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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
B(a)P	benzo(a)pyrene
CDC	Centers for Disease Control and Prevention
C_{max}	maximum concentration
CMC	chemistry, manufacturing, and control
COPD	chronic obstructive pulmonary disease
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRP2.1	CORESTA Smokeless Tobacco Reference Product 2.1
ENDS	Electronic Nicotine Delivery Systems
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
HPHC	harmful and potentially harmful constituent
MRTPA	modified risk tobacco product application
NNK	(4-methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
PK	pharmacokinetics
PMTA	Premarket Tobacco Product Application
PSWL	portion snus white large
QRA	quantitative risk assessment
ST	smokeless tobacco
TNP	tobacco/nicotine product
TPL	Technical Project Lead
TSNA	tobacco-specific nitrosamine
US	United States

1 INTRODUCTION

Pursuant to Section 910(c)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Swedish Match USA, Inc. (Swedish Match) requests marketing authorization in this Premarket Tobacco Product Application (PMTA) for ZYN®. ZYN is currently marketed in the United States (US), Sweden, Denmark, and selected locations in Europe. Although ZYN has been marketed in the US since 2014 (ie, prior to 08 August 2016), the product is a "new tobacco product" under Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the US as of 15 February 2007.

In the absence of other relevant Food and Drug Administration (FDA) guidance documents, the *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)* Guidance for Industry (June 2019) (FDA PMTA ENDS Guidance 2019) is relied on for this PMTA because the guidance can be applied to a smokeless nicotine product, such as ZYN. In addition, this application is also reflective of the proposed rule for PMTAs (FDA Proposed Rule 2019).

1.1 Product

ZYN is a non-heated, tobacco-free, smoke-free, and spit-free nicotine pouch intended for oral use with an appearance similar to that of Swedish snus products that is intended for adult tobacco and nicotine consumers. As with other nicotine-containing products, ZYN packaging includes the following warning:

- WARNING: This product contains nicotine. Nicotine is an addictive chemical.

ZYN comes in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 and 6 mg per pouch). ZYN is intended to be placed between the gum and the upper lip and enjoyed for up to 60 minutes, then discarded, as the product is not intended to be swallowed or reused.

1.2 Relevant Comparators

In terms of health effects a reasonable comparator to ZYN is cigarettes as cigarette smoking accounts for the vast majority of tobacco-related morbidity and pre-term mortality in the US and by far represent the most commonly used tobacco product on the US market. In the PMTA ENDS Guidance, the FDA recommends that a new product be compared to an existing product within the same category. Consumer data from the study (b) (4) shows that moist snuff was the most commonly used tobacco product the weeks before starting to use ZYN.

Therefore, in this PMTA, ZYN is compared with one moist snuff reference product, CRP2.1 (Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) Smokeless Tobacco Reference Product 2.).

Bridging to Swedish snus products is relevant since the products are similar in terms of use topography. In this PMTA, ZYN is also compared with the existing smokeless tobacco product General snus.

1.2.1 General Snus

General Snus, a Swedish-style snus, received PMTA marketing authorizations (PM0000010 - PM0000017) on 10 November 2015 and modified risk orders (MR0000020 – MR0000022,

MR0000024 – MR0000025, and MR0000027 – MR0000029) on 22 October 2019. Both the ZYN and General Snus products can be categorized as smokeless pouch products, are used in the same way (between the gum and the upper lip), and are similar in shape and size (although ZYN is slightly smaller). Both products are manufactured by the same company. The snus products to which the ZYN products are compared are produced under Swedish Match proprietary quality standard GOTHIATEK®. The ZYN products are produced under a quality management system ensuring that almost none of the harmful and potentially harmful constituents (HPHCs), which are governed by the GOTHIATEK standard, can be detected in the ZYN products.

As noted in the FDA PMTA TPL Review 2015, Section V. Conclusions and Recommendations, the topline reasons for granting PMTA marketing authorization of General Snus included the following:

- The manufacturing under the GOTHIATEK quality system as described above.
- The General Snus products have significantly lower levels of what are likely the most carcinogenic constituents in tobacco products (N-nitrosonornicotine [NNN] and (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) compared to >97% of the ST products currently on US market.
- The levels of other HPHCs in General Snus are similar or lower than the levels in other ST products.
- When used exclusively instead of other US market ST products or cigarettes, General Snus offers potential for reductions in oral cancer.
- When used exclusively instead of cigarettes, General Snus offers lower risk of developing respiratory diseases (ie, chronic obstructive pulmonary disease [COPD], emphysema, and chronic bronchitis) and certain cancers (such as oral, esophageal, and lung).
- It is anticipated that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

