

## Module 5.1: Clinical Individual Health Studies

### TABLE OF CONTENTS

1.	INTRODUCTION .....	2
2.	TABULAR LISTING OF INDIVIDUAL HEALTH STUDIES .....	2
3.	DATA FROM CROSS-REFERENCED APPLICATIONS .....	2
4.	NEW CLINICAL CROSS-SECTIONAL BIOMARKER STUDY (SM22-03) .....	5
5.	ADVERSE EXPERIENCE REPORTS AND MISUSE POTENTIAL.....	5
6.	INDIVIDUAL HEALTH EFFECTS AND HEALTH OUTCOMES LITERATURE REVIEW .....	5

### TABLE OF FIGURES

Figure 1.	Comparison of plasma nicotine levels (ng/mL) across products.....	4
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## 1. INTRODUCTION

As demonstrated by the cross-referenced information in Module 3 of these MRTPAs, the *proposed MRTPs* and *authorized MRTPs* are oral tobacco products, intended to be used in the same manner (i.e., held between the lip and gum for a period of use and then discarded). The nicotine content of the *proposed MRTPs* (3 or 6 mg/unit of use) is lower compared to the *authorized MRTPs*; however, differences in nicotine formulation result in similar nicotine delivery and uptake, discussed further in this module. As demonstrated by the cross-referenced information in Module 4, the toxicological risk profile of the *proposed MRTPs* is the same or most likely lower compared to the *authorized MRTPs*, and thus significantly lower compared to combusted cigarettes. In general, HPHC levels are comparable or lower in the *proposed MRTPs* compared to the *authorized MRTPs*, and significantly lower compared to cigarettes. HPHCs presenting a carcinogenic risk (e.g., NNN, NNK, and B[a]P) are not detectable in the *proposed MRTPs*, whereas they are present in very low quantities in the *authorized MRTPs*.

Comparisons of the health risks associated with the *proposed MRTPs* and *authorized MRTPs*, and associated comparisons with both product lines to combusted cigarettes, continue in this Module. A brief summary of cross-referenced clinical study data and literature from the original PMTAs is below. Additionally, data from a new biomarker study is discussed in Module 5.2 of these MRTPAs and updated adverse experience report data is summarized in Module 5.3.<sup>1</sup> Overall, the clinical data show measures of individual health (PK, PD, abuse liability potential, BoEs, BoPHs) are comparable between the *proposed MRTPs* and *authorized MRTPs* or are improved in the *proposed MRTPs* compared to the *authorized MRTPs*, which are significantly improved compared to combusted cigarettes.

## 2. TABULAR LISTING OF INDIVIDUAL HEALTH STUDIES

A tabular listing of cross-referenced individual health studies in these MRTPAs can be found in Module 1, [Attachment 1-3-1](#).

## 3. DATA FROM CROSS-REFERENCED APPLICATIONS

We included four sponsored clinical pharmacology studies and a post-hoc analyses in the original PMTAs.<sup>2,3,4,5,6</sup> Three of these sponsored studies<sup>7</sup> assessed pharmacokinetics and two of these sponsored studies<sup>8</sup> evaluated pharmacodynamics and subjective effects associated with abuse liability (e.g., “head buzz”) in the *proposed MRTPs* compared to the *authorized MRTPs*. The fourth clinical

<sup>1</sup> Previously submitted AE data is in (b) (4)

and (b) (4)

<sup>2</sup> Study information is in (b) (4). All documents are relevant.

<sup>3</sup> Study information is in (b) (4). All documents are relevant.

<sup>4</sup> Study information is in (b) (4). All documents are relevant.

<sup>5</sup> Post-hoc analyses of all three studies are in (b) (4). All documents are relevant.

<sup>6</sup> Study information is in (b) (4). All documents are relevant.

<sup>7</sup> (b) (4)

<sup>8</sup> (b) (4)

pharmacology study assessed oral safety measures (e.g., dental plaque acidogenicity, oral lesions) after both short-term use (60 min) and *ad libitum* use of the *proposed MRTPs* over (b) (4). Complete analysis and discussion of these studies can be found in the cross-referenced locations.

