"). One item assessed risk compared to quitting ("Camel Snus [is/is NOT] a safer alternative than quitting tobacco entirely").
- Understanding: three items. "Is quitting the best choice for a smoker who is concerned about the health risks from smoking?" (Yes/No); "Should adults who do not use or who have quit using tobacco products start using Camel Snus?" (Yes/No); "According to the ad, what do smokers need to do in order to receive a health benefit from using Camel Snus?" (Stop smoking completely and use Camel Snus instead/ Continue to smoke, but use Camel Snus as well/Don't know)." In Execution 1, RJRT included an additional response category for the question on what smokers need to do to get a health benefit, "Reduce smoking by half and use Camel Snus in addition." This response option was removed in studies of Executions 2 and 3.

RJRT developed these measures and assessed their clarity in two interview studies. While RJRT provided brief summaries of study results, it did not provide full results or the underlying data, nor did it provide other information to support the measures' validity. While the measure of absolute risk perceptions appears to be generally consistent with the published research, the measures of understanding may be problematic due to potential bias in the wording and/or response options; thus, results should be interpreted cautiously.

Results

Overall perception and understanding of three-page advertisements

RJRT provided results by tobacco use status (current, former, and never users) and not cigarette smoking status. Current tobacco users were mostly smokers (74-75%), and the rest were current smokeless tobacco or snus users. Former tobacco users were almost all ever cigarette users (91-92%), and 18-21% were ever smokeless or snus users. RJRT did not provide any statistical tests of differences, but FDA noted where there were differences in outcomes by execution by comparing confidence intervals. While comparing confidence intervals can indicate statistically significant differences when they are not overlapping, overlapping confidence intervals could still be significantly different and thus our assessment may have missed noting some differences (Ryan & Leadbetter, 2002).

Overall, mean Camel Snus risk ratings were moderate to high for lung cancer (4.6-4.8), oral cancer (5.6-6.0), respiratory disease (4.5-4.7), heart disease (5.1-5.4), generally poorer health (5.5-5.8), and addiction (5.9-6.1). Camel Snus risk perceptions were significantly lower (by about 1 scale point) compared to cigarettes (6.0-6.6), and lower by about .5 scale points than those for other smokeless tobacco products (5.0-6.3).

Most participants responded that Camel Snus was not safer than NRT (62-68%) or cessation (69-71%), with 12-25% responding that they did not know. People were more likely to believe Camel Snus was not safer than NRT after viewing Execution 1 compared to the other executions. A small proportion responded that Camel Snus was a safer alternative to NRT (12-14%) and quitting (14-17%).

For understanding, most participants understood that quitting is the best choice for smokers (87-89%), non-tobacco users should not use Camel Snus (83-84%), and smokers had to stop smoking and use Camel Snus instead to benefit (72-78%). In studies of Execution 1 (but not 2 and 3), RJRT included an additional response category for the question on what smokers need to do to get a health benefit ("Reduce smoking by half and use Camel Snus in addition"), and 10% of respondents selected this response.

Tobacco use status

Risk perceptions differed by tobacco use status. Current tobacco users had significantly lower risk perceptions (range 3.8-5.7) compared to former users (range 4.6-6.3) and never users (range 5.0-6.1). Former users had significantly lower risk perceptions compared to never users for lung cancer and respiratory disease, but risk perceptions were similar for oral cancer, heart disease, and generally poorer health. Former users thought the product was significantly more addictive than never users.

Understanding also differed by tobacco use status. Compared to never tobacco users (84-86%), significantly more former (93-95%) and current users (89-91%) responded correctly that quitting is the best choice for smokers concerned about health risks. Compared to current (77-80%) and never users (82-83%), significantly more former users (88-90%) answered correctly that tobacco nonusers should not start using Camel Snus. More former users (80-85%) also answered correctly that smokers have to stop smoking completely and use Camel Snus instead to get a health benefit compared to current (72-77%) and never users (69-77%).

Differences among subpopulations of interest

RJRT provided results for several subpopulations of interest (Table 12). Here we summarize how these subgroups compare with the overall sample regarding risk perceptions and understanding. However, note that these descriptions do not reflect statistically significant differences because the applicant did not provide tests that assessed whether these subgroups were statistically significantly different from the overall sample.

Recall that mean risk ratings ranged from 4.5 to 6.1 overall on a 7-point scale (see above). Below we list the range of subgroups' mean risk ratings across health outcomes and executions, and describe how they relate to the overall sample.

Table 12. Results of RJRT consumer perception studies by subpopulation (Data Source: Section 7.5 of the MRTPAs, Appendix C of amended final reports of "Comprehension and Perception Among Tobacco Users and Non-users," Executions 1, 2, and 3)

Subgroup	Risk Rating Range
Overall Sample	**4.5-6.1**
Tobacco experimenters	4.3-5.6
Potential tobacco quitters	3.9-5.9
People with limited health literacy[4]	4.6-5.7
Young adults age 18-24[5]	4.4-6.1
White males	4.1-6.1
People who are not White	4.7-5.9

With regard to understanding, 87-89% of the overall sample understood that quitting is the best choice for smokers, and a similar majority of each subgroup understood this (76-93%). Potential quitters were the most likely subgroup to understand this (91-93%), and people with limited health literacy were the least likely (76-79%). Most of the overall sample understood that tobacco nonusers should not use Camel Snus (83-84%), and a similar majority of each subgroup mentioned this (71-85%). Experimenters and people with limited health literacy were the least likely to understand this (71-73%), and white males and young adults were the most likely to understand this (81-85%).

Most (72-78%) of the overall sample understood that smokers had to stop smoking and use Camel Snus instead to benefit; some subgroup differences are noted in these responses. A similar majority of the subgroups understood this (69-86%), although people with limited health literacy were less likely to understand this (53-65%) and more likely to respond "don't know" (26-31%). Only the study of Execution 1 included the response option "Reduce smoking by half and use Camel Snus in addition." A percentage (10%) of the overall sample selected this, and experimenters (19%), people with low health literacy (16%), and potential quitters (15%) were more likely to select this.

In sum, subgroups largely reported similar risk perceptions and understanding as the overall sample. However, risk ratings appeared slightly lower for tobacco experimenters and tobacco users who were

[4] Scored 3 or less out of a maximum 6 points on the Newest Vital Sign health literacy test.
[5] Of minimum legal age to purchase tobacco in their state.

potential quitters, though they still overlapped with the ranges in the overall sample. Understanding was slightly lower among tobacco experimenters and people with limited health literacy.

Limitations and considerations for interpreting findings

These results have four main limitations. First, results were presented by tobacco use status rather than cigarette smoking status. According to the applicant, the marketing of this product is aimed at cigarette smokers, and therefore it is important to evaluate how well cigarette smokers understand the risks of the products and the claims. FDA has requested this information from RJRT. Second, the study did not provide a robust assessment of perceptions of risk reduction from partially switching to Camel Snus. As it appears that this is the predominant use pattern (see Section III), it is important to understand whether consumers understand that the statements in the ad do not convey that partial switching has been demonstrated to reduce risk. Only the Execution 1 study included an answer option that began to address this issue, and results showed that 10% of respondents thought that reducing smoking by half and using Camel Snus would confer benefits. Third, the measures of understanding may be problematic due to potential bias in the question wording and available response options. Specifically, using the phrase "quitting is the best choice" could invoke social desirability to agree with the statement, and studies of Executions 2 and 3 removed a response option that would have allowed for respondents to note if they thought partial switching yielded health benefits. Using better measures may have changed the results. Finally, these studies were not experiments that assessed the *effect* of modified risk information on risk perceptions and understanding; it is unknown whether the data from these studies reflect preexisting perceptions of the product or how much the perceptions may have changed as a result of seeing the modified risk information in the ad execution. However, experimental studies of the impact of modified risk information on consumer perceptions reported in the literature (and discussed above) suggest that exposure to modified risk information can lower consumer perceptions of risk.

Two additional considerations can provide context for interpreting findings. First, these studies only tested a single, brief exposure to a print ad. One might expect that repeated exposure to ads across the various communication platforms could strengthen their effect for some viewers, potentially decreasing their risk perceptions. Second, the studies in the applications were designed to test the advertisement that RJR planned to use as a whole. Therefore, with the available information, we cannot directly assess how participants would understand any single piece of modified risk information in any other context besides the full advertisement that was tested, nor can we directly assess how participants would respond to the ads if they were changed to remove modified risk or other descriptive information. We note that modified risk claims varied in specificity, with some specifying conditions of use (switching completely) and health risks reduced (lung cancer, oral cancer, heart disease, respiratory disease), and others (e.g., "NO SMOKE=LESS RISK) being less specific. It is possible that removing the more specific modified risk claims could result in consumers believing that completely switching is not required or that all health risks are reduced. Furthermore, it is possible that the presence of information describing the intended audience of the product (cigarette smokers) and noting that quitting is still preferable is the reason many of these results are favorable.

D. Summary and Conclusions

Overall, RJRT's studies indicate that consumers generally answered questions about the modified risk information correctly, though important gaps remain due to limitations of the studies. RJRT's studies consisted of three non-experimental online studies, one assessing each execution of the print ad. Participants answered survey questions during and after viewing the ad. Across studies on a 7-point

scale (7=substantial risk), participants rated using Camel Snus as moderate to high for lung cancer (4.6-4.8), oral cancer (5.6-6.0), respiratory disease (4.5-4.7), heart disease (5.1-5.4), generally poorer health (5.5-5.8), and addiction (5.9-6.1). Ratings were approximately 0.5 points higher for smokeless tobacco other than Camel snus and 1.0 points higher for cigarettes. Tobacco users (75% of whom were smokers) rated the product as lower risk than former and never users. Most participants reported that smokers had to switch completely to Camel Snus to accrue the relative benefit (vs. continuing to smoke and use the product in addition, or "don't know"). While results are largely consistent with the literature, studies had four limitations: (1) a lack of information on how current, former, and never smokers responded to the ads; (2) a lack of a robust assessment of perceived risk reduction from partial switching, which is the predominant use pattern (see Section III); (3) potential bias in question wording and response options of understanding questions; and (4) not experimentally assessing the effect of modified risk information on consumer perceptions and understanding. We also note that several published studies may help address the fourth limitation to some degree. Published studies find that compared to control stimuli (smokeless tobacco/snus labels, advertising, and news articles without relative risk information), tobacco users and nonusers exposed to stimuli with relative risk information have slightly lower risk perceptions of smokeless tobacco relative to cigarettes. These findings can be considered along with other research, which finds that almost all U.S. youth and adults believe smokeless tobacco and snus use is harmful, and the vast majority believe it is as or more harmful than cigarettes. We also note that while RJRT's studies provide information on responses to each ad as a whole, they do not provide information on the role of specific ad components (e.g., specific claims or product description information) in consumer perceptions and understanding.