As noted in the FDA MRPTA TPL Review 2019 for General Snus,

- "The applicant **has demonstrated** that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information 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. The claim 'Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis' is scientifically accurate."
- "In sum, FDA's assessment of the scientific evidence supports the conclusion that exclusive users of snus have lower risk relative to cigarette smokers for each of these health outcomes: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. This assessment supports the revised modified risk claim as scientifically accurate. Overall, the available scientific evidence demonstrates that the products that are the subject of these applications, as actually used by consumers, will

significantly reduce harm and the risk of tobacco-related disease to individual tobacco users."

- "Subsequent to the completion of FDA's review, Rostron and colleagues (2018) conducted a systematic review and meta-analysis of studies pertaining to smokeless tobacco use and circulatory disease risk, providing a more comprehensive examination of this relationship, including more recent data (e.g., Timberlake et al., 2017). Based on this review, risk of ischemic heart disease was not increased in Swedish studies of current smokeless tobacco users who were never smokers (vs. non-users) (RR=1.04, 0.93-1.16, n=3), but was significantly increased in U.S. studies of smokeless tobacco users who were never smokers (RR=1.17, 95% 1.08-1.27, n=3). By comparison…cigarette smoking has been found to increase risk of cardiovascular disease by a factor of about 1.5- to 3-fold. This most recent review provides clear evidence that the heart disease risks due to Swedish snus use are lower than the risks from cigarette smoking."

Therefore, this PMTA presents a full assessment of ZYN, demonstrating that it compares favorably to General Snus and is appropriate for the protection of the public health.

1.2.2 CRP2.1

CRP2.1 is an American-style loose moist snuff ST product that was produced without added flavorings, except for those required to produce a product that is characteristic of the style. It is manufactured for use in scientific studies as a reference standard product and is packaged in plastic cans that contain 34 g of the product (CORESTA 2019).

1.3 Systematic Literature Review

Swedish Match began selling ZYN in 2014, and to date, there is no published literature on the use of ZYN. Because ZYN exposes the user to similar levels of nicotine to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, health effects of snus could be considered to be a measure of maximum health risks. Therefore, a systematic review of the literature on the health effects, tobacco use behaviors, and perceptions of risk pertaining to the use of Swedish snus, a relevant comparator product, was performed as part of an update to the Section I.1 (b) (4) , which was previously conducted for the General Snus PMTA and modified risk tobacco product application (MRTPA) and included a comprehensive review of the available literature on snus through December 2012 and also selected important new publications as available through April 2013. In addition to the previous (b) (4) (b) (4), this PMTA includes two updates of the literature published since 01 December 2012 through 28 July 2017 and not included in the previous review:

- Section I.1 Health Effects and Meta-Analysis Update Report, which reviews the health effects of Swedish snus, both absolute and relative to combustible cigarette smoking, as well as *in vitro* and *in vivo* toxicology studies of Swedish snus.
- Section I.1 Use Behavior Update Report, which reviews tobacco use behaviors and perceptions of risk pertaining to the use of Swedish snus.

These reports include full details on the search strategy and methods as well as the synthesis of results.

When relevant, additional literature published after 28 July 2017 was included.

2 CHEMISTRY, MANUFACTURING, AND CONTROLS

ZYN is a tobacco-free, nicotine pouched product. Section C Descriptive Product Information provides an executive summary of the chemistry, manufacturing, and control (CMC) information for ZYN. Detailed summaries of the CMC for ZYN are presented in Section G.2 Product Design Summary, Section G.3 Product Manufacturing and Controls Summary, and Section G.4 Product Composition Summary.

3 NONCLINICAL EVALUATION

As FDA considers the chemical composition of a product as a major indicator of risk to consumers' health, Swedish Match conducted extensive product testing including chemical analyses of ZYN. ZYN only contains ingredients that are approved by health authorities.

The mutagenic and genotoxic potential of ZYN was assessed using the Ames and *in vitro* micronucleus assays (Section H.2.3 Study (b) (4)). *In vivo* nonclinical studies have not been conducted with ZYN, as nicotine, the active ingredient, has been studied extensively and is well characterized.