### 3.1. PK, PD, and Abuse Liability Assessment

Results from [REDACTED], and [REDACTED] generally showed the *proposed MRTPs*, (b) (4) (b) (4)<sup>9</sup>, were associated with a nicotine exposure comparable to or lower than the *authorized MRTPs* and a product representative of the market leader moist snuff pouch (b) (4). Compiled data for these products, also compared to combusted cigarette data from the literature<sup>10</sup>, are in Figure 1 below.

Figure 1<sup>11</sup> demonstrates the *proposed MRTPs* and *authorized MRTPs* are similar in terms of the onset, peak, and duration of their respective dose response curves, and both were notably different relative to the onset, peak, and duration of the combusted cigarettes dose response curve. The data for the different *proposed MRTPs* tested were comparable, regardless of individual flavor tested.

Plasma levels for cigarette users initially spiked within the first 5 minutes of use and rapidly declined after, as is typically observed for cigarettes. However, as seen in Figure 1, the PK profiles for the oral products (*proposed MRTPs*, *authorized MRTPs*, (b) (4)) are completely different from that of cigarettes. Plasma levels after use of the *authorized MRTP* steadily increased, plateaued between 60 – 75 minutes, and began steadily decreasing after 75 minutes. The profiles for both the 3 mg and 6 mg *proposed MRTPs*, in terms of onset, peak, duration,<sup>12</sup> and decline in plasma levels,<sup>13</sup> was similar to that of the *authorized MRTPs*. The decline in efficacy after the 60 minutes is consistent with product labeling, which recommends keeping the product in your mouth for “up to one hour.” The profile for the 3 mg *proposed MRTPs* was most similar to the profile for the *authorized MRTPs*, though plasma levels were lower overall for the 3 mg *proposed MRTPs* compared to the *authorized MRTPs*. The profile for the 6 mg *proposed MRTPs* was most similar to the profile for the (b) (4), though at and after the 60 min time point, plasma nicotine levels were higher for users of the (b) (4) compared to users of the 6 mg *proposed MRTPs*. Overall, all four oral products had similar PK profiles in terms of timing, though a range of plasma nicotine levels were observed for all four products over the 120 minute window. These data demonstrate the PK profiles for both the 3 mg and 6 mg *proposed MRTPs* are within the ranges observed for other smokeless tobacco products, and closely resemble those observed for the *authorized MRTPs*.

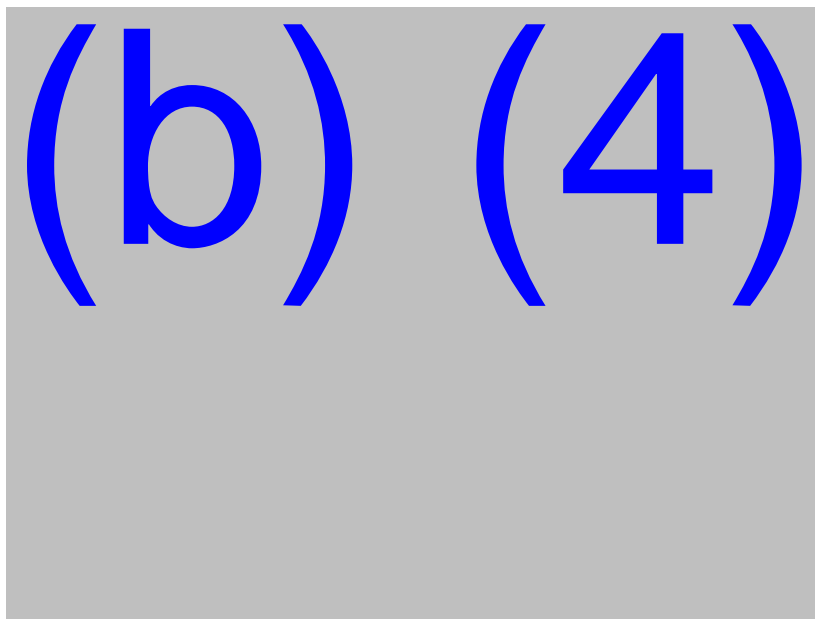
<sup>9</sup> (b) (4)