III. LIKELIHOOD OF USE

A. Potential Users of the Proposed Modified Risk Tobacco Products

This section provides a summary of the published literature on how an instance of viewing relative risk information on a smokeless tobacco or snus product causes changes in self-reported likelihood of purchase for trial for smokers and nonsmokers. This section also describes three online experimental studies that the applicant conducted to assess the effect of modified risk information on likelihood of use for smokers and nonsmokers. In this section, when we refer to likelihood of use, we refer to participants' self-reported likelihood of use rating. For example, this could be their rating of the likelihood they will use the product on 1 ("not at all likely") to 5 ("extremely") scale. Additional detail on the applicant's studies can be found in Section 7.5 of the MRTPAs.

Published experiments that assess the effect of modified risk information on intentions to use

FDA identified several published experimental studies that assessed the effect of modified risk information on cigarette smokers' intention to use smokeless tobacco and snus (as measured by asking to participants to report their intention to use, likelihood of trying, or likelihood of using these products). Results of two experiments manipulating the presence of modified risk information on a label (Callery et al., 2011; Rodu et al., 2016) found that the modified risk information significantly increased likelihood of trying snus and smokeless tobacco (Callery et al., 2011) and motivation to buy and likelihood of using snus (Rodu et al., 2016). However, studies manipulating modified risk information on a Camel Snus ad (Capella et al., 2012) and a General snus ad (Mays et al., 2016) found no significant effect of modified risk information on smokers' intention to use snus in the next year (Mays et al., 2016) or intention to switch to smokeless tobacco (Capella et al., 2012).

Three experiments assessed the effect of modified risk information on nonsmoker intention to use smokeless tobacco. Two studies found that modified risk information presented on Camel Snus (Capella et al., 2012) or General Snus (Mays et al., 2016) ads did not increase nonsmoker intentions to use snus. One study (Rodu et al., 2016) found that one version of modified risk labels slightly increased motivation to buy (but not self-reported likelihood of using) General Snus (Rodu et al., 2016).

Published studies on the effect of relative risk information on intentions to use

One qualitative and one quantitative study looked at the effect of providing information on the risk of smokeless tobacco and snus relative to cigarettes on smokers' intentions to use the products (as measured by asking participants their willingness to try, interest in trying, likelihood of buying, and likelihood of switching). In a small qualitative study, 30 smokers were randomized to read an imitation news article describing research showing smokeless tobacco and snus to be lower risk than cigarettes, or other article conditions (Wackowski et al., 2015). Most participants in each condition (6-7 of 10) were willing to try snus in the future, and this did not differ by the article condition (Wackowski et al., 2015). In a larger experiment (n=1,008) where smokers were randomly assigned to read the same articles, participants who read the article about smokeless tobacco/snus being lower risk reported a statistically significant increase in likelihood of trying snus in the next six months, buying snus in the next six months, using smokeless tobacco to quit smoking, and completely replacing cigarettes with smokeless tobacco compared to those who read other articles (Wackowski et al., 2017).

RJRT likelihood of use studies

Methods

RJRT conducted three methodologically identical "likelihood of use" studies, which assessed the likelihood that consumers would purchase a Camel Snus product for trial. Each study randomly assigned tobacco users and nonusers to see one execution of the three-page print advertisement either as proposed (e.g., see Appendix G), or with all of the modified risk information removed (as a control). Recall that Execution 1 of the print ad was developed first, Execution 2 was developed to simplify Execution 1, and Execution 3 was identical to Execution 2 except that it removed two health effects (heart disease and oral cancer; see Section II.B for more information). Each ad contained photos of the front of the package of five flavors of Camel Snus. Each study was conducted online, and there were three main outcomes:

- Likelihood of purchasing Camel Snus (flavor was not specified) "to try it" on a 1 ("Definitely would not purchase it to try") to 10 ("Definitely would purchase it to try") scale.
- Purchase probability, based on the idea that self-reported likelihood of purchase ratings of a specific new product (assessed prior to the product's marketing) can be transformed by an algorithm to estimate actual purchase rates of that product after it is marketed. RJRT conducted three studies to develop and assess the validity of an algorithm that transformed the self-report ratings to estimate overall purchase probabilities of Camel Snus (flavor/size not specified; for both modified risk and control conditions). The algorithm, based on logistic regression, predicted purchase rates of newly marketed specific cigarette and smokeless tobacco products based on age group, tobacco use status, and self-report likelihood of purchase rating from nine months prior (before the product was marketed). The assessments of the algorithm's validity involved comparing predicted purchase rates to actual purchase rates. Results found that the overall predicted purchase rate was the same as the actual purchase rate for a study of one cigarette sub-brand (Marlboro Special Blend, including any variety), but was 2.2 percentage

points higher for a study of two specific varieties of a cigarette sub-brand (Marlboro Special Blend, blue and black varieties only), and 1.0 percentage points higher for a study of a new size of an existing specific Camel Snus product (Frost Large). In sum, this algorithm provides helpful information, though validation information indicates that it may overestimate (by 1-2 percentage points) actual use rates.

- Intention to use Camel Snus "instead of my current tobacco products(s) (would stop using my current tobacco product completely)," "in place of some of my current tobacco product(s) (leading to no net increase in tobacco use)," or "in addition to my current tobacco product(s) (leading to an overall increase in tobacco use)." This was only asked of current smokers who answered at least a 2 on the likelihood question and who were not intending to quit tobacco (41% of smokers in Execution 1, 45% in Execution 2, and 46% in Execution 3).

Results

Likelihood that cigarette smokers will purchase Camel Snus for trial

RJRT provided tests of statistical significance comparing conditions with and without modified risk information. RJRT did not provide statistical tests assessing other differences. FDA describes other differences by comparing confidence intervals. While non-overlapping confidence intervals can indicate statistical significance (Ryan & Leadbetter, 2002), overlapping confidence intervals may still be significantly different, meaning that some differences may not be noted.

Table 13. Likelihood of purchase for current smokers (Data Source: Section 7.5 of the MRTPAs, amended final reports for "Likelihood of Use among Tobacco Users and Non-Users," Executions 1, 2, and 3)

	Mean likelihood of purchase rating (95% CI half-width) (1-10 scale, 10="Definitely would purchase it to try")		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	3.0(2.85-3.15)*	3.7(3.48-3.92)*	3.8(3.59-4.01)*
Control	2.8(2.66-2.94)	3.4(3.20-3.60)	3.4(3.20-3.60)
	Purchase probability (derived from algorithm) (95% CI) (0-100%)		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	5.8%(4.2-8.0%)	8.2%(6.0-10.9%)*	8.0%(5.9-10.8)*
Control	5.4%(3.8-7.5%)	6.9%(5.1-9.4%)	6.9%(5.1-9.4)

*Indicates statistically significant difference from control group.

On average, smokers reported low likelihood of purchasing Camel Snus for trial (mean 3.0-3.8 on a 10-point scale, Table 13). Mean purchase intentions were significantly higher for Executions 2 and 3 compared to Execution 1. The presence of the modified risk claims significantly increased purchase intention for all executions; however, using the transformed purchase probabilities, this was not the case for Execution 1.

Smokers who rated intention to purchase at least a 2 on a 10-point scale and reported not intending to quit tobacco (41-46%) were asked about how they intended to use Camel Snus (switch completely, switch partially, or add to their tobacco use). Among these smokers, 14-22% said they would switch completely; 18-27% said they would use it in addition to their current tobacco use; 26-35% said they

would use it in place of some of their current tobacco use; and 26-37% said don't know. While there were no statistically significant differences between the modified risk and control groups, fewer smokers said they would switch completely in: (a) both the Execution 1 conditions compared to both the Execution 2 conditions, and (b) the Execution 1 control condition compared to the Execution 3 control condition.

Likelihood that former smokers will purchase Camel Snus for trial

On average, former smokers reported very low likelihood of purchasing Camel Snus for trial (mean 1.8-1.9 on a 10-point scale,

Table 14). Mean purchase intentions did not differ significantly by execution or presence of modified risk information. Across executions and conditions, former smokers' mean purchase intention was significantly lower compared to current smokers. The pattern of results remained when mean purchase intentions were translated to purchase probabilities (1.9-2.2%).

Table 14. Likelihood of purchase for former smokers (Data Source: Section 7.5 of the MRTPAs, amended final reports for "Likelihood of Use among Tobacco Users and Non-Users," Executions 1, 2, and 3)

	Mean likelihood of purchase rating (95% CI half-width) (1-10 scale, 10="Definitely would purchase it to try")		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	1.9(1.82-1.98)	1.8(1.69-1.91)	1.9(1.79-2.01)
Control	1.9(1.82-1.98)	1.8(1.69-1.91)	1.8(1.69-1.91)
	Purchase probability (derived from algorithm) (95% CI) (0-100%)		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	2.1%(1.3-3.4%)	1.9%(1.2-3.3%)	2.0%(1.3-3.4%)
Control	2.2%(1.4-3.6%)	2.0%(1.2-3.3%)	2.0%(1.2-3.3%)

*Indicates statistically significant difference from control group.

Likelihood that never smokers will purchase Camel Snus for trial

On average, never smokers reported very low likelihood of purchasing Camel Snus for trial (mean 1.4-1.7 on a 10-point scale, Table 15). Mean purchase intentions did not differ significantly due to the presence of modified risk information. Mean purchase intentions were significantly lower in Execution 1 compared to Executions 2 and 3. Across executions and conditions, never smoker mean purchase intention was significantly lower compared to current smokers. The pattern of results was the same when mean purchase intentions were translated to purchase probabilities (which ranged from .4-.5%), though purchase probabilities were also significantly lower than those of former smokers.

Table 15. **Likelihood of purchase for never smokers** (Data Source: Section 7.5 of the MRTPAs, amended final reports for "Likelihood of Use among Tobacco Users and Non-Users," Executions 1, 2, and 3)

	Mean likelihood of purchase rating (95% CI half-width) (1-10 scale, 10="Definitely would purchase it to try")		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	1.4(1.35-1.45)	1.7(1.60-1.80)	1.7(1.60-1.80)
Control	1.4(1.34-1.46)	1.7(.1.61-1.79)	1.7(.1.61-1.79)
	Purchase probability (derived from algorithm) (95% CI) (0-100%)		
	Execution 1	**Execution 2**	**Execution 3**
Modified risk	.4%(.2-.7%)	.5%(.3-.8%)	.4%(.3-.8%)
Control	.4%(.2-.7%)	.4%(.3-.8%)	.4%(.3-.8%)

*Indicates statistically significant difference from control group.

Differences among subpopulations of interest

RJRT provided results for cigarette smokers by quit status. For all executions, purchase likelihood ratings were statistically significantly lower among potential quitters (range 2.1 -2.7 across executions and conditions) than non-potential quitters (range 2.9-3.9), and were not affected by the presence of modified risk information. RJRT provided results separately for young adult and white male *tobacco users*, though they did not provide results for these subpopulations of *cigarette smokers*. About 81-84% of tobacco users were current smokers (based on unweighted sample size). Mean purchase ratings for all *tobacco users* ranged from 3.0 to 3.7, and were significantly higher for the modified risk condition only in Execution 3. Young adult current tobacco users' mean purchase intentions had a higher upper range (range2.9 to 4.8), and were only significantly higher for the modified risk condition in Execution 1. White male current tobacco users' mean purchase intentions ranged from 3.2 to 3.6, and they did not differ by presence of modified risk information.