There is extensive published literature on the toxicology of Swedish snus, and although ZYN does not contain tobacco-specific nitrosamines (TSNAs), it serves as a surrogate for ZYN as noted in Section 1.2.

3.1 HPHCs

In its evaluation of HPHCs in the General Snus PMTAs (FDA PMTA TPL Review 2015), FDA focused mainly on NNN and NNK and noted that the

> "products contain significantly lower levels of NNN and NNK compared to over 97% in the smokeless tobacco (ST) products currently on US market. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers using ST products. Assuming persons who would have used other US ST products use these product instead, an individual using these products with reduced NNN levels could decrease the excess cancer risk by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of United States (US)-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor."

No threshold level has been set for NNN and NNK in relation to the risk of cancer from a toxicologic standpoint. However, the levels of carcinogenic substances such as TSNAs (eg, NNN and NNK) and benzo(a)pyrene (B(a)P) are below the limit of quantification in ZYN, whereas General Snus contains low levels of TSNAs and B(a)P.

The nicotine content of ZYN is lower compared to the General Snus products, which received PMTA marketing authorizations and modified risk orders. As noted in the FDA PMTA TPL Review 2015, "these nicotine values are within the reported ranges from other marketed US moist snuff." Nicotine pharmacokinetic (PK) studies on ZYN are provided as part of this application (Section G.6 Human Health Impact Evaluation Summary, Section 5).

In the FDA PMTA ENDS Guidance 2019, FDA recommends testing for HPHCs and biomarkers of harm/exposure (eg, cotinine and NNN). However, as noted above, ZYN contains no measurable levels of nitrosamines or polycyclic hydrocarbons. For this application, the HPHCs in ZYN were compared to two ST products: General Snus and CRP2.1. Quantitative health risk assessments were also performed for measurable HPHCs and for the flavor component (b) (4) (b) (4) .

3.1.1 Analysis of HPHCs

Of the 93 HPHCs identified in tobacco products and tobacco smoke (FDA Established List of HPHCs 2012), only 20 HPHCs are present in General Snus. Swedish Match analyzed 45 HPHCs for ZYN, and 37 were below the limit of quantification.

Notably, ZYN does not contain measurable quantities of TSNAs (NNN and NNK) or B(a)P, which were present at low levels in General Snus. The broad chemical characterization of ZYN has shown that the product contains a very limited number of harmful and potentially harmful constituents, of which most were significantly reduced compared to the levels found in General Snus. The levels of HPHCs found in ZYN were always lower than those in the CRP2.1 reference product comparator based on per unit of use, and the only exception was the flavoring substance coumarin that is specific to the ZYN Cinnamon product.

The levels of HPHCs in all of the finished product of ZYN SKUs and the analysis of HPHCs in ZYN relative to General Snus and CRP2.1 comparators are discussed in detail in Section G.5 Nonclinical Evaluation Summary, Section 3.

3.1.2 Quantitative Health Risk Assessments of HPHCs Detected in ZYN

Quantitative health risk assessments (QRAs) were performed for measurable HPHCs in ZYN and the flavor component, (b) (4) , which is found in ZYN Wintergreen.

Based on the QRAs, the levels of HPHCs (formaldehyde, acetaldehyde, coumarin, naphthalene, (b) (4) , and (b) (4)) in ZYN were below health-based- threshold limit values. Under reasonably foreseeable conditions of use of ZYN, the levels do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.

Based on the QRA, Swedish Match concludes that the level of (b) (4) in ZYN Wintergreen is not likely to have an adverse effect on public health.

Thus, the toxicological safety profile of ZYN represents a significant improvement over snus.

The QRAs are discussed in detail in Section G.5 Nonclinical Evaluation Summary, Section 4.

3.2 Nonclinical Safety

The mutagenic and genotoxic potential of ZYN was assessed using the Ames assay and the *in vitro* micronucleus assay, and CRP2.1 was also tested as a comparator. The studies conducted in support of each of the 10 flavors of ZYN 6 mg demonstrate that the products are not mutagenic or genotoxic under the study conditions employed. The lack of biological response associated with ZYN is aligned with the results of CRP2.1 testing. The results from the *in vitro* studies of genotoxic or mutagenic effects indicate a low potential for carcinogenic effects of ZYN. The *in vitro* toxicology testing is detailed in Section G.5 Nonclinical Evaluation Summary, Section 5.

