# Amendment – Section VIII.D
# Scientific Studies and Analyses
# Clinical Studies

This amendment

- Appends the list of studies table, titled "Studies Conducted with VLNC Cigarettes," in Section VIII.D.3 of 22nd Century Group Inc.'s Pre-Market Tobacco Product Applications (PMTA); STNs PM0000491 and PM0000492 and Modified Risk Tobacco Product Applications (MRTPA) STNs MR0000159 and MR0000160, bringing the total to 69 clinical studies identified that provided relevant safety and efficacy data on VLNC cigarettes.

- Replaces Section VIII.D.3.iii of 22nd Century Group Inc.'s PMTA; STNs PM0000491 and PM0000492 and MRTPA; STNs MR0000159 and MR0000160.

- Adds Section VIII.D.3.lxix to 22nd Century Group Inc.'s PMTA; STNs PM0000491 and PM0000492 and MRTPA; STNs MR0000159 and MR0000160.

- Adds a Section VIII.D.4.vii to 22nd Century Group Inc.'s PMTA; STNs PM0000491 and PM0000492 and MRTPA; STNs MR0000159 and MR0000160.

**Reason for Amendment:** At the time these applications were filed, the six-week study, A Longitudinal Ambulatory Study to Assess Changes in Cigarettes Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine (NCT03571724), was ongoing. The study is now complete, and the report has become available. Also, information on an additional clinical study, *Effects of immediate versus gradual nicotine reduction in cigarettes on biomarkers of biological effects. (NCT: 02139930),* was published that provides relevant safety and efficacy data on very low nicotine content (VLNC) cigarettes.

**Confidentiality:** A version with proposed redactions is also being submitted.

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# VIII. Scientific Studies and Analyses

## D. Clinical Studies

### 3. Individual Study Summaries

Table VIII.D-2 below summarizes a clinical study that was recently published and is reviewed in this amendment. This table appends the table titled, "*Studies conducted with VLNC cigarettes,"* in PMTA; STNs PM0000491 and PM0000492 and MRTPA; STNs MR0000159 and MR0000160.

Table VIII.D-2. Studies Conducted with VLNC Cigarettes

| Section Number | Product | Cigarette Exposure Duration | Study/Article Title | No. of Subjects | End Points | Reference |
|---|---|---|---|---|---|---|
| lxix | SPECTRUM | 20-weeks | Effect of immediate verses gradual nicotine reduction in in cigarettes on biomarkers of biological effects | 1250 | Biomarkers of biological effects – inflammation, oxidative stress, hematological parameters. | Hatsukami *et al.* 2019 |

### *iii.* A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure *during a 6-Week Switch to Very Low Nicotine Cigarettes (NCT03571724).*

#### (a) Study Design

This was an open-label, randomized, forced-switching study conducted at two study sites. Seventy-two (72) self-affirmed exclusive filtered king size non-mentholated cigarette smokers and 70 self-affirmed exclusive filtered king size mentholated cigarette smokers were enrolled and began the study at Week -1.

All potential subjects provided informed consent and successfully complete the screening procedures prior to participation in the study. Subjects also engaged in a brief product trial with the VLN™ cigarettes. Subjects who reacted negatively (i.e., unwilling to use and/or could not tolerate the product [experience adverse events (AEs) that would have prevented them from continuing to use the product as judged by the Investigator]) to the VLN™ cigarettes during the product trial period did not continue in the study.

At the start of Week -1, all subjects were asked to smoke their usual brand (UB) cigarettes as per their usual daily consumption for the following week. Subjects received an electronic diary (e-diary) to record daily cigarette use (cigarettes per day [CPD]). Training in completion of the e-diary was provided at the visit at the start of Week -1.

Subjects returned at the end of Week -1 for collection of blood and 24-hour urine samples for baseline biomarker of exposure (BOE) assessments. Subjective questionnaires for dependence, withdrawal symptoms, urges to smoke, and perceived health risk were also completed at scheduled times. A subset of 18 non-menthol and 18 menthol smoker subjects completed an assessment of puffing topography with their UB cigarettes during this visit. A

further subset of 12 of the non-menthol and 12 of the menthol smoker subjects, who completed the topography assessment, also completed a nicotine PK assessment at the end of this visit. Subjects who underwent topography and PK assessments were assigned to switch to smoking VLN™ cigarettes.