RJRT provided results separately for two subpopulations of *former* and *never tobacco* users (young adults and white males), though they did not provide this for subpopulations of *former* and *never cigarette* smokers. About 93-95% of former tobacco users were ever smokers (based on unweighted sample size).

For *young adult former tobacco users*, mean purchase intentions were slightly higher (2.2-3.8) compared to former tobacco users overall (1.3-1.6). For white male *former tobacco users*, mean purchase intentions were similar (1.3-1.8) to former tobacco users overall (1.3-1.6). Mean purchase intentions for *young never tobacco users* (1.6-1.8) and white male never tobacco users (1.4-1.6) were similar to never tobacco users overall (1.4-1.7). For young adult and white male former and never tobacco users, ratings were not affected by presence of modified risk information.

Study limitations and considerations for interpreting findings

Two considerations and two limitations can aid in interpreting findings. First, these studies tested a single, brief online exposure to a print advertisement. It is likely that repeated exposure to advertisements across various communication platforms could strengthen their effect for some viewers. Second, the studies were designed to test the effect of groups of modified risk statements in the context

of the whole advertisement that RJRT plans to use. We do not have information on how participants would respond to any single modified risk statement in any context other than the full advertisement as it was tested, nor do we have any information on how participants would respond to the ads if only some modified risk information or "balancing information" were removed.

There were two main limitations to the applicant's studies. First, the estimated purchase probabilities could be overestimates, based on the applicant's validation studies of the algorithm used to generate them. While one validation study (predicting use of any variety of a sub-brand) found the purchase probability to be accurate, two validation studies (predicting use of specific product varieties) found the algorithm yielded overall estimates that were about 1-2 percentage points higher than overall actual purchase rates. However, these overestimates were relatively small, and these algorithms still provide helpful information. Second, one outcome we described, intended use patterns (e.g., switch completely, switch partially, or add to tobacco use; assessed among smokers who did not want to quit tobacco and reported an interest in purchasing Camel Snus), may not be a valid predictor of behavior. The applicant did not provide validity information for this item, and we are unaware of similar items used in the literature. Furthermore, the way the response options are worded could invoke social desirability to avoid selecting the response option "in addition to my current tobacco product(s) (leading to an overall increase in tobacco use)," because people might not want to admit they would increase their tobacco use.

Summary and Conclusions

RJRT's likelihood of use studies found results that were generally consistent with the peer-reviewed literature on the effects of modified risk and relative risk information on use intentions: smokers were slightly more likely to use Camel snus after viewing ads with the proposed modified risk information compared to without it. Results of most published experiments (Callery et al., 2011; Capella et al., 2012; Mays et al., 2016; Rodu et al., 2016; Wackowski et al., 2015) suggest that, compared to control stimuli (smokeless tobacco/snus labels, advertising, and news articles without modified or relative risk information), smokers exposed to stimuli with modified and relative risk information have slightly higher intentions to use the product. RJRT's experimental studies indicate that only a small percentage of smokers are likely to purchase Camel Snus for trial (5.4-8.2%). However, the presence of modified risk information slightly (but significantly) increased likelihood that smokers would purchase the product. Among smokers who did not plan on quitting tobacco and had at least some interest in purchasing the product, a minority said they would switch completely to Camel Snus (14-22%), about half planned to use the product and continue to smoke, and the remainder answered "don't know."

RJRT's experimental studies indicate that nonsmokers' likelihood of purchasing Camel Snus is very low (about 2% for former smokers and 0.4% for never smokers). The presence of modified risk information did not affect nonsmokers' likelihood of purchase.

Integrating findings about smokers switching and the effect of modified risk information

Perceptions of the risks of smokeless tobacco/snus may play a role in low rates of switching for some smokers. In the absence of modified risk information, most smokers believe that smokeless tobacco and snus are equally or more harmful than cigarettes (see findings in Section II), and few smokers switch to snus (see findings below). The perception that snus is not less harmful than smoking may be one reason why some smokers are not switching to snus, given that risk perceptions may play a role in tobacco use behavior (e.g., Choi & Forster, 2013; Elton-Marshall et al., under review; Lund, 2012). However, a recent study (Hatsukami et al 2016) found that among smokers seeking alternatives who were randomized to

completely switch to snus or medicinal nicotine, satisfaction with the product after trying it, not perceived health risk after trying it, was related to some patterns of product use.

For a small proportion of smokers, the presence of modified risk information has the potential to change these perceptions and the potential to change use behavior. Published experimental studies show that being exposed to relative risk information about smokeless tobacco/snus on one occasion causes smokers to rate using smokeless tobacco/snus as slightly lower risk compared to cigarettes (see Section II). In addition, both published experiments and RJRT's studies have reported that being exposed to modified and relative risk information may cause a small increase in likelihood of using the product among smokers.

B. Findings from Clinical Studies

The clinical studies (Appendix B) reviewed here are found in Section 7.4 of the MRTPAs and are further described in Section I of this document. The scope of review for these studies included use behavior, abuse liability, and biomarkers of nicotine exposure and metabolism.

Product Use

Tobacco product use was a primary or secondary objective in the submitted reports. A study of natural Camel Snus adopters (CSD0904_PMS) found that exclusive Camel Snus users (600 mg, Frost and Mellow flavors) used more product on a per unit basis than dual users of snus and cigarettes. One study (CSD0804_SMA) found that over 11% of participants used more than one Camel Snus pouch (600 mg, Frost, Original, or Spice flavors) at a time during seven days of ad libitum use. In forced switching studies (CSD0901_SSSO, CSD0905_SL, CSD1010_SS), participants did not completely quit smoking cigarettes, were likely to dual use Camel Snus (600 mg, Frost and Mellow flavors) and cigarettes, and increased Camel Snus use for the study duration. Lastly, in a smoking cessation trial (CSD1010_SS), Camel Snus users (600 mg, Frost and Mellow flavors) had similar cessation rates as participants using nicotine lozenges; additional cessation information provided to Camel Snus users did not change these rates.

Acceptability, Compliance, and Switching

In general, participants found Camel Snus products to be acceptable, and there was evidence that acceptability may increase over time as users get more experience (CSD0905_SL; 600 mg, Frost and Mellow flavors). However, study compliance or study completion rates were low (particularly within the Camel Snus groups), indicating that Camel Snus may be inadequate to completely substitute for cigarettes in some daily smokers and suggesting a low likelihood that cigarette smokers will completely switch to exclusive Camel Snus use. For example, in a four-week study where participants were instructed to reduce CPD by 75% while using Camel Snus (CSD0905_SL), participants reduced CPD by 59% by study completion. Another study (HSD0702_QOL) found that 55% of participants in the per-protocol subgroup (i.e., participants who have no missing data and have fulfilled all study tasks) were classified as compliant; the Camel Snus group (400 mg, Frost, Original, or Spice flavors) was the least likely to complete the study and be compliant with the study protocol (only using the product assigned). Additionally, in a long-term study of smoking cessation where some participants received information on the "benefits of smoking cessation and the relative risks of smoking cigarettes vs. smokeless tobacco products (STP) use" (CSD1010_SS), only 33% of enrolled participants completed the study, and there was no difference in smoking cessation rates between those who received that information and those who did not. Lastly, Hatsukami and colleagues published data from a randomized controlled trial in

cigarette smokers interested in switching to Camel Snus, and found that only 38% and 27% of the population used Camel Snus exclusively at 6 and 12 weeks, respectively (Hatsukami et al., 2016).

Abuse Liability (Subjective Effects, Purchase Intentions, Misuse)

The abuse liability of Camel Snus (600 mg, Frost and Mellow flavors) was assessed using standard measures of dependence, withdrawal, and subjective effects in natural adopters as well as participants who were asked to switch products during the study. Overall, dependence measures and subjective effects were similar between Camel Snus and other smokeless tobacco products (e.g., Camel Orbs, Camel Strips, Camel Sticks, (b) (4)). Two studies (CSD0914_SUL and CSD1101_STM) examined the subjective effects of Camel Snus, other smokeless tobacco products, and usual brand cigarettes and found that the greatest decrease in urge to smoke during the trial was for usual brand cigarettes; Camel Snus was ranked second best at decreasing urge to smoke. These data suggest that the abuse liability of Camel Snus may be lower than cigarettes; traditionally the likelihood of complete substitution or switching completely from a higher abuse liability product to a lower abuse liability product is relatively low.

Nicotine Exposure

Two studies assessed the nicotine pharmacokinetics of Camel Snus 600 mg pouches (CDS0914_SEL, Frost and Mellow flavors; CSD1101_STM, Frost flavor) and other tobacco products under tightly-controlled laboratory conditions. Camel Snus produced a lower maximum plasma concentration (C_{max}) and area under the curve from 0-3 hours ($AUC_{0\text{-}3hr}$) after single use compared to usual brand cigarettes. Mean time to maximum concentration (T_{max}) was approximately 3.5 times longer for Camel Snus compared to usual brand cigarettes.

Biomarkers of nicotine exposure (e.g., unconjugated nicotine, norcotinine) were also examined in six actual use clinical studies with varying duration (five days to 52 weeks). Here we summarize these results in the context of making comparisons between Camel Snus and other tobacco products. When compared to control groups (nontobacco users or periods of abstinence), biomarkers of nicotine exposure were generally higher after Camel Snus use. Biomarkers of nicotine exposure were generally not significantly different or significantly lower in Camel Snus users compared to usual brand cigarette smokers or baseline usual brand cigarette smoking. However, pooled data for 600 mg pouches in Frost and Mellow flavors and 1000 mg pouches in Winterchill flavor suggest that nicotine-N-oxide was increased in Camel Snus natural product adopters compared to smokers (04_CSD0904_PMS), and serum cotinine was increased compared to baseline cigarette smoking after 24 weeks of use of 400 mg pouches in Frost, Spice, and Original flavors (01_HSD0702_QOL). Plasma cotinine was reduced compared to baseline cigarette smoking after five days of confined use with 600 mg pouches in Frost and Mellow flavors (03_CSD0901_SSSO). In one study (HSD0702_QOL; 400 mg pouches in Frost, Spice and Original flavors), five nicotine metabolites were significantly higher after 24 weeks in participants who switched to Camel Snus compared to the cohort who switched to ultra-light cigarettes. Lastly, biomarkers of nicotine exposure were generally lower in Camel Snus users compared to users of other moist snuff products. Although pharmacokinetic endpoints and exposure to some nicotine metabolites were reportedly lower for Camel Snus users, these data suggest that Camel Snus products may produce reinforcing effects and have an abuse liability similar to other moist snuff products, but lower than cigarettes.