There is no literature about the *in vitro* and *in vivo* toxicology of ZYN; therefore, a systematic review was performed of the *in vitro* and *in vivo* toxicology studies of Swedish snus, a relevant comparator as noted previously in Section 1.2. Toxicology data on Swedish snus are sparse, likely because the strength of the epidemiology data from Sweden obviates the need to obtain toxicology data retrospectively. Although ZYN is in a similar product category to snus and is used in the same way as snus, ZYN does not contain tobacco or TSNAs, which are found in other ST products. Therefore, the toxicological profile of Swedish snus represents a conservative estimate for ZYN. The literature assessment of Swedish snus showed minimal activity in toxicology assays. This lends further support for the potential of ZYN being less harmful than combusted tobacco, most notably cigarettes.

The literature describing *in vitro* toxicology and *in vivo* research studies with Swedish snus and with other ST products is described in Section G.5 Nonclinical Evaluation Summary, Section 6.

4 HUMAN HEALTH IMPACT EVALUATION

Swedish Match has conducted four clinical studies and two consumer research studies to support this PMTA for ZYN:

- Three clinical pharmacology studies (SM 17-01, SM 17-03, and SM 18-01)
- One oral safety clinical study (SM 17-02)
- One likelihood of use consumer research study ((b) (4))
- One patterns of use consumer research study ((b) (4))

Summaries of each of these studies is provided in Section G.6 Human Health Impact Evaluation Summary, Section 4. Full reports for each of these studies are provided in Section H.3.

The four clinical studies were conducted in Sweden, and the two consumer research studies were conducted in the US. In the three clinical pharmacology studies (SM 17-01, SM 17-03, and SM 18-01), the reference product was General Snus (referred to as General portion snus white large [PSWL]), a Swedish-style snus within the same category that has received PMTA marketing authorizations and modified risk orders from FDA.

Findings from these studies are supplemented by data from an extensive systematic review of the literature on the health effects, tobacco use behaviors, and perceptions of risk pertaining to the use of Swedish snus, a relevant comparator product as noted previously in Section 1.2, since there is no pubished literature on ZYN.

4.1 Health Effects

TSNAs (eg, NNN and NNK) and B(a)P are considered to be among the most carcinogenic constituents in tobacco. Importantly, the levels of carcinogenic substances including TSNAs and B(a)P are too low to quantify in ZYN (Section G.5 Nonclinical Evaluation Summary, Section 4), whereas General Snus contains low levels of TSNAs and B(a)P. Therefore, cancer risk is assumed to be lower with ZYN than with General Snus.
As noted in the FDA PMTA TPL Review 2015, Section V. Conclusions and Recommendations, FDA concluded that:

- When used exclusively instead of other US market ST products or cigarettes, General Snus offers potential for reductions in **oral cancer**.

- When used exclusively instead of cigarettes, General Snus offers lower risk of developing respiratory diseases (ie, COPD, emphysema, and chronic bronchitis) and **certain cancers (such as oral, esophageal, and lung)**.

As noted in the FDA MRPTA TPL Review 2019 for General Snus, "In the scientific review of the original applications, epidemiological studies provided the strongest evidence for assessing the long-term health risk of Swedish snus use as compared to the risks from cigarette smoking. Although the epidemiological literature is not product specific, the body of literature from Sweden and Norway is particularly relevant to the assessment of the long-term health risks of the General Snus products that are the subject of these MRTPAs, as noted in the 2016 TPL review (p.33)."

There is no literature on the health effects of ZYN; therefore, a systematic review of the literature was conducted on the health effects of Swedish snus, a relevant comparator product as noted previously in Section 1.2. From the literature reviewed for this PMTA, there was limited/suggestive evidence of no association found between snus and cardiovascular (ischemic heart disease, myocardial infarction, heart failure, cardiovascular disease, atrial fibrillation, and stroke), cancer (head and neck, pancreatic, stomach, and lung), metabolic, and gastrointestinal effects. The current evidence suggests an approximately 30% decreased risk of all-cause mortality in snus users compared to smokers. There is also no evidence that snus causes chronic obstructive lung disease, a major contributor to smoking mortality in the US (CDC 2018, CDC 2008).

Use of snus or ZYN is not associated with secondary exposure and therefore decreases risk for both users and non-users. Some studies provided evidence for an increased risk in dual users (ie, snus and cigarettes) and switchers (ie, switched from cigarette use to snus use) compared to never tobacco users; however, most studies also provided evidence of decreased or statistically non-significant risks in dual users and switchers compared to smokers.