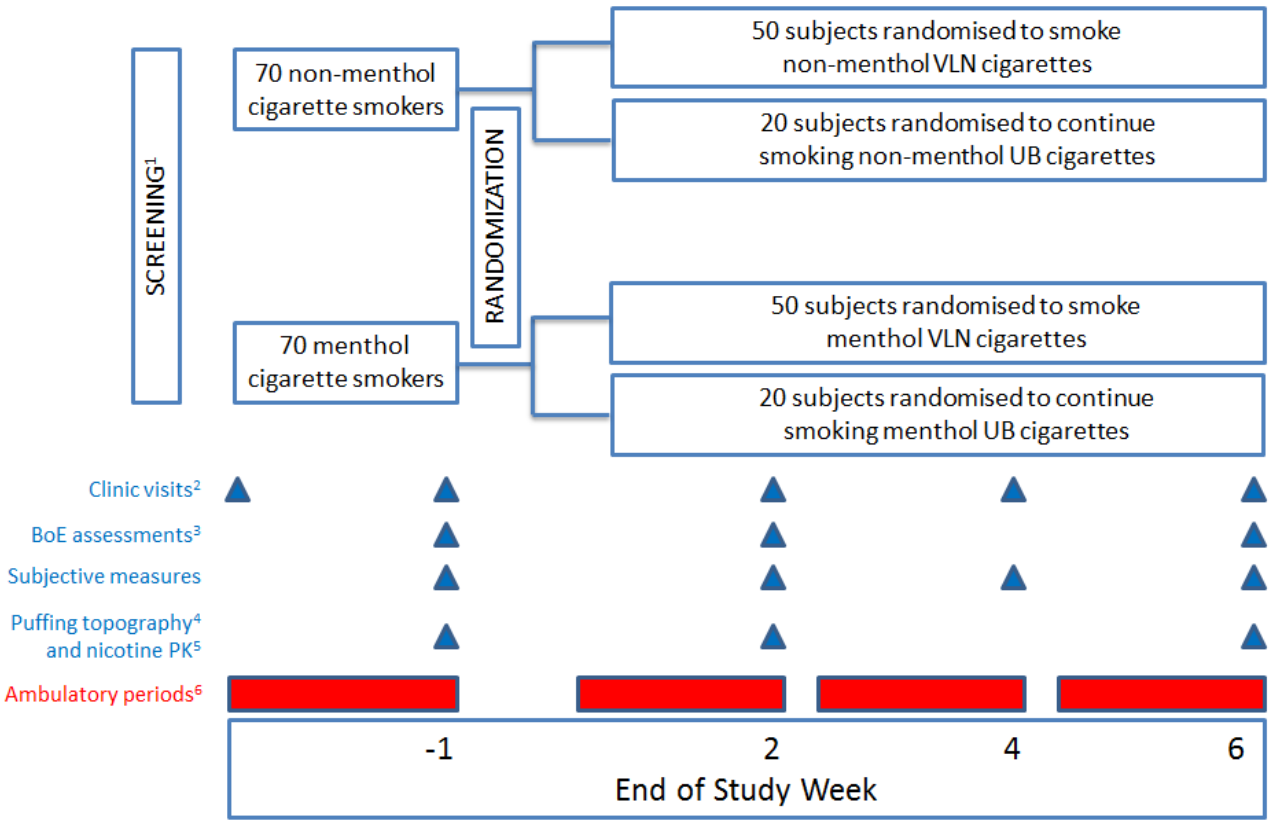
On Day -1 of Week 1, subjects were randomly selected to either remain smoking their non-menthol (22 subjects) or menthol (20 subjects) UB cigarettes, or to switch to smoking non-menthol (50 subjects) or menthol (50 subjects) VLN™ cigarettes as per their UB cigarette flavor. Subjects returned at the end of Weeks 2 and 6, for collection of blood and 24-hour urine samples for BOE assessments. Subjective effects questionnaires were also completed at scheduled times. Subjects continued recording their CPD in their e-diaries. A subset of 18 non-menthol and 18 menthol smoker subjects completed an assessment of puffing topography with the VLN™ cigarettes at these visits, and a further subset of 12 non-menthol and 12 menthol smoker subjects also completed an assessment of nicotine PK at the end of these visits. Subjects undergoing topography and PK assessments were assigned to switch to smoking VLN™ cigarettes.