Major Study Limitations

Data from more than one of the proposed MRTP Camel Snus products (e.g., Frost and Mellow flavors; 600 mg pouch) were combined for assessments, including pharmacokinetic and biomarker assessments, limiting the ability to adequately determine individual product effects. Camel Snus (600 mg pouch) flavored products have different nicotine content, which may impact product use behaviors and pharmacokinetic assessments. Furthermore, differences in mouth level exposure, and perhaps nicotine uptake, have been shown between Camel Snus pouches of the same size but different flavor (CSD0804_SMA). Therefore, individual product comparisons are important for proper study conclusions.

No submitted RJRT-sponsored or published clinical studies included data on Camel Snus 1000 mg in Robust or Frost flavors, and none provided data analyses by product. Only one RJRT-sponsored study (04_CSD0904_PMS) used Camel Snus 1000 mg in Winterchill flavor in a small number of participants (n=2 to 5 in various submitted documents).

One study (HSD0702_QOL) included data from 400 mg pouches in Frost, Spice, and Original flavors. However, Camel Snus products in Frost, Mint, Mellow (600 mg pouch) and Frost, Winterchill, and Robust (1000 mg pouch) flavors are the proposed MRTPs; applying data from this study to the application's products is difficult since the constituents (including flavor additives) vary between the referenced study products and the application-specific products. Furthermore, the referenced studies do not include individual product data for all proposed MRTP Camel Snus products (e.g., no clinical studies with 1000 mg pouch products). Bridging data for product size and flavors are missing. Without such data or bridging rationale, conclusions regarding untested product size/flavor combinations are limited.

Interpretation of results from Study CSD0905_SL in support of the submitted MRTPAs is limited because the study did not include an exclusive Camel Snus condition. Similarly, in several studies, interpretation is also limited due to differences in the dependence measures for cigarettes and snus, which impedes the ability to compare scores between these two groups. Lastly, without additional data or explanation, it is unclear whether potential differences in the biomarkers assessed have clinical significance and would positively affect the health risks for smokers who would completely switch to using the six proposed MRTP Camel Snus products.

Summary and Conclusions

In summary, biomarkers of nicotine and nicotine metabolites were generally not different between Camel Snus use of 400 mg pouches (Frost, Spice, and Original flavors) and 600 mg pouches (Frost and Mellow flavors) compared to cigarette smoking at baseline or within a control group. Nicotine pharmacokinetic parameters showed lower C_{max} and $AUC_{0\text{-}3hr}$ and longer T_{max} for Camel Snus 600 mg pouch (Frost and Mellow flavors) compared to cigarettes; systemic nicotine exposure was similar between Camel Snus and UB cigarettes. Therefore, Camel Snus products are expected to produce reinforcing effects, but may have a lower abuse liability than cigarettes. Behavioral data from the submitted clinical studies also suggests that, in general, Camel Snus has a similar abuse liability as other smokeless tobacco products, and perhaps a lower abuse liability than cigarettes. The reduced abuse liability of Camel Snus may decrease the odds of the proposed MRTPs adequately substituting for cigarette smoking. In fact, evidence of cigarette smokers switching to exclusive Camel Snus use is limited, and dual use was common in the provided studies.

C. Evidence on Current Users of Snus from Observational Studies

The applicant conducted analyses of several observational studies to assess product usage across tobacco user categories, including current cigarette smokers. The primary study used in the applications to describe characteristics of adult current users and non-users of Camel Snus, as well as use behaviors, was RAIS' National Tobacco Behavior Monitor (NTBM) survey (Section 3.5 of the MRTPAs). Analyses of two additional observational studies were conducted to compare descriptive findings from the NTBM: (1) RJRT's Consumer Brand Tracker (Section 3.5 of the MRTPAs); and (2) publicly available data from the Population Assessment of Tobacco and Health (PATH) Study. Where appropriate, clinical studies described in other sections of the application (e.g., Section 6.1.2 of the MRTPAs) as well as studies from the broader peer-reviewed literature, particularly studies that were published after the application was submitted, are described below to aid in interpretation and evaluation of the MRTPAs, including the data provided by the applicant. While the NTBM provides some information on use of the six Camel Snus sub-brands (i.e., Frost, Mint, Mellow, Robust, Winterchill, Frost Large), findings reported in this section generally refer to all Camel Snus products, irrespective of sub-brand. When specific product or brand information is not available in a given study, information is presented on pouched snus or smokeless tobacco use more generally.

To assess the impact of the proposed modified risk tobacco products on the health of the population as a whole, the statue mandates that FDA consider both users and non-users of tobacco products in the population. Given that the applicant focused on adult use patterns in its actual use studies, the primary focus for this section will be on adults of legal age to purchase tobacco in the U.S. However, because smokeless tobacco products are currently available on the U.S. market, we have some evidence to suggest that current use of pouched snus products (and smokeless tobacco more generally) among youth is low. For instance, data from the 2014 National Youth Tobacco Survey (NYTS) reported that past 30-day use of any snus product among U.S. high school and middle school students was low (1.9% and 0.5%, respectively) compared to chew/snuff/dip use (5.5% and 1.6%, respectively), or other tobacco products (e.g., electronic cigarettes: 3.9%-13.4%; cigarettes 2.5%-9.2%) (Arrazola et al., 2015). Additionally, recent analyses of the 2017 NYTS report a linear decrease in smokeless tobacco product use among high school students from 7.9% in 2011 to 5.5% in 2017 (Wang et al., 2018). However, it should be noted that some studies have suggested that youth who use snus or other smokeless tobacco products may be more likely to initiate other tobacco products (i.e., combustible cigarettes) (Haddock, et al., 2001; Severson, et al., 2007; Soneji, et al., 2015; Tam, et al., 2015; Tomar, 2003; Watkins, et al., 2018).

D. Evidence on Snus Use Patterns from Observational Studies

A brief summary of the observational studies used by the applicant to assess characteristics and behaviors of adult Camel Snus users and users of non-Camel Snus and other smokeless tobacco products is provided in Table 16. Additional detail on each study's methodology can be found in the appendices of the applicant's Camel Snus Use Report (Section 3.5 of the MRTPAs).

Table 16. Description of observational studies of Camel Snus and smokeless tobacco use patterns (Data Source: Section 3.5 of the MRTPAs)

	The National Tobacco Behavior Monitor (NTMB)	Brand Tracker (BT)	The Population of Assessment of Health (PATH) Study [a]
Study design	Cross-sectional	Cross-sectional	Cross-sectional analysis of Wave 1
Time period	Applicant used data collected from January 2013-March 2016	Applicant used data collected from January 2013-March 2016	Applicant used data from Wave 1 (2013-2014)
Sample size	94,678 (weighted sample) adults; 555 (weighted) past 30 day Camel Snus users.	Total sample for study period sample unknown; 1,783 (weighted) Camel Snus users.	32,320 (unweighted sample) same of adults at Wave 1; 109 adults (weighted) reported Camel Snus as their usual brand.
Description of study population	Nationally-representative sample of U.S. adults of legal age to purchase tobacco products in their respective states.	Nationally-representative sample of U.S. adults of legal age to purchase tobacco products.	Nationally-representative sample of the U.S. civilian, non-institutionalized adult population.
Assessment of Camel Snus and smokeless tobacco	(1) Past 30 day users of Camel Snus (who identified Camel Snus as their usual brand); (2) past 30-day users of other snus brands (i.e., those who identified a usual brand other than Camel Snus); and (3) users of other smokeless tobacco product types (i.e., loose moist snuff, portioned moist snuff and loose leaf chew tobacco)	(1) Past 7 day use of any snus; (2) past 7 day use of 'moist snuff' (including loose moist snuff and portioned moist snuff); (3) loose leaf chew. "Snus" use based on brand(s) currently used, versus usual brand.	Current snus use among adults was defined as any past 30-day use.

[a]Analyses of the PATH Study data (Wave 1) presented below include analyses conducted by the Applicant using public use files as well as published data from Cheng et al. (2017). This table presents only information provided by the Applicant for their independent analysis of the Wave 1 dataset.

Study Findings

Characteristics of Camel Snus Users

Data from RAIS' NTBM show that an estimated 0.5% of U.S. adults reported use of Camel Snus on one or more of the past 30 days (internal FDA analysis). Table 1 of the Camel Snus Use Report presents descriptive analyses from the NTBM, which suggest that characteristics of adult current Camel Snus users are generally consistent with current users of other smokeless tobacco products. Specifically, past 30-day users of Camel Snus, as well as other types of smokeless tobacco products, are predominately between the ages of 25 and 49 (69.2-75.2%), male (80.8-85.7%), identify as Caucasian (52.3-65.2%), and generally report greater versus lesser educational attainment (63.8-69.4%). Findings from RJRT's Brand Tracker on demographic characteristics of Camel Snus and other smokeless tobacco products (moist snuff and loose leaf chew) were generally consistent with the NTBM; that is, past seven-day users of Camel Snus were similar to past seven-day users of other types of smokeless tobacco products in terms of age, sex, race/ethnicity, and educational attainment. Similarly, published analyses of Wave 1 of the PATH Study report prevalence of current established pouched snus use (currently uses every day or on some days, and reported ever using the product "fairly regularly") among adults was 0.4%, with

prevalence of use being highest among those who were 25-49 years old, male, and non-Hispanic white (Cheng et al. 2017).

Patterns of Camel Snus Use

Descriptive analyses of the NTBM show that the vast majority of past 30-day users of Camel Snus (92.8%) were dual/poly-users of other combustible and/or non-combustible tobacco products. Specifically, poly-use of Camel Snus, combustible and non-combustible products was the most common pattern of use among past 30-day Camel Snus users (68.1%), with a much smaller proportion of users reporting dual use of Camel Snus with other non-combustible products (11.0%), dual use with cigarettes (8.6%), or dual use with non-cigarette combustible products (5.0%) in the past 30-days. Exclusive past 30-day Camel Snus use was low (7.2%), although more common than exclusive past 30-day use of non-Camel snus use (3.7%) or portioned moist snuff (6.7%). The applicant observed similar patterns in the Brand Tracker data, noting that an estimated 3.5% of snus users (including all brands) reported exclusive use in the past seven days, and found that the predominant behavioral pattern among current smokeless tobacco users was dual/poly-use of other tobacco product types.

Published analyses of the 2013-2014 PATH Study found that poly-use was more common among adults who concurrently used pouched snus and other smokeless tobacco products (74.9%), and exclusive pouched snus users (64.0%), compared with those who used other smokeless tobacco products only (44.7%) (Cheng et al., 2017). Similarly, current established cigarette smoking in this study was most common among current dual users of pouched snus and other smokeless tobacco (48.7%), followed by exclusive pouched snus users (42.6%) and other exclusive smokeless tobacco uses (31.1%).