4.2 Pharmacokinetics, Pharmacodynamics, and Abuse Liability

It is widely accepted that nicotine is the main dependence-producing constituent in tobacco and that rate of delivery is an important determinant of abuse potential (SCENIHR 2008). As with other nicotine-containing products, ZYN packaging includes the following warning:

- WARNING: This product contains nicotine. Nicotine is an addictive chemical.

Commercially available snus products in the US have a nicotine content ranging between 5 and 20 mg per pouch. Previous studies (Lunell and Curvall 2011) have indicated that, on average, about 15% to 20% of the total nicotine content of snus products is extracted and absorbed, with large inter-individual variation. When comparing the nicotine content of different nicotine-delivery products, it is important to consider that the nicotine uptake varies considerably depending on product type (tobacco versus a non-tobacco-based matrix) and product formulation (pouch geometry, water content, particle size, pH, etc.). The nicotine delivery profile of a product is probably a main determinant of its efficacy to function as an alternative to cigarettes among current smokers. Therefore, the nicotine delivery profile of ZYN was compared with

commercially available snus products (which have a documented ability to replace cigarettes as a source of recreational nicotine among current tobacco consumers).

Three clinical pharmacology studies were conducted for this PMTA to assess the PK of nicotine (extraction and uptake) and the pharmacodynamics (including changes in pulse rate and subjective effects for abuse liability) of different flavors and nicotine strengths of ZYN. In two of the studies (SM 17-01 and SM 17-03), the reference product was General Snus (referred to as General PSWL [8 mg nicotine]), a Swedish-style snus within the same category, which has received PMTA marketing authorizations and modified risk orders from FDA.
In Study SM 18-01, the reference products included another US marketed product with higher nicotine content (American moist snuff Longhorn Pouch [18 mg nicotine]). As noted in the FDA PMTA TPL Review 2015 for General PSWL, "these nicotine values are within the reported ranges from other marketed US moist snuff, therefore the abuse potential for these products is similar to other marketed smokeless tobacco products." The release of nicotine from a General PSWL (8 mg nicotine) following use over 30 minutes has previously been investigated (Lunell and Curvall 2011). The main methodological strength of the three clinical studies was their use of randomized, cross-over designs, highly standardized administration of study products, and state-of-the-art methods for the chemical and PK analyses.

Post hoc analyses were also performed across these clinical studies; see Section G.6 Human Health Impact Evaluation Summary, Section 5.1.4, and Section H.3.1.2.4 Report for complete details.

4.2.1 Pharmacokinetics of Nicotine

In both Studies SM 17-01 and SM 17-03, the extracted dose of nicotine was lower in ZYN 3 mg products compared to General PSWL 8 mg; however, it was higher in ZYN 6 mg products compared to General PSWL 8 mg despite the lower nicotine content (Section G.6 Human Health Impact Evaluation Summary, Section 5.1.1). In Study SM 17-03, mean area under the plasma concentration-time curve (AUC) and maximum concentration (C_{max}) from ZYN 3 mg products were also significantly lower compared to those of General PSWL 8 mg, whereas these PK parameters from the ZYN 6 mg products were significantly higher compared to those of General PSWL 8 mg (Section G.6 Human Health Impact Evaluation Summary, Section 5.1.2). However, there were no statistically significant differences between any of the ZYN products (3 and 6 mg) and General PSWL 8 mg in terms of terminal half-life or time to C_{max} (approximately 1 hour). Results from Study SM 18-01 demonstrated that nicotine exposure from a ZYN 8 mg product was not higher than other commercially available tobacco-based snus and snus-like products currently on the Scandinavian and US markets (Section G.6 Human Health Impact Evaluation Summary, Section 5.1.3).

Across studies from post hoc analyses, a dose-related response in nicotine uptake (AUC and C_{max}) was observed (ZYN 3 mg < General PSWL 8 mg < ZYN 6 mg < Longhorn and ZYN 8 mg < General PSWL 2 × 8 mg). The PK profiles (AUC and C_{max}) demonstrated that ZYN 3 and 6 mg products expose individuals to nicotine levels that are broadly similar to cigarettes and traditional ST products on the market. Therefore, systemic exposure to nicotine following the intended use of ZYN is expected to produce reinforcing effects and have an abuse liability similar to other smokeless products.