Additionally, all subjects visited the clinic at the end of Week 4 to receive further supplies of cigarettes (if assigned to the VLN™ groups) and to complete subjective effects questionnaires.

Subjects randomized to the VLN™ groups were provided with a supply of VLN™ cigarettes at each visit, which was 150 % of their usual daily consumption as reported during Week -1. If a subject ran out of cigarettes between clinic visits, the subject visited the clinic

to receive further cigarettes. All subjects were asked to smoke their cigarettes *ad libitum,* recording their actual daily consumption in their e-diaries. Non-compliant nicotine product consumption was also recorded. Used cigarette butts were collected during ambulatory periods to verify product use and/or assess compliance. During Week -1 (all subjects) and all subsequent weeks (subjects randomized to continue smoking UB cigarettes) subjects were asked not to change their UB cigarette brand or flavor. Figure VIII.D-100 below shows the study plan.

Figure VIII.D-100. 6-Week Study Plan.




[1]Including trial of VLN cigarettes.
[2]E-diary training at start of Week -1
[3]24h urine BoE, blood COHb and plasma cotinine
[4]Subset of 18 subjects assigned to smoke non-menthol VLN cigarettes and 18 subjects assigned to smoke menthol VLN cigarettes
[5]Subset of 12 subjects assigned to smoke non-menthol VLN cigarettes and 12 subjects assigned to smoke menthol VLN cigarettes
[6]E-diary completion for cigarette consumption, and used cigarette butt collection

### (b) Results

The statistical analysis of the data was based on the Intent to Treat (ITT) population (essentially everyone enrolled in the study) and the per-protocol (PP) population. The PP population included all subjects who had valid recording of cigarette consumption and completed the study according to the protocol. There were a number of exclusion criteria:

- If a subject self-reported smoking a significant number of cigarettes other than those which they had been assigned according to the protocol, or if this was apparent following checking of their collected used cigarette butts.
- If there was a significant discrepancy between the self-reported number of CPD and the number of used cigarette butts collected.
- If a subject was non-compliant based on a published method of assessing compliance (Benowitz et al. 2015, *Cancer Epidemiology…*). After switching, subjects were deemed non-compliant if their ratio of [plasma cotinine/CPD VLN]/[plasma cotinine/CPD baseline] exceeded 0.2.
- If it was determined that a subject was pregnant during the study, the pregnant subject's data was to be listed but excluded from all PK parameter summaries.

Lack of Compliance in reduced nicotine cigarette studies is well documented (Benowitz et al. 2015, *Addiction*; Nardone et al. 2016, 2019). In this study, a significant number of subjects were non-compliant leading to their being excluded from the PP as required by the protocol. The study design required the subjects to be confined overnight during the 24-hour urine collection for biomarkers and total nicotine equivalents, pharmacokinetic evaluation of

nicotine blood levels and smoking topography. The subjects identified for these measurements (PK and topography) were a subset of the total study population. By protocol many of these subjects were excluded from the PP because of their high plasma cotinine levels indicating non-compliance. These subjects were confined and only allowed to smoke study cigarettes during the confinement period. Since the subjects could not "cheat" during this period, the ITT population is an accurate population for measurement of the biomarkers and total nicotine equivalents, nicotine PK and smoking topography.