In terms of frequency of use, data from the NTBM show that nearly half (46.2%) of past 30-day Camel Snus users reported use of the product on 0-1 days of the past week, with 39.2% using on 2-5 days of the past week, and 13.9% using on 6-7 days of the past week. The average number of days used per week among Camel Snus users was 2.4, which did not vary widely across different Camel Snus products (i.e., Frost, Mint, Mellow, Robust, Winterchill, Frost Large) (2.2-3.0 days per week). Compared to other smokeless tobacco products, the estimated mean use frequencies were generally consistent among past 30-day users of Camel Snus, non-Camel snus, portioned moist snuff and loose leaf chew tobacco (ranging from 2.4 to 2.5 days per week); however, the mean frequency of use among loose moist snuff users was higher (3.7 days per week). Brand Tracker data found slightly different patterns of snus and other smokeless tobacco use frequency in the past week, such that among past seven-day snus users the majority (53.8%) reported use on 2-5 days of the past week (compared to 38.5% of moist snuff users and 48.9% of loose leaf chew users), while 25.0% of snus users reported use on 0-1 days of the past week (compared to 10.1% of moist snuff users and 29.8% of loose leaf chew users), and 21.2% reported use on 6-7 days of the past week (compared to 51.4% of moist snuff users and 21.3% of loose leaf chew users). The mean use frequency among past 7-day snus users from the Brand Tracker data was 3.5 days per week. Additionally, the applicant analyzed publicly available data from Wave 1 of the PATH Study and found that among past 30-day Camel Snus users the use mean use frequency in the past month was 17.0 (or slightly more than 4 days per week). Thus, compared to the NTBM analyses, data from the 2013-2014 Wave 1 PATH Study and Brand Tracker data show slightly higher mean use frequencies for current users of Camel Snus (2.4 days/week in NTBM vs. >4 days/week in the PATH Study and 3.5 days/week in Brand Tracker, respectively).

Patterns of Cigarette Smoking and Smokeless Tobacco Use Behavior

The applicant did not provide evidence from population-level studies to directly assess the likelihood that U.S. cigarette smokers would switch to (a) smokeless tobacco products or (b) the six Camel snus products specifically. Since RAIS' NTBM study was a repeated cross-sectional analysis of users, behavioral transitions assessing switching behavior within users cannot be assessed. Instead, the applicant utilized data from the NTBM Study to compare frequency of cigarette smoking (number of days in the past 30) among exclusive cigarette smokers to dual users of Camel Snus and cigarettes. The applicants' findings suggest that dual users of cigarettes and Camel Snus were less likely to report "near daily/daily use" compared to exclusive cigarette smokers (55.1% vs. 76.5%, respectively). In this analysis, dual users of Camel Snus and cigarettes were more likely to report smoking cigarettes on 2-5 days of the past week compared to exclusive smokers (25.3% vs. 15.1%) or on 0-1 days of the past week (19.6% vs. 8.4%). In a weighted linear regression analysis looking at trends of cigarette use frequency from 2013-2016, NTBM data suggested that frequency of cigarette use (number of days in the past 30) declined over time among dual users of cigarettes and Camel Snus, whereas frequency of cigarette use among exclusive smokers remained unchanged.

A clinical study conducted by the applicant (Section 6.1 of the MRTPAs) provided some insight into switching patterns among adult smokers. First, a randomized control trial conducted by the applicant (CSD1010) compared smoking cessation rates after 12 months among smokers intending to quit who were assigned to one of the following three groups: (1) those supplied with Camel Snus products and given one-time information about the relative risks of smoking versus smokeless tobacco use, (2) those supplied with Camel Snus products but not provided such information, or (3) those supplied with NRT (Nicorette nicotine lozenges). Findings from this study found no statistically significant difference in smoking cessation rates among smokers who were supplied Camel Snus or nicotine lozenges (regardless of whether they received the relative risk information). By study completion (Month 12), overall quit rates were low for all cessation endpoints (1%-10% depending on the endpoint). In a separate randomized control trial conducted by Hatsukami and colleagues (2015), investigators found no statistically significant differences in switching from cigarettes to Camel snus versus NRT at Week 6 (37.6% vs. 36.6%, respectively) or at Week 12 (26.8% vs. 28.4%, respectively). Notably, findings from subjective measures suggest that compared to nicotine gum users, snus users in this study reported less satisfaction and psychological reward from the product.

Under current real-world conditions, observational studies from the peer-reviewed literature have examined transitions from cigarette smoking to exclusive smokeless tobacco use. For example, Tam et al. (2015) published a systematic review that examined the proportion of tobacco users and non-users who transition between four tobacco use states over time: never use, exclusive smokeless use, exclusive smoking, and dual use. In this study, authors reported that the proportion of users demonstrating switching behaviors from exclusive smoking to exclusive smokeless tobacco use among adults was low (0%-1.4%), with transitions from exclusive smoking to dual use of cigarettes and smokeless tobacco being slightly more common (0.1%-3.2%). Compared to rates of switching from exclusive smoking to exclusive smokeless tobacco use, transitions from exclusive smokeless tobacco use to exclusive smoking also appeared to be more common (0.9%-26.6%), although significant variability in these estimates exist. Additionally, published analyses from the National Adult Tobacco Survey found that among recent former cigarette smokers (quit smoking within the past year), complete switching from cigarette smoking to smokeless tobacco in the past year was low (4.6% in 2012-2013, 4.5% in 2013-2014) (Anic et al., 2018). Similarly, data from the 2010-2011 Tobacco Use Supplement of the Current Population Survey (TUS-CPS) found that quitting one form of tobacco and switching to the other was infrequent (1.2% for cigarettes to smokeless tobacco vs. 1.4% from smokeless tobacco to cigarettes) (Chang, Levy &

Meza, 2017). Lastly, a naturalistic study of U.S. smokers found that despite a high degree of trial (84%) of snus through Week 58 of the study, only 11% reported purchasing the product at the end of the study period. Current snus use declined from 47.1% at Week 6 (when snus stopped being provided to participants for free) to 6.5% at Week 58 (Burris et al., 2016).

Summary and Conclusions

The prevalence of Camel Snus and other pouched snus use among U.S. adults is low, ranging from 0.4%-0.5%, depending on the data source and definition of current use. Based on data provided by the applicant from its NTBM and Brand Tracker surveys, characteristics of adults who currently use Camel Snus products are generally consistent with those of users of other smokeless tobacco products, such that current users are more likely to be aged 25-49 years, male, identify as non-Hispanic white, and report greater versus lesser educational attainment. In terms of patterns of use, cross-sectional data from the NTBM, Brand Tracker, and published data from the PATH Study suggest that patterns of dual/poly tobacco use among current users of Camel Snus is high—with concurrent use of Camel Snus, other smokeless tobacco products, and cigarettes being the most common. Additionally, findings from Cheng and colleagues (2017) found that pouched snus users in the U.S. were more likely to report non-daily and poly tobacco use than other users of other types of smokeless products.

Research submitted by the applicant and the published literature on smokeless tobacco provide limited evidence to suggest that current cigarette smokers, including those intending to quit, would switch completely to Camel Snus or other smokeless tobacco products. Data from the applicant's clinical study indicated low cigarette smoking quit rates ranging from 1-10%, depending on outcome. Hatsukami et al. (2015) found no statistically significant differences in switching from cigarettes to Camel snus versus NRT at Week 6 (37.6% vs. 36.6%, respectively) or at Week 12 (26.8% vs. 28.4%, respectively). Evidence from the broader peer-reviewed literature suggests that transitions from exclusive cigarette smoking to exclusive smokeless tobacco were rare (0%-1.4%), with transitions from exclusive cigarette smoking to dual use of cigarettes and smokeless tobacco being somewhat more common (0.1%-3.2%) (Tam et al., 2015). The applicant did not provide data on non-users of tobacco, particularly youth. An internal FDA assessment of existing evidence noted generally low prevalence of smokeless tobacco use in general and snus use, in particular among U.S. youth, compared to other tobacco products. However, it should be noted that some evidence exists regarding the likelihood that non-users who adopt smokeless tobacco may switch to other tobacco products, including cigarettes. As noted above, in a systematic review of multiple studies on smokeless tobacco use transitions (Tam et al., 2015), there was evidence of smokeless tobacco users moving to exclusive cigarette smoking (16.6% to 25.5% among adolescents).

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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)]. This means any 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) for which the tobacco product manufacturer 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 June 22, 2009, 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 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.congress.gov/111/plaws/publ31/PLAW-111publ31.pdf).

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

In 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 the MRTP presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the MRTP;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP;
- The risks and benefits to persons from the use of the MRTP compared to the use of smoking cessation drug or device products approved by FDA 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 file it. In general, after filing an application, FDA begins substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee (TPSAC). FDA intends to review and act on a complete MRTPA within 360 days of FDA filing an application. An order authorizing an MRTP refers to a specific product, not an entire class of tobacco products (e.g., all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is for a fixed period of time that will be determined by FDA and specified in the order. To continue to market an MRTP after the set term, an applicant would need to seek renewal of the order and FDA would need to determine that the findings continue to be satisfied. Also, 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. Before FDA withdraws an MRTP order, it will provide an opportunity for an informal hearing as required under the law.

Appendix B: Overview of RJRT-Sponsored Submitted Clinical Studies Conducted in the United States (Data Source: Study Reports in Section 7.4 of the MRTPAs)

Study Identifier & Dates	Study Design	Study Population (N=enrolled/completed)	Product(s) Groups (n=enrolled/completed)	Relevant Endpoints
01_HSD0702_QOL Conducted from: 2/2007 – 11/2007	Actual Use Study – Parallel group randomized controlled, 5-center,4-arm feasibility study (24-week ambulatory)	Generally healthy 28-55 year-old smokers (≥ 15 cpd, for ≥ 10 years) who were not intending to quit and willing to switch their tobacco product. Excluded asthma and 9.2% of enrollees had mild or moderate COPD (N=163 /130)	Camel Snus 400 mg: Frost, Original, or Spice (n=43/19) Tobacco Heated Cigarette Eclipse: Menthol or Regular (n=44/34) Ultra-low tar combusted cigarette: Regular or Menthol (n= 44/35) Never smokers (provided baseline data only) (n=32/32)	Behavior Pharmacology: Compliance with study product Biomarkers: 12 biomarkers of nicotine exposure, COHb, 21 BOE, 21 BOPH, urine mutagenicity (strain TA98 and strain YG1024), Sister Chromatid Exchange, Circulating endothelial precursor cells (CSR, Section 9.7.2-9.7.3, pp. 103-108/337 of the MRTPAs) Health Effects: SGRQ, LCQ, and SCQoL Medical history, Physical & Oral exams BMI Safety: Spirometry (statistically analyzed), ECO, Clinical labs (Table 9-3, p. 83/337), 12-Lead EKG, Vital Signs, AEs (HDYF? Inquiry with oral health questions)
Primary Objectives 1. Determine the feasibility of the study design and its analysis methodology 2. Assess subject compliance 3. Obtain data on the ability of Eclipse (a Tobacco-Heating Cigarette) and Snus to modify patient-reported health status in a comparison of Chronic Obstructive Pulmonary Disease (COPD) related health status as measured by the St. George's Respiratory Questionnaire (SGRQ) in subjects who smoked and were switched to either a Tobacco- Heating Cigarette or Snus relative to a control group (a tobacco-burning ultra-low "tar" cigarette [Tobacco-Burning Cigarette]) **Secondary Objectives** 1. Obtain data on the ability of a Tobacco-Heating Cigarette and Snus to modify health status as measured by the SGRQ, Leicester Cough Questionnaire (LCQ), and the Smoking Cessation Quality of Life Questionnaire (SCQoL) in subjects who smoked and were switched to either a Tobacco Heating Cigarette or Snus relative to a control group (a Tobacco-Burning Cigarette) 2. Obtain data in a comparison of health status measures (SGRQ, LCQ, SCQoL) in subjects who smoked and were switched to a Tobacco-Heating Cigarette to subjects who smoked and were switched to Snus 3. Evaluate selected biomarkers from subjects who smoked and who were switched to a Tobacco-Heating Cigarette, Snus, or a Tobacco-Burning Cigarette 4. Compare baseline data from all tobacco-using groups to baseline data from the never-smoking (nontreatment) group 5. Measure amount and repeatability of smoke components yielded from the cigarettes (yield in use [YIU]) and determine relative uptake of selected smoke components 6. Assess issues subjects might have bad with switching from their regular tobacco form to either a Tobacco-Heating Cigarette or Snus			
♦02_CSD0804_SMA Conducted during: 9/2008	Actual Use Study – Exploratory 4-center, open-label (seven-day ambulatory)	Generally healthy adult current smokers (N=56/53; 46 males)	Camel Snus 600 mg: Frost, Original or Spice	Behavior Pharmacology: Use behavior (consumption, use patterns) Mouth level exposure: nicotine, 5 TSNAs, B[a]P, arsenic, cadmium, chromium, lead,