The flavoring agent (b) (4) has been hypothesized to facilitate oral nicotine uptake. Data analyzed from studies that included ZYN Wintergreen (Studies SM 17-01 and SM 18-01) showed that the (b) (4) in ZYN Wintergreen does not increase the delivery of nicotine; results were similar for Longhorn in which wintergreen did not enhance nicotine delivery. There was also no evidence that the extraction of nicotine was affected by the other ZYN flavors (Peppermint and Spearmint) tested in Study SM 17-01.

As demonstrated in the clinical studies conducted with ZYN and snus for this PMTA, ZYN delivers nicotine at similar rates as snus (Section G.6 Human Health Impact Evaluation Summary, Section 5.1.4.5); therefore, it is presumed that it would also fall between combustible cigarettes and NRT in the "continuum of dependence."

4.2.2 Pharmacodynamics

4.2.2.1 Pulse Rate in Clinical Studies

Pulse rate was also collected in two of the clinical studies (Studies SM 17-01 and SM 17-03). There were no statistically significant differences in change in pulse rate at the majority of time points between the ZYN products and General PSWL in either study (Section G.6 Human Health Impact Evaluation Summary, Section 5.2.1). In both studies, the larger nicotine exposure observed with ZYN 6 mg products was not associated with a statistically significantly larger increase in pulse rate compared to General PSWL.

4.2.2.2 Subjective Effects for Abuse Liability Assessment

Subjective nicotine effect was assessed by "head buzz" in Studies SM 17-01 and SM 17-03 using a visual analog scale. Head buzz changed over time to a similar extent for all products (ZYN and General PSWL) in Study SM 17-01; however, the increase in head buzz was larger with General PSWL product compared to each of the ZYN 3 and 6 mg products in Study SM 17-03 (Section G.6 Human Health Impact Evaluation Summary, Section 5.2.2). In both studies, there were no statistically significant differences in the change in head buzz between the ZYN and General PSWL products at the majority of time points.

4.3 Safety

To assess the safety and tolerability of ZYN, the following safety-related assessments were collected in the studies conducted for this PMTA:

- Treatment-emergent adverse events (AEs) were collected in all four clinical studies as secondary endpoints. There were no deaths, other serious AEs, or discontinuations due to AEs in any of the studies. All AEs were mild or moderate. Details are provided in Section G.6 Human Health Impact Evaluation Summary, Section 6.1, and the individual clinical study reports in Section H.3 (Section H.3.1.2.1 Report Body; Section H.3.1.3.1 Report Body; Section H.3.1.2.2 Report Body; Section H.3.1.2.3 Report Body).
- Oral safety as measured by dental plaque acidogenicity, changes in oral microflora, changes in plaque amount, and the appearance and number of oral mucosal lesions was assessed in Study SM 17-02. Single-dose and 6-week *ad libitum* exposure to ZYN did not elicit an acidogenic response. During the study, substitution of snus use with ZYN improved oral mucosal lesions (also commonly referred to as snuff dipper's lesions) in

healthy snus users after ZYN administration *ad libitum* for 6 weeks. The number of subjects with no lesions increased from 9% at screening to 30% at 6 weeks. There were no statistically significant changes for the subjects for the majority of plaque amount assessments or change from baseline for Lactobacilli. There was also no indication of changes in the incidence of gingival retraction during the study. See Section G.6 Human Health Impact Evaluation Summary, Section 6.2, and the report located in Section H.3.1.3.1 Report Body for additional details.

4.4 Consumer Use and Risk Perception

Swedish Match conducted two consumer research studies:

- Likelihood of Use study ((b) (4)), which enrolled both non-users and users of tobacco/nicotine products (TNPs) ((b) (4)) and oversampled people who use TNPs of legal age to 24 years of age (b) (4)). Using a web-based survey of invited consumers who met inclusion and exclusion criteria, respondents were given study stimuli consisting of a one-page ZYN description and packaging label for ZYN Cool Mint 3 mg that indicated product information, including instructions for use, strengths, number of pouches in a canister, and flavors, as well as the required warning label that nicotine is an addictive chemical. The primary objectives were to assess whether being exposed to ZYN stimuli had an impact on perceptions and intentions related to the use of TNP and to measure the appeal of various ZYN brand and product attributes. The full report is provided in Section H.3.1.1.2 Report Body.
- Patterns of Use study ((b) (4)), which enrolled ZYN users ((b) (4)) and non-users ((b) (4)) and consisted of two distinct phases:
    - Retrospective Study, which utilized a cross-sectional design to measure recalled TNP usage among ZYN users and ZYN non-users in a retrospective survey
    - Prospective Study, which longitudinally evaluated TNP patterns of use among ZYN users and ZYN non-users from the Retrospective Study over a (b) (4) observation period

  The full report is provided in Section H.3.1.1.1 Report Body.