This study was designed to evaluate the effects of complete switching to VLN™ cigarettes in subjects with no intent to quit. From a population perspective this represents the best possible outcome, if one switches completely to VLN™ then there should be predicted benefits based on this study. The reality, as was demonstrated in this study, is that the subjects had a hard time adhering to the protocol and only smoking VLN™ cigarettes. Nardone (Nardone et al. 2019) found it was hardest for the first cigarette of the day. This is not unexpected since the subject would be in withdrawal at that point depending on their degree of addiction. VLN™ is not a prescribed drug where the subject will be required to use it on a set timeline. VLN™ smokers will make a choice to purchase the product, to use it, and to not use it. This will be a continuous set of decisions every time the smoker decides to light up. In analyzing the data, one should consider the PP to be those who switch completely and the ITT to represent real users who desire to quit and alternate between conventional cigarettes and VLN™ cigarettes. Table VIII.D-84 is a demographic summary of the various populations. Table VIII.D-85 and Figure VIII.D-101. outline the disposition of the subjects in the study and also shows the number of compliant subjects.

Table VIII.D-84. Demographic Summary (Safety, ITT, and PP Populations)

| | | | Study Product Group | | | | |
|---|---|---|---|---|---|---|---|
| Population | Trait | | VLN Non-Mentholated | VLN Mentholated | UB Non-Mentholated | UB Mentholated | Overall |
| Safety | Sex | Female | 19 (38.0%) | 22 (44.0%) | 9 (40.9%) | 10 (50.0%) | 60 (42.3%) |
| | | Male | 31 (62.0%) | 28 (56.0%) | 13 (59.1%) | 10 (50.0%) | 82 (57.7%) |
| | Race | American Indian or Alaska Native | 1 ( 2.0%) | 1 ( 2.0%) | 0 ( 0%) | 0 ( 0%) | 2 ( 1.4%) |
| | | Asian | 0 ( 0%) | 1 ( 2.0%) | 0 ( 0%) | 0 ( 0%) | 1 ( 0.7%) |
| | | Black or African American | 3 ( 6.0%) | 29 (58.0%) | 2 ( 9.1%) | 12 (60.0%) | 46 (32.4%) |
| | | Multiple | 1 ( 2.0%) | 2 ( 4.0%) | 1 ( 4.5%) | 0 ( 0%) | 4 ( 2.8%) |
| | | Other | 1 ( 2.0%) | 0 ( 0%) | 1 ( 4.5%) | 0 ( 0%) | 2 ( 1.4%) |
| | | White | 44 (88.0%) | 17 (34.0%) | 18 (81.8%) | 8 (40.0%) | 87 (61.3%) |
| | Ethnicity | Hispanic or Latino | 1 ( 2.0%) | 1 ( 2.0%) | 1 ( 4.5%) | 1 ( 5.0%) | 4 ( 2.8%) |
| | | Not Hispanic or Latino | 49 (98.0%) | 49 (98.0%) | 21 (95.5%) | 19 (95.0%) | 138 (97.2%) |
| | Age* (yrs) | n | 50 | 50 | 22 | 20 | 142 |
| | | Mean | 45.9 | 40.5 | 45.8 | 42.7 | 43.5 |
| | | SD | 10.85 | 9.34 | 12.39 | 10.82 | 10.76 |
| | | Minimum | 29 | 26 | 26 | 26 | 26 |
| | | Median | 45.0 | 39.0 | 50.0 | 41.0 | 42.0 |
| | | Maximum | 65 | 60 | 60 | 59 | 65 |
| | Weight (kg) | n | 50 | 50 | 22 | 20 | 142 |
| | | Mean | 86.76 | 83.53 | 84.37 | 89.33 | 85.61 |
| | | SD | 17.579 | 14.118 | 18.462 | 17.657 | 16.542 |
| | | Minimum | 54.3 | 54.8 | 54.7 | 56.7 | 54.3 |
| | | Median | 85.30 | 81.95 | 83.10 | 86.50 | 84.30 |
| | | Maximum | 118.7 | 114.2 | 125.1 | 122.8 | 125.1 |

Note: * Age is derived from birth date to date of informed consent, BMI = Body Mass Index
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
ITT = Intent-to-treat (ITT) population, PP = Per-protocol (PP) population

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The study was designed to evaluate potential effects after an interim 2 weeks of use and after 6 weeks of use. The 2-week results give some insight into the onset of potential effects and the 6-week results confirm the effects. Lack of an effect at 2 weeks does not mean that the effect was not real, only that it had not reached statistical significance or been completely developed. Some of the biomarkers are based on analytes that have long half-lives and would not be expected to be affected after 2 weeks.