Study Identifier & Dates	Study Design	Study Population (N=enrolled/completed)	Product(s) Groups (n=enrolled/completed)	Relevant Endpoints
				nickel (pouches assessed after use for chemical constituents, not included in review; deferred to toxicology or chemistry) Health Effects: None Safety: None
Primary Objective 1. Assess the MLE to selected tobacco constituents due to Camel Snus use among U.S. consumers who regularly use Camel Snus				
03_CSD0901_SSSO Conducted from: 9/2010 – 2/2011	Actual Use Study – Randomized controlled 3-center, open-label, forced-switching, parallel-group (5-day confined)	Generally healthy adult current smokers (N=181/167)	Camel Snus 600 mg: Frost or Mellow (n=31/30) Dual Camel Snus/Combusted Cigarettes (60% reduction) (n=30/29) Dissolvable Camel Strips (n=26/25) Dissolvable Camel Sticks (n=31/29) Dissolvable Camel Orbs (n=31/29) Abstinence (n=32/35)	Behavior Pharmacology: Abuse liability (dependence: QSU-B and MNWS) Biomarkers: 3 biomarkers of nicotine exposure, eCO, COHb, 26 BOE, urine mutagenicity (CSR, Table 14.2.3-1, pp. 417-418/3693) Health Effects: Medical history, Physical & Oral exams Safety: ECO & CoHb, Clinical labs, Vital signs, EKG, AEs
Primary objectives 1. Assess participant product usage rates, subjective responses, and mouth level exposure (MLE) to "tar" and/or nicotine when switched from usual brand (UB) cigarettes to 1 of 6 conditions: a. dual use of UB cigarettes and Snus b. exclusive use of Snus c. exclusive use of Sticks d. exclusive use of Strips e. exclusive use of Orbs f. tobacco abstinence 2. Measure and compare, within and between conditions, nicotine, and carbon monoxide (CO) exposures in expired-air, blood, and/or urine specimens during Baseline and at various times during the 5-day intervention period 3. Measure and compare, within and between conditions, select biomarkers of exposure and/or effect in blood and/or urine specimens during Baseline and on Day 5 of the intervention period 4. Determine the potential of the interventions to influence subjective responses by way of questionnaires on smoking urges, nicotine withdrawal, and product preferences				
04_CSD0904_PMS Conducted from: 2/2010 – 8/2010	Actual Use Study – Six-center cross-sectional cohort study of natural adopters (7 days' collection of used Snus pouches from *ad lib* ambulatory use; 1 days' collection of cigarette butts and retained Moist	Generally healthy, ≥19 years old current users of tobacco products of interest, (≥1 tin or can per week or ≥5 cpd as applicable for ≥6 months;) not intending to quit, and non-tobacco users (≥12 months with lifetime limits for use of various tobacco products).	Camel Snus 600 mg Frost or 600mg Mellow or 1000 mg ♦Winterchill (n=50/50) Dual Camel Snus/Combusted cigarette (n=50/50)	Behavior Pharmacology: Abuse liability (dependence: FTND), Use behavior (YIU and usage rate [time of day, quantity and types of tobacco products used daily]) Biomarkers: 11 biomarkers of nicotine exposure, COHb, 25

Study Identifier & Dates	Study Design	Study Population (N=enrolled/completed)	Product(s) Groups (n=enrolled/completed)	Relevant Endpoints
	Snuff containers from *ad lib* ambulatory use; 24-hour confinement for biomarker and physical measures)	(N=320/317)	Moist Snuff (any brand, style or flavor) (n=50/49) Dual Moist Snuff/Combusted cigarette (n=50/49) Combusted Cigarettes (excluded charcoal filters or crush-capsule cigarettes) (n=60/60) Non-tobacco Users (n=60/59)	BOE, 84 BOPH, micronucleated buccal cells (genotoxicity), urine mutagenicity (CSR, pp. 6-8/8490 in the MRTPAs) Health Effects: Medical history, Physical & Oral Exam, ScQOL (includes SF-36v2 and ATS), EKG, BMI, Clinical labs, Spirometry, Six-minute walk test Safety: Vital signs, AEs
Primary Objectives: The primary objective of this study was to establish baseline values for tobacco exposure levels, tobacco effect biomarker levels, and health status of natural adopters of each product class (i.e., cigarettes, moist snuff, Camel Snus, dual use of cigarettes and Camel Snus, dual use of cigarettes and moist snuff) and of Non-Tobacco Users to which similar values from future post-marketing studies may be compared. Measures of the current tobacco exposure, tobacco effect biomarker levels, and health status were established by: a. Determining the uptake of select tobacco constituents by measuring the level of biomarkers of tobacco exposure in blood, urine, and other biological samples b. Measuring the level of select biomarkers of tobacco effect in blood, urine, and other biological samples c. Estimating the maximum potential exposure to select smoke components by measuring the amount of smoke components yielded from the subject's usual brand (UB) of cigarettes (yield-in-use [YIU]) d. Estimating the maximum potential exposure to select tobacco components by measuring the amount consumed from used Camel Snus pouches (snus-after-use [SAU]); e. Determining tobacco use behavior by measuring usage rate (time of day, quantity and types of tobacco products used per day) f. Determining functional capacity based on subject performance in the Six-Minute Walk Test (6MWT) and on spirometry measures (i.e., difference in forced expiratory volume in 1 second [FEV1], taken before and after the 6MWT) g. Obtaining quality of life (QOL) measures as self-reported on select health status questionnaires h. Comparing obtained values to the National Health and Nutrition Examination Survey (NHANES) or other nationally-representative values, if available. **Secondary Objectives:** The secondary objective of this study was to evaluate current differences in tobacco exposure, effect measures, and health status among balanced subsets of subjects in the 5 groups of natural adopters of tobacco products (i.e., cigarettes, moist snuff, Camel Snus, dual use of cigarettes and Camel Snus, dual use of cigarettes and moist snuff) and the Non-Tobacco Users by: a. Comparing select biomarkers of tobacco exposure b. Comparing select biomarkers of tobacco effect c. Comparing the maximum potential exposures to select smoke components, as measured by YIU, between dual and exclusive users of cigarettes d. Comparing the maximum potential exposure to tobacco components, as measured by SAU, between dual and exclusive users of Camel Snus e. Comparing tobacco use behavior, as measured by usage rates **f.** Comparing functional capacity, as measured by subject performance in the 6MWT and by spirometry measures **g.** Comparing QOL measures, as self-reported on select health status questionnaire				
05_CSD0905_SL Conducted from: 3/2009 – 6/2009	Actual Use Study - Exploratory Single-center, open-label, within subjects, smoking reduction by dual use (4 weeks ambulatory)	Generally healthy adult current smokers (≥ 7 cpd) (N=36/32)	Camel Snus 600 mg: Frost or Mellow with usual brand combusted cigarettes	Behavior Pharmacology: Abuse liability (dependence: FTND and MNWS), Use behavior (use patterns) Biomarkers: 2 biomarkers of nicotine exposure, COHb, 27 BOE (CSR, Table 11, p. 15/43) Health Effects: Oral exams Safety: AEs

Study Identifier & Dates	Study Design	Study Population (N=enrolled/completed)	Product(s) Groups (n=enrolled/completed)	Relevant Endpoints
Primary Objective 1. To evaluate changes in product use patterns, biomarkers of tobacco exposure, and subjective responses of smokers as they changed their daily tobacco usage to include Camel Snus and reduce smoking				
06_CSD0914_SUL Conducted from: 9/2009 – 11/2009	Pharmacokinetic Study - Single-center, open-label, randomized, within-subjects crossover (single unit used per day for 6 days then one unit used under observation in lab for each product)	Generally healthy adult current smokers (10-30 cpd) [13/15 subjects also in previous RJRT study of short-term migrations to dual use of Orbs, Strips, Sticks, or Snus] (N=15/15)	Camel Snus 600 mg: Frost or Mellow Camel Orbs Camel Strips Camel Sticks Usual Brand combusted cigarette (lab visit one and between lab visits)	Behavior Pharmacology: Abuse liability (dependence: MPSS) Biomarkers: 2 biomarkers of nicotine exposure (PK assessment), eCO, COHb, 1 BOE Health Effects: None Safety: AEs
Primary objective 1. To determine serum nicotine uptake over a three-hour period following initiation of product use to clarify nicotine uptake results from use of modem smoke-free tobacco (MSFT) products observed in previous RJRT studies **Secondary objectives** 1. To assess tobacco abstinence symptoms prior to and at designated intervals following initiation of MSFT product use 2. To assess carboxyhemoglobin levels prior to and for one hour following initiation of product use after overnight tobacco abstention				
07_CSD1010_SS Conducted from: 2/2011 – 6/2012	Actual Use Study - Six-center, randomized open-label, 3 group, cessation study (52-weeks ambulatory)	Generally healthy, 21-65 year-old smokers (≥10 cpd for ≥ 1 year) who were willing to quit smoking, (N=649/216)	Camel Snus 600 mg: Frost or Mellow (n=218/72) Camel Snus 600mg: Frost or Mellow with relative risk information (n=218/66) Nicorette® Nicotine Polacrilex Lozenge 4mg: Original or Mint (n=213/78)	Behavior Pharmacology: Abuse liability (dependence: FTND, QSU-B, MNWS), Use behavior (cigarette smoking cessation rates) Biomarkers: 2 biomarkers of nicotine exposure (plasma nicotine and cotinine), eCO, COHb, 1 BOE (plasma thiocyanate) Health Effects: Current medications at baseline & weeks 2, 7, 11, 12, 24-25, 26, 39, 51, 52 Body weight at screening, weeks 12 & 52 Safety: Vital signs at baseline, weeks 2, 7, 12, 26, & 52; Oral exams (baseline & week 12); Clinical labs (at screening only); AE assessments at baseline & weeks 2, 7, 11, 12, 24-25, 26, 39, 51, 52
Primary Objective The primary objective of this study was to compare smoking cessation rates among 3 study cohorts for up to 12 months: • Cohort 1: Cigarette smokers who were switched to Camel Snus and informed of the benefits of smoking cessation and the relative risks of smoking cigarettes vs. smokeless tobacco product (smokeless tobacco) use				