Both studies were designed based on the FDA draft guidance for industry entitled *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*, dated May 2016, and feedback was received from FDA (Section A.4, FDA Meeting Minutes, 12 October 2017 – TC0002533). Results of the studies were subject to recall bias and self-reporting intentions, which are limited in terms of predicting behavior and can overestimate the likelihood of purchase, particularly when participants' responses have no consequences. However, Swedish Match believes that these studies were robustly designed and conducted based on FDA guidances and feedback, the use of qualitative cognitive interviews prior to the execution of the quantitative surveys, the use of validated scales, and enrollment of large sample sizes that included various TNP user groups and ages (at least the minimum legal age for TNP use per local state requirements). Youth under the legal age limit were not included in the consumer research studies because it was not considered ethical.

4.4.1 User Topography and Patterns of Use

Since ZYN has been marketed in the US since 2014, Swedish Match was able to recruit actual US consumers for the Patterns of Use study to confirm that ZYN users are primarily former tobacco users . In this study, ZYN users reported an average use of eight pouches a day and low rates of dual use with cigarettes ([redacted] reportedly smoked cigarettes [every day or some days] over the past 30 days and [redacted] reportedly smoked every day) (Section G.6 Human Health Impact Evaluation Summary, Section 7.5.1). Also, ZYN users who were smokers had greater intention to quit smoking than ZYN non-users (Section G.6 Human Health Impact Evaluation Summary, Section 7.5.2). See Section G.6 Human Health Impact Evaluation Summary, Sections 7.2 and 7.3, and the report located in Section H.3.1.1.1 Report Body for additional details.

4.4.2 Likelihood of Use

In the Likelihood of Use study, respondents who did not use TNPs (ie, never and former users) were not likely to initiate or reinitiate TNPs after exposure to ZYN stimuli. Current TNP users demonstrated some interest in purchasing ZYN in the future. Notably, cigarette smokers with intention to quit showed greater interest in purchasing ZYN than cigarette smokers without intention to quit. See Section G.6 Human Health Impact Evaluation Summary, Section 7.6, and the report located in Section H.3.1.1.2 Report Body for additional details.

4.4.3 Perceptions of Health Risk

When evaluating the perception of absolute and relative risk of TNP types, respondents in both consumer research studies conveyed an understanding of a continuum of risk when considering use of TNP, ZYN, and cigarettes. Across all health conditions (adult tooth loss, mouth cancer, gum disease, and serious health problems), most respondents perceived low/minimal absolute risks for never having used any TNPs, low-to-moderate absolute risks for using only ZYN, and moderate-to-very high absolute risks for smoking cigarettes (Section G.6 Human Health Impact Evaluation Summary, Section 7.7).

In the Likelihood of Use study, which did not enroll current ZYN users, TNP users tended to perceive lower risks of developing a health condition due to daily use of ZYN relative to other TNPs compared with TNP non-users after exposure to ZYN stimuli. Respondents consistently attributed high relative risk to the presence of cigarette usage. However, the majority of respondents across all cohorts perceived the daily use of only ZYN to carry the same or lower relative risk of each health condition as cigarettes, both cigarettes/ZYN, moist snuff, chewing tobacco, and snus. Additionally, ZYN was perceived to carry a higher relative risk compared with quitting all TNP and never using TNP.

In the Patterns of Use study, ZYN users perceived a lower relative risk of daily use of only ZYN compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN and cigarettes. When comparing the relative risk of daily ZYN use to aids to help stop smoking or never having used any TNP, ZYN users perceived ZYN as being equally risky or of higher risk, respectively. ZYN users perceived the relative risk of adding ZYN to existing TNP use as being the same [redacted] or higher [redacted]; results varied depending on the specific TNP (eg, lowest when adding ZYN to aids to help stop smoking and highest when adding to cigarette use), indicating that respondents perceived adding ZYN as posing the highest risk in the context of using the highest-risk TNP. When comparing the relative risk of quitting all TNP except ZYN versus quitting all TNP, ZYN users perceived continued

ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether.