<sup>10</sup> Data adapted from Hajek, P., Pittaccio, K., Pesola, F., Myers Smith, K., Phillips-Waller, A., & Przulj, D. (2020). Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction* (Abingdon, England), 115(6), 1141–1148. <https://doi.org/10.1111/add.14936>

<sup>11</sup> Combusted cigarette data in Figure 1 is based on published data, which assessed *ad libitum* use, whereas all other product data is based on our clinical data where products were used for 60 minutes. Cigarette data collection in publication ended at 30 min. Data from 60-, 90-, and 120-min time points extrapolated using exponential decay.

<sup>12</sup> Relative to combusted cigarettes.

<sup>13</sup> (b) (4)



**Figure 1. Comparison of plasma nicotine levels (ng/mL) across products.<sup>14</sup>**

Additionally, the previous clinical study data shows there were no statistically significant differences in pulse rate changes between the *proposed MRTPs* and *authorized MRTPs*, except for a significantly lower pulse rate associated with use of the 3 mg *proposed MRTPs* compared to the *authorized MRTPs* at 10 minutes. Additionally, there was an increase in “head buzz” in all treatment groups compared to baseline; however, the increase was larger for the *authorized MRTPs* than for all *proposed MRTPs* at all time points.

### 3.2. Oral safety study

Results from (b) (4) show single-dose and (b) (4) *ad libitum* administrations of the *proposed MRTPs* do not promote plaque acidogenesis. During the study, substitution of snus with the *proposed MRTPs* improved oral mucosal lesions (also commonly referred to as snuff dipper’s lesions) in healthy snus users after *ad libitum* use of the *proposed MRTPs* (i.e., the number of subjects with no lesions increased, and the number of subjects with lesions and the severity of lesions decreased during the study). There were no other statistically significant differences between the period of snus use and the period of *proposed MRTP* use for any other parameters measured. These data demonstrate oral health risks are lower after use of the *proposed MRTPs* compared to the *authorized MRTPs*.

### 3.3. Overall

These data demonstrate the *proposed MRTPs* and *authorized MRTPs* have similar PK/PD profiles and abuse liability potentials. As the *authorized MRTPs* have already been demonstrated to be lower risk to individual health compared to combusted cigarettes, it is evident the *proposed MRTPs* are similarly lower in risk compared to combusted cigarettes. These data are further supported by new biomarker study data below, demonstrating how the low levels of toxicants in the *proposed MRTPs* translate to low

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<sup>14</sup> General PSWL is the *authorized MRTP*, General Portion White Large. ZYN 6 mg / ZYN 3 mg are representative of the different *proposed MRTPs*

levels of exposure and low levels of disease risk associated with these products, similar or better than what has been observed for the *authorized MRTPs*.

#### 4. NEW CLINICAL CROSS-SECTIONAL BIOMARKER STUDY (SM22-03)

SM 22-03 is a 14-day cross-sectional study designed to assess BoEs (e.g., nicotine, cotinine, OH-cotinine, NNAL, NNN) and BoPHs (e.g., soluble intercellular adhesion molecule-1 [sICAM-1], growth differentiation factor 15 [GDF-15]) in the plasma and/or urine of (b) (4) participants equally dispersed across cohorts of non-users of tobacco and nicotine products (TNPs), and current, daily users of nicotine pouches, snus, or combusted cigarettes. Data from this study show users of nicotine pouches are exposed to similar levels of nicotine as combusted cigarette users and snus users, while having lower exposure to potential carcinogens like NNN, NNK, and B[a]P compared to both snus and combusted cigarette users. Additionally, levels of BoPH for cardiovascular disease and lung cancer were comparably low between nicotine pouch users, snus users, and non-users of TNPs, while all three groups have significantly lower levels compared to combusted cigarette users. Combined with the HPHC and toxicological data cross-referenced in Module 4, these data scientifically substantiate using the same reduced risk claim with the *proposed MRTPs* as for the *authorized MRTPs*. Results are discussed in more detail in Module 5.2 of these MRTAs. Complete study information is in Attachments 5-2-1 through 5-2-5.