Study Identifier & Dates	Study Design	Study Population (N=enrolled/completed)	Product(s) Groups (n=enrolled/completed)	Relevant Endpoints
• Cohort 2: Cigarette smokers who were switched to Camel Snus and informed of the benefits of smoking cessation, but not informed of the relative risks of smoking cigarettes vs. smokeless tobacco use • Cohort 3: Cigarette smokers who were switched to a nicotine lozenge and informed only of the benefits of smoking cessation **Secondary Objectives** 1. To determine relationships between the following subject-reported outcomes and study endpoints: a. The relationship between Fagerström Test for Nicotine Dependence (FTND) scores and smoking cessation rates for each cohort at Months 3, 6, and 12, for each smoking cessation rate b. The relationship between Smoking Urges (Brief Questionnaire of Smoking Urges [B-QSU) endpoints and time (study week) by cohort for: o Successful quitters who continued to use smokless tobacco/nicotine replacement therapy (NRT) o Successful quitters who ceased smokeless tobacco/NRT use c. The relationship between nicotine withdrawal symptoms (Minnesota Nicotine Withdrawal Scale–Revised [MNWS-R]) endpoints versus time (study week) by cohort for: o Successful quitters who continued to use smokeless tobacco/NRT o Successful quitters who ceased smokeless tobacco/NRT use d. The relationship of plasma concentrations of nicotine and cotinine to: o MNWS-R score o B-QSU score 2. To better understand product usage, the relationship between product usage and biomarkers of exposure and smoking cessation rate at Month 12, regardless of earlier "treatment failure", the following secondary objectives were explored: a. The relationship of plasma concentrations of nicotine and cotinine versus time (study week) for: o Quitters who stopped using NRT by Week 12 (ie, Month 3) o Quitters who stopped using Camel Snus by Month 3 o Quitters who continued to use NRT after Month 3 o Quitters who continued to use smokeless tobacco after Month 3 b. The relationship between exhaled carbon monoxide (ECO) levels and time (study week) for quitters in each cohort c. The relationship between cigarette usage and time (study week) for/by: o Treatment failures (excluding dual use) o Dual-users (smokeless tobacco and NRT handled separately) o Gender o Race d. By cohort, the percentage of smokers who ceased smoking (point prevalence) at Month 12. e. By cohort, the percentage of smokers who continued to use study product beyond Month 3 f. By cohort, the percentage of smokers who used any smokeless tobacco beyond Month 3 g. By cohort, the percentage of smokers who used any NRT beyond Month 3				
08 CSD1101 STM Conducted from: 10/2011 – 12/2011	Pharmacokinetic Study - Single-center, open-label, randomized, within subjects crossover design (single use days for each product)	Generally healthy adult current smokers (10-30 cpd) (N=17/16)	Camel Snus 600 mg: Frost (b) (4) (b) (4) (b) (4)	Behavior Pharmacology: Abuse liability (dependence: MPSS) Biomarkers: 2 biomarkers of nicotine exposure (serum nicotine and cotinine) Health Effects: None Safety: Physical and oral exams, Clinical labs, Vital signs, AEs
Primary Objectives 1. To assess the following after a 12-hour of tobacco and nicotine abstinence: a. Nicotine uptake in blood over a 3-hour period with respect to in-clinic product administration b. Tobacco abstinence symptoms over a 3-hour period with respect to in-clinic product administration				

♦ Submission consisted of a published paper (Caraway & Chen, 2013) with a statistical analysis plan and data files and was characterized in the August 24, 2017 amendment to the applications as a "marketing study."

♦ Number of subjects using Winterchill is unclear but very small (n=2 to 5 in various documents)

Note: No submitted clinical studies were conducted outside the U.S.

Glossary: cpd = cigarettes per day. QSU = Questionnaire of Smoking Urges brief version. MNWS = Minnesota Nicotine Withdrawal Scale. FTND = Fagerström Test for Nicotine Dependence. MCEQ = Modified Cigarette Evaluation Questionnaire. MPSS = Mood and Physical Symptoms Scale. TSNA = tobacco-specific nitrosamine. B[a]P = benzo(a)pyrene. eCO = exhaled carbon monoxide. COHb = carboxyhemoglobin. SGRQ= St. George's Respiratory Questionnaire. LCQ = Leicester Cough Questionnaire. SCQoL = Smoking Cessation

Quality of Life Questionnaire. SF-36 = Standard Form 36. ATS = American Thoracic Society Questionnaire. BMI = body mass index. AE = adverse event or adverse experience. EKG = electrocardiogram. CSR = Clinical Study Report. HDYF? = How Do You Feel?. BOE= Biomarkers of Exposure. BOPH = Biomarkers of Potential Harm. AE = Adverse experience.

Appendix C: Summary of the Study Characteristics of National Health Examination Survey I (NHANES-I) Epidemiological Follow-up Study, the Cancer Prevention Study (CPS)-I and CPS-II (Data Source: Section 6.1.1 of the MRTPAs)

Study Characteristic	National Health Examination Survey I (NHANES-I) Epidemiological Follow-up Study (NHEFS) (Accortt et al. 2002)	Cancer Prevention Study (CPS)-I (Henley et al. 2005)	Cancer Prevention Study (CPS)-II (Henley et al. 2005)
Study population	Participants from First National Health Examination Survey (NHANES-I) who participated in ≥1 round of NHANES-I Epidemiologic Followup Studies (NHEFS) conducted in 1982-84, 1986, 1987, 1992	Friends, neighbors, acquaintances of American Cancer Society (ACS) volunteers who at baseline identified as either: -current smokeless tobacco users who never used any other tobacco product - never users of any tobacco product (cigarettes, smokeless tobacco, cigars, pipes)	Friends, neighbors, acquaintances of American Cancer Society (ACS) volunteers who at baseline identified as either: -current smokeless tobacco users who never used any other tobacco product -former smokeless tobacco users who never used any other tobacco product - never users of any tobacco product (cigarettes, smokeless tobacco, cigars, pipes)
Study period	1971-1975 to 1992; 10, 15, 20 years follow up	1959-1971; 12 years follow up	1982-2000; 18 years of follow up
Age at baseline	45 to 75 years of age	≥30 years	≥30 years
Sex	Males and females	Males	Males
Study size (approximate)	500 exclusive ever smokeless tobacco users 900 ever users of smokeless tobacco and cigarettes 5,000 never users of smokeless tobacco or cigarettes Both exclusive ever smokeless tobacco users and the never users of smokeless tobacco or cigarettes could have used pipes or cigars Analyses excluded those with the disease outcome at baseline.	7,700 current exclusive smokeless tobacco users (never used any other tobacco product(s)) 70,000 never tobacco users Analyses excluded those with the disease outcome at baseline.	2,400 current exclusive smokeless tobacco users (never used any other tobacco product(s)) 800 former exclusive smokeless tobacco users 111000 never tobacco users Analyses excluded those with the disease outcome at baseline.
Smokeless tobacco type	Smokeless tobacco	Smokeless tobacco, chewing tobacco, snuff (study authors refer to as "spit tobacco")	Smokeless tobacco, chewing tobacco, snuff (study authors refer to as "spit tobacco")
Exposure ascertainment	Responses to NHANES I via in-person interview on current smokeless use status and when missing, applied responses from 1982-84 NHEFS on ever smokeless tobacco use	Tobacco use status ascertained from questionnaire completed at baseline. Cohort was not re-interviewed for potential changes in tobacco use status over time.	Tobacco use status ascertained from questionnaire completed at baseline. Cohort was not re-interviewed for potential changes in tobacco use status over time.
Mortality Outcome	Lung cancer (ICD-9: 162), respiratory diseases (ICD-9: 460-519), ischemic heart disease (ICD-9: 410-414), stroke (ICD-9: 430-438), all causes.	Lung cancer (ICD-8: 162-163), oral cancer (ICD-8: 140-148), COPD (ICD-8: 480-493), coronary heart disease (ICD-8: 420), stroke (ICD-8: 330-334), all causes, plus additional smoking-related causes of disease.	Lung cancer (ICD-9: 162), oral cancer (ICD-9: 140-149), COPD (ICD-9: 490-492, 496), coronary heart disease (ICD-9: 410-414), stroke (ICD-9: 430-438), all causes plus additional smoking-related causes of disease.
Outcome ascertainment	Cause of death codes obtained from death certificate	Vital status determined through personal enquiry from ACS volunteers with	From 1982-88, through personal inquiries from volunteers of ACS with

	Death certificate information obtained for 98% of known deaths	reported deaths verified by death certificate Death certificate information obtained for 97% of known deaths	reported deaths verified by death certificate; From 1988-2000, through automated linkage with the National Death Index Death certificate information obtained for 98.9% of deaths
Measure	Hazard ratio	Hazard ratio	Hazard ratio
Adjustment factors	Age, race, poverty index ratio, region, alcohol, exercise, fruit/vegetable intake, systolic blood pressure, cholesterol, BMI	Age, race, educational level, BMI, exercise, consumption of: alcohol, fat, fruit/vegetables, aspirin intake	Age, race, education level, BMI, exercise, consumption of: alcohol, fat, fruit/vegetables, aspirin intake, employment type and status

Appendix D: Disease Endpoints used in Epidemiological Studies of Health Risks of Tobacco Use (Data Source: Section 6.1.1 of the MRTPAs)

Disease Endpoint	Corresponding ICD-code(s)[a]	Description of Conditions Included in Each Disease Endpoint
Lung Cancer	ICD-9: 162	Malignant neoplasms of the trachea, bronchus, lung
Respiratory Disease	ICD-9: 460-519: Respiratory diseases ICD-9: 480-487: influenza/pneumonia ICD-9: 490-492, 496: COPD	Asthma, chronic obstructive pulmonary disease (including chronic bronchitis, emphysema, chronic obstructive bronchopulmonary disease), chronic respiratory symptoms (cough, phlegm, wheeze), influenza, pneumonia, acute respiratory illnesses
Oral Cancer	ICD-9: 140-149	Mouth including tongue, gums, cheeks and roof of the mouth. Pharynx including back of the mouth and throat (nasopharynx, oropharynx, and hypopharynx) Cancer of the lips may be included in oral cancer
Heart Disease	ICD-9: 410-414	Acute myocardial infarction, other acute and subacute forms of ischemic heart disease, old myocardial infarction, angina pectoris, other forms of chronic ischemic heart disease Coronary heart disease and ischemic heart disease are used interchangeably in the applications

[a] The available epidemiological evidence was collected over several decades. While multiple studies relied on ICD-9 (e.g., Accortt et al., 2002; Henley et al. 2007; Henley et al. 2005 for CPS-II only), studies also relied on corresponding disease codes for ICD-8 and ICD-10. To simplify the table, only ICD-9 codes are reported.
COPD is chronic obstructive pulmonary disease.