Figure VIII.D-101. Subject Disposition

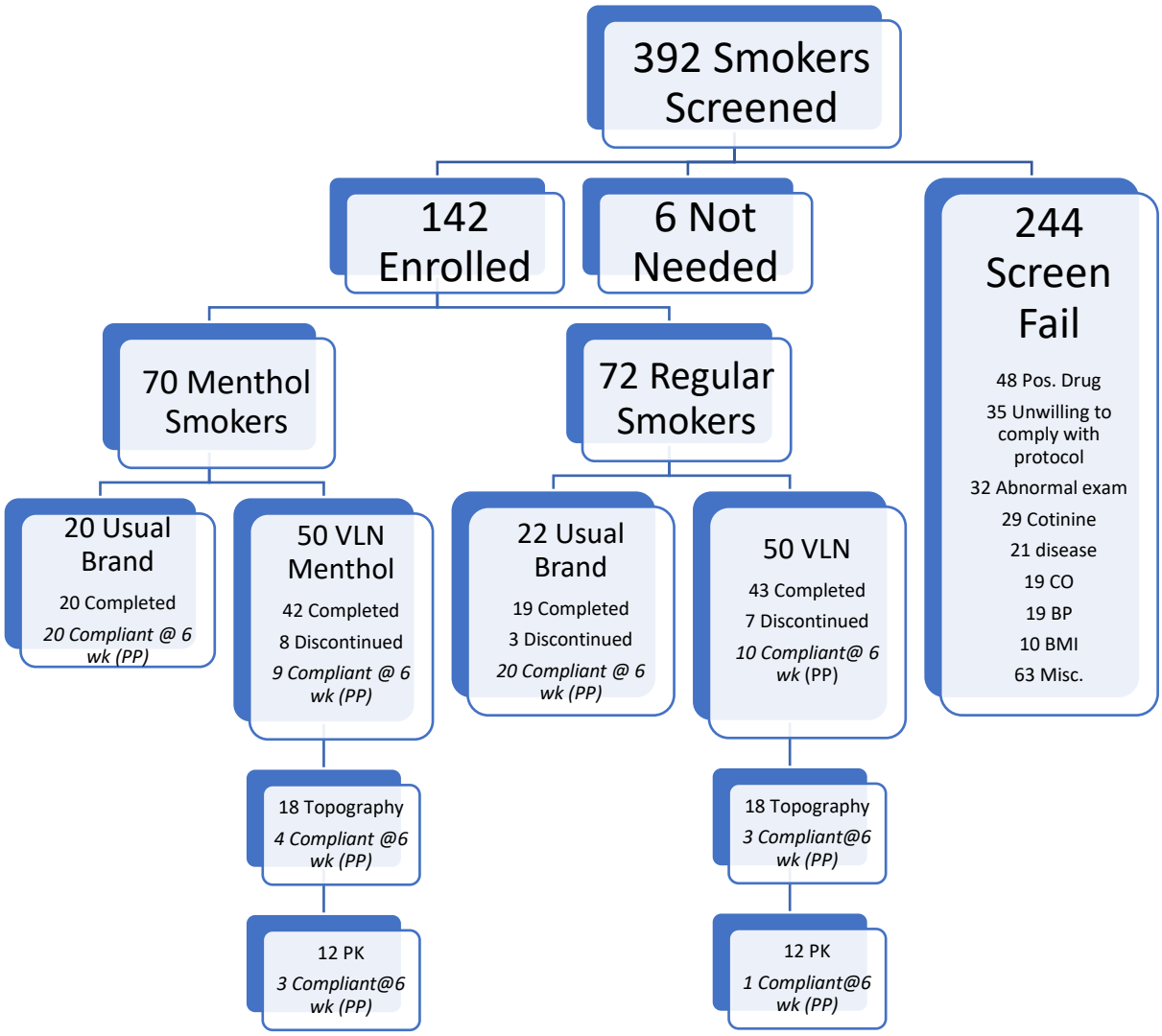


Table VIII.D-85. Disposition Summary (Safety, ITT, and PP Populations)