#### 5. ADVERSE EXPERIENCE REPORTS AND MISUSE POTENTIAL

No deaths have been reported for the *proposed MRTPs* since the products were first marketed in 2014. The reported adverse experiences for the *proposed MRTPs* and *authorized MRTPs* are similar in category, and (b) (4)

Further detail on reported adverse experiences and comparisons between the *proposed MRTPs* and *authorized MRTPs* is in Module 5.3 of these MRTAs.

The misuse potential of the *proposed MRTPs* is similar to that of the *authorized MRTPs*. The *proposed MRTPs* are intended to be placed between the gum and the upper lip and enjoyed for up to 60 minutes and then discarded; the product is not intended to be swallowed or reused. According to the Centers for Disease Control, an average adult needs to consume at least 50–60 mg of nicotine to develop overdose symptoms. Based on a study of case reports of nicotine intoxication by e-cigarette liquids, the lethal dose is assumed to be 4.4 – 8.9-fold higher.<sup>15</sup> According to this estimate, an individual would have to ingest about (b) (4) of the (b) (4) mg *proposed MRTPs* to achieve a lethal dose. However, in reality, such exposure would result in nausea and vomiting well before the entire dose is absorbed. Similarly, no lethal snus intoxication has ever been reported to the Swedish Poisons Information Center, despite there being over one million current snus users.

#### 6. INDIVIDUAL HEALTH EFFECTS AND HEALTH OUTCOMES LITERATURE REVIEW

At the time of the submission of the cross-referenced PMTAs for the *proposed MRTPs*, there was limited published literature on the health effects and outcomes specific to use of the *proposed MRTPs* or nicotine pouches generally. Given the similarities in product design, product use, and toxicological risk

<sup>15</sup> Maessen GC, Wijnhoven AM, Neijzen RL, et al. Nicotine intoxication by e-cigarette liquids: a study of case reports and pathophysiology. Clin Toxicol (Phila). 2020;58(1):1-8.

profile of the *proposed MRTPs* and *authorized MRTPs*, and our proposal to use the same claim for the *proposed MRTPs* as for the *authorized MRTPs*, the snus-specific individual health effects literature (b) (4) <sup>16</sup> is applicable to these MRTPAs. However, the nicotine pouch category has been investigated more thoroughly in the last four years and additional research has been published since the PMTAs were submitted. A systematic literature review conducted on the published clinical and behavioral pharmacology and individual health literature related to nicotine pouches can be found in the cross-referenced (b) (4) <sup>17</sup>.

Additionally, one recently published review<sup>18</sup> especially relevant to these MRTPAs, discusses nicotine pouches in the context of tobacco harm reduction, comparing available non-clinical and clinical individual health data between nicotine pouches, snus, and cigarettes. The review concludes based on available evidence, the reduction in toxicant exposure translates to harm reduction potential in smokers switching to nicotine pouch products. The data and conclusions in this review further support and scientifically substantiate the data and information we provide in these MRTPAs specific to the *proposed MRTPs*.

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<sup>16</sup> Snus-related literature review documents are in (b) (4) All documents are relevant.

<sup>17</sup> Nicotine pouch-related literature review documents are in (b) (4)

<sup>18</sup> Grandolfo E, Ogden H, Fearon I M, et al. (February 15, 2024) Tobacco-Free Nicotine Pouches and Their Potential Contribution to Tobacco Harm Reduction: A Scoping Review. Cureus 16(2): e54228. doi:10.7759/cureus.54228