Appendix E: Cohort and Case-Control Studies of Smokeless Tobacco Use and Lung Cancer, Oral Cancer and Heart Disease Cited in Selected Meta-Analyses

(Data Source: Sections 6.1.1.3.1, 6.1.1.3.3 and 6.1.1.3.4 of the MRTPAs)

Disease endpoint	Meta-analysis reference	Smoker adjustment for summary relative risk	No. estimates for summary relative risk	Underlying references/study populations
Heart disease (fatal)[a]	Boffetta and Straif (2009)	Never smokers	3	1: NHANES-I/NHEFS (Accortt et al. 2002) 2. CPS-I (Henley et al. 2005) 3. CPS-II (Henley et al. 2005)
	Lee (2007)	Never smokers	3	1: NHANES-I/NHEFS (Accortt et al. 2002) 2. CPS-I (Henley et al. 2005) 3. CPS-II (Henley et al. 2005)
Lung cancer (fatal)	Boffetta et al. (2008)	Never smokers	3	1: CPS-I (Henley et al. 2005) 2. CPS-II (Henley et al. 2005) 3. Not provided[b]
	Lee and Hamling (2009a)	Overall data	6	1: NHANES-I/NHEFS (Accortt et al. 2002) 2. CPS-I (Henley et al. 2005) 3. CPS-II (Henley et al. 2005) 4. Williams and Horm 1977 (males only) 5. Williams and Horm 1977 (females only) 6. Wynder and Stellman 1977
		Smoking-adjusted	4	1: NHANES-I/EFS (Accortt et al. 2002) 2. CPS-I (Henley et al. 2005) 3. CPS-II (Henley et al. 2005) 4. Williams and Horm 1977 (males only)
		Never smokers	3	1: NHANES-I/EFS (Accortt et al. 2002) 2. CPS-I (Henley et al. 2005) 3. CPS-II (Henley et al. 2005)
Oral cancer (fatal or incident)	Boffetta et al. (2008)	Never smoking or smoking-adjusted	9	1. CPS-I (Henley et al. 2005) 2. CPS-II (Henley et al. 2005) 3. Blot et al. 1988 4. Mashberg et al. 1993 5. Kabat et al. 1994 6. Winn et al. (1981), white women only 7. Winn et al. (1981), African-American women only 8. Stockwell and Lyman (1986) tongue cancer 9. Stockwell and Lyman (1986) mouth cancer
	Lee and Hamling (2009a)	Overall data	31	1. CPS-I (Henley et al. 2005) 2. CPS-II (Henley et al. 2005) 3. Keller et al. 1970 4. Blot et al. 1988 (males only) 5. Blot et al. 1988 (females only) 6. Kabat et al. 1994 7. Broders 1920 8. Wynder and Bross 1957 9. Winn et al. 1981 10. Sterling et al. 1992 11. Mashberg et al. 1993 12. Perry et al. 1993[c] 13. Schwartz et al. 1998 14. Moore et al. 1953

				15. Peacock et al. 1960 (males only) 16. Peacock et al. 1960 (females only) 17. Volger et al. 1962 (males only) 18. Volger et al. 1962 (females only) 19. Vincent and Marchetta 1963 (males only) 20. Vincent and Marchetta 1963 (females only) 21. Martinez et al. 1969 22. Williams and Horm 1977 (males only) 23. Williams and Horm 1977 (females only) 24. Wynder and Stellman 1977 25. Zahm et al. 1992 26. Westbrook et al. 1980 27. Wynder et al. 1983 28. Stockwell and Lyman (1986) 29. Spitz et al. 1988 30. Maden et al. 1992 31. Muscat et al. 1998
		Smoking-adjusted	12	1. CPS-I (Henley et al. 2005) 2. CPS-II (Henley et al. 2005) 3. Keller et al. 1970 4. Blot et al. 1988 5. Kabat et al. 1994 6. Broders 1920 7. Wynder and Bross 1957 8. Winn et al. 1981 9. Sterling et al. 1992 10. Mashberg et al. 1993 11. Perry et al. 1993 12. Schwartz et al. 1998
		Never smokers	5	1. CPS-I (Henley et al. 2005) 2. CPS-II (Henley et al. 2005) 3. Keller et al. 1970 4. Blot et al. 1988 5. Kabat et al. 1994

[a] Also referred to in the meta-analyses as fatal myocardial infarction or ischemic heart disease

[b] According to Table 2 of Boffetta et al. 2008, three estimates from U.S. studies on risks of lung cancer among smokeless tobacco users were used to produce the summary relative risk estimate, however Table 1 of their publication only presents the values for two U.S. estimates of lung cancer: CPS-I and CPS-II

[c] Lee and Hamling 2009a explain the attributable oral cancer risk due to smokeless tobacco use based on a case-control study at Sinai Hospital in Detroit, Perry et al., unpublished. Cited by Gross et al. 1995.

Note: NHANES-1/NHEFS is the National Health and Nutrition Examination Survey-I, Epidemiologic Followup Survey; CPS-I is Cancer Prevention Study-I; CPS-II is Cancer Prevention Study-II

Appendix F: Estimates of the Relative Risks (RR) for Adult Mortality from Selected Smoking-Related Diseases among U.S. Males and Females Aged >35 years, According to Smoking Status, as Compared to Never Smokers, Cancer Prevention Study-II (Data Source: Section 6.1.1.2 of the MRTPAs)

	Men		Women	
Disease Category (ICD-10)	**RR Current Smokers**	**RR Former Smokers**	**RR Current Smokers**	**RR Former Smokers**
Malignant neoplasms				
Lip, oral cavity pharynx (C00-C14)	10.89	3.40	5.08	2.29
Esophagus (C15)	6.76	4.46	7.75	2.79
Stomach (C16)	1.96	1.47	1.36	1.32
Pancreas (C25)	2.31	1.15	2.25	1.55
Larynx (C32)	14.60	6.34	13.02	5.16
Trachea, lung, bronchus (C33-C34)	23.26	8.70	12.69	4.53
Cervix uteri (C53)	n/a	n/a	1.59	1.14
Kidney and renal pelvis (C65-C65)	2.72	1.73	1.29	1.05
Urinary bladder (C67)	3.27	2.09	2.22	1.89
Acute myeloid leukemia (C92.0)	1.86	1.33	1.13	1.38
Cardiovascular diseases				
Coronary heart disease (I20-I25)				
Persons aged 35-64 years	2.80	1.64	3.08	1.32
Persons aged ≥65 years	1.51	1.21	1.60	1.20
Other heart disease (I00-I09, I26-I28, I29-I51)	1.78	1.22	1.49	1.14
Cerebrovascular disease (I60-I69)				
Persons aged 35-64 years	3.27	1.04	4.00	1.30
Persons aged ≥65 years	1.63	1.04	1.49	1.03
Atherosclerosis (I70)	2.44	1.33	1.83	1.00
Aortic aneurysm (I71)	6.21	3.07	7.07	2.07
Other arterial disease (I72-I78)	2.07	1.01	2.17	1.12
Respiratory diseases				
Influenza, pneumonia (J10-J11, J12-J18)	1.75	1.36	2.17	1.10
Bronchitis, emphysema (J40-J42, J43)	17.10	15.64	12.04	11.77
Chronic airways obstruction (J44)	10.58	6.80	13.08	6.78

Notes: This information is also presented in Table 12.1, page 652 of US DHHS, 2014. Appendix E combines the information presented in Tables 6.1.1-1 and 6.1.1.-2 of Section 6.1.1.2 of the MRTPAs. Never smokers defined as never users of cigarettes, pipes or cigars. N/A is not available. RR is relative risk.

Appendix G: Example of the Three-Page Print Ad Submitted in the MRTPAs
(Execution 2; Source: Section 4 of the MRTPAs)


CAMEL
WHAT IS CAMEL SNUS?
• Camel SNUS (rhymes with "moose") is finely ground premium tobacco in a soft fleece pouch.
• Like all tobacco products, Camel SNUS contains nicotine and is addictive.
HOW IS IT DIFFERENT?
• Many smokeless tobacco products, like dip and chew, are fermented loose tobacco.
• Sure, they're smoke-free, but they can get messy and require spitting.
• Snus is different. It's smoke-free, mess-free and spit-free.
• Camel SNUS is heat-treated, not fermented, and crafted with four main ingredients: tobacco, water, salt and flavoring.
HOW DO I USE IT?
• Slide a pouch under your upper lip.
• Taste the real, premium tobacco.
• Dispose of the pouch in the trash when you are finished.
• Switch completely from cigarettes to Camel SNUS.
4 SIMPLE MAIN INGREDIENTS
TOBACCO
WATER
SALT
FLAVORING
Regular
Large
2 POUCH SIZES
(actual size)
5 FLAVORS
15 POUCHES PER TIN
CUSTOMIZE YOUR ENJOYMENT WITH UP TO
30 MINUTES
OF FLAVOR PER POUCH
SNUS
WARNING: This product can cause mouth cancer.

NO SMOKE = LESS RISK

Smokers who **SWITCH COMPLETELY** from cigarettes to Camel SNUS can greatly reduce their risk of lung cancer, oral cancer, respiratory disease and heart disease.

Scientific studies have shown that Camel SNUS contains less of the harmful chemicals than cigarette smoke.

Camel SNUS is smoke-free, so there are no secondhand smoke risks for those around you.

DISCOVER MORE @ SNUSNATION.COM*

NO TOBACCO PRODUCT IS SAFE

- Like all tobacco products, Camel SNUS **contains nicotine** and **is addictive.**
- Adults who do not use or have quit using tobacco products should not start.
- **Minors and pregnant women should never use tobacco products.**
- If you're a smoker concerned about the health risks from smoking, the best choice is to quit. A good place to begin is talking with a healthcare provider.
- But if you're not going to quit using tobacco products, you should think about switching to Camel SNUS.

I'M A SMOKER. WHY SHOULD I SWITCH?

Switching to SNUS means...

- Less of the harmful chemicals found in cigarette smoke
- Less risk for you and those around you
- No lingering smoke smell
- Hassle-free tobacco

SNUS

*WEBSITE RESTRICTED TO AGE 21+ TOBACCO CONSUMERS

WARNING: This product can cause mouth cancer.