| Population | Disposition | VLN Non-Mentholated | VLN Mentholated | UB Non-Mentholated | UB Mentholated | Overall |
|---|---|---|---|---|---|---|
| Safety | Enrolled | 50 (100%) | 50 (100%) | 22 (100%) | 20 (100%) | 142 (100%) |
| | Completed | 43 (86%) | 42 (84%) | 19 (86%) | 20 (100%) | 124 (87%) |
| | Discontinued Early | 7 (14%) | 8 (16%) | 3 (14%) | 0 (0%) | 18 (13%) |
| | Adverse Event | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| | Lost To Follow-Up | 0 (0%) | 1 (2%) | 3 (14%) | 0 (0%) | 4 (3%) |
| | Non-Compliance With Study | 6 (12%) | 5 (10%) | 0 (0%) | 0 (0%) | 11 (8%) |
| | Withdrawal By Subject | 1 (2%) | 1 (2%) | 0 (0%) | 0 (0%) | 2 (1%) |
| ITT | Enrolled | 50 (100%) | 50 (100%) | 22 (100%) | 20 (100%) | 142 (100%) |
| | Completed | 43 (86%) | 42 (84%) | 19 (86%) | 20 (100%) | 124 (87%) |
| | Discontinued Early | 7 (14%) | 8 (16%) | 3 (14%) | 0 (0%) | 18 (13%) |

| Population | Disposition | VLN Non-Mentholated | VLN Mentholated | UB Non-Mentholated | UB Mentholated | Overall |
|---|---|---|---|---|---|---|
| | Adverse Event | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| | Lost To Follow-Up | 0 (0%) | 1 (2%) | 3 (14%) | 0 (0%) | 4 (3%) |
| | Non-Compliance With Study | 6 (12%) | 5 (10%) | 0 (0%) | 0 (0%) | 11 (8%) |
| | Withdrawal By Subject | 1 (2%) | 1 (2%) | 0 (0%) | 0 (0%) | 2 (1%) |
| PP | Enrolled | 12 (100%) | 17 (100%) | 22 (100%) | 20 (100%) | 71 (100%) |
| | Completed | 10 (83%) | 9 (53%) | 19 (86%) | 20 (100%) | 58 (82%) |
| | Discontinued Early | 2 (17%) | 8 (47%) | 3 (14%) | 0 (0%) | 13 (18%) |
| | Adverse Event | 0 (0%) | 1 (6%) | 0 (0%) | 0 (0%) | 1 (1%) |
| | Lost To Follow-Up | 0 (0%) | 1 (6%) | 3 (14%) | 0 (0%) | 4 (6%) |
| | Non-Compliance With Study | 1 (8%) | 5 (29%) | 0 (0%) | 0 (0%) | 6 (8%) |
| | Withdrawal By Subject | 1 (8%) | 1 (6%) | 0 (0%) | 0 (0%) | 2 (3%) |

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
ITT = Intent-to-treat (ITT) population, PP = Per-protocol (PP) population

Source: Table 14.1.1
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The primary objective of the study was to characterize cigarette consumption and smoking topography after switching to VLN™ cigarettes for 6 weeks. Comparing to baseline (week -1) there was no effect on overall cigarette consumption in the compliant subjects (Figure VIII.D-102)[1]. In the non-compliant ITT population (not exclusive VLN™ smokers) there was a significant decrease in cigarette consumption (Figure VIII.D-103). These results are very similar to the ones reported by Donny (Donny et al. 2015) after 6 weeks of use (Figure VIII.D-104).

[1] CPD was increased in the VLN™ Regular smokers at 6 weeks (n=11).

Figure VIII.D-102. Mean Number of Cigarettes Smoked per Day by Study Product Group and Study Week (Combined menthol and regular) (PP)