4.4.4 Marketing Plan and Youth Appeal

The target adult audience of ZYN is consumers who currently use tobacco or nicotine products and who are 21 years or older. The use of ST and snus, which is similar to the ZYN product, is currently low among US youth (Gentzke et al 2019). Swedish Match has chosen flavors for ZYN that appeal more toward adult consumers (eg, Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Smooth, Chill, and Fresh) and avoided youth-appealing flavors.

As part of the marketing and ethical code of conduct, Swedish Match takes proactive measures to ensure that all marketing communication for ZYN is targeted to adults who are current tobacco consumers. Swedish Match believes in responsibility above all to prevent youth access and youth exposure to brand communication whether it be labeling, promotions, advertising, or social media. Swedish Match limits exposure to youth by only conducting marketing efforts in age-verified mediums and by adhering to any and all regulations for warnings at the local, state, and federal levels. The marketing plan for ZYN is provided in Section E.2 Marketing Plan.

5 OVERALL PUBLIC HEALTH IMPACT

Given the totality of evidence, Swedish Match believes that the information provided in this PMTA supports that the continued marketing of ZYN would be appropriate for the protection of the public health based on the following:

- Appropriate quality systems together with the fact that there is no tobacco in the product ensure that HPHC levels are well below the GOTHIATEK standards.
- The levels of carcinogenic substances such as TSNAs (eg, NNN and NNK) and B(a)P are too low to quantify in ZYN.
- The levels of HPHCs are generally similar to or lower than the levels of General Snus products, which have received both PMTA marketing authorizations and MRTP marketing orders from FDA. Based on the QRAs performed for measurable HPHCs in ZYN, the HPHC levels in ZYN were below health-based threshold limit values. Thus, the toxicological safety profile of ZYN represents a significant improvement over General Snus and CRP2.1 (moist snuff reference product). The HPHC results and QRAs suggest that the exposure of an individual, under reasonably foreseeable conditions of use of ZYN, would be less than that from other marketed products such as General Snus and even less than that from smoking combustible cigarettes. The HPHC levels in ZYN do not raise concern from a public health perspective and support that ZYN is appropriate for the protection of the public health.
- The non-clinical Ames and *in vitro* micronucleus assays demonstrated no evidence of genotoxic or mutagenic effect.
- As ZYN exposes the user to levels of nicotine similar to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, the health effects of snus could be considered to be a measure of maximum health risks. From a systematic review of the literature, there was limited/suggestive evidence of no association found between Swedish snus, a relevant comparator product to ZYN, and cardiovascular, cancer,

metabolic, or gastrointestinal effects. There is also no evidence that snus causes chronic obstructive lung disease, a major contributor to smoking mortality in the US.

- A comprehensive clinical program was conducted that included PK, pharmacodynamics (including changes in pulse rate and subjective effects for abuse liability), AEs, and oral safety and demonstrated that:
    - There were no differences in time to maximum concentration (approximately 1 hour) across products.
    - A dose-related response in nicotine uptake (AUC and C_{max}) was observed (ZYN 3 mg < General PSWL 8 mg < ZYN 6 mg < Longhorn and ZYN 8 mg < General PSWL 2 × 8 mg).
    - The abuse potential for ZYN is similar to other marketed ST products.
    - No safety issues, including oral safety, were identified.
- Two consumer research studies were robustly designed and conducted based on FDA guidances and feedback and demonstrated that:
    - The likelihood of initiation of ZYN by non-users (both legal age to 24 years of age and >24 years of age) and former TNP users was low.
    - Cigarette smokers intending to quit were more likely to buy ZYN than cigarette smokers not intending to quit.
    - Dual use of ZYN and cigarettes was low.
    - Respondents including ZYN non-users and users conveyed an understanding of a continuum of risk ranging from low/minimal absolute risks for never having used any TNPs, low-to-moderate absolute risks for using only ZYN, and moderate-to-very high absolute risks for smoking cigarettes.
    - ZYN users perceived a lower relative risk of daily use of only ZYN compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN and cigarettes.

In summary, findings from the mentioned research program support that use of ZYN is likely associated with substantially lower health risks among individual consumers than most, or even all, of the tobacco products that currently dominate the US tobacco market (cigarettes and moist snuff). These conclusions are mainly based on the substantially more favorable toxicological profile of ZYN. and the method of use which does not involve inhalation of smoke or vapor:

- ZYN offers a less risky alternative to combusted tobacco products.
- ZYN offers additional options for less toxic smokeless products, thereby potentially decreasing the negative health impact from tobacco use.
- It is anticipated that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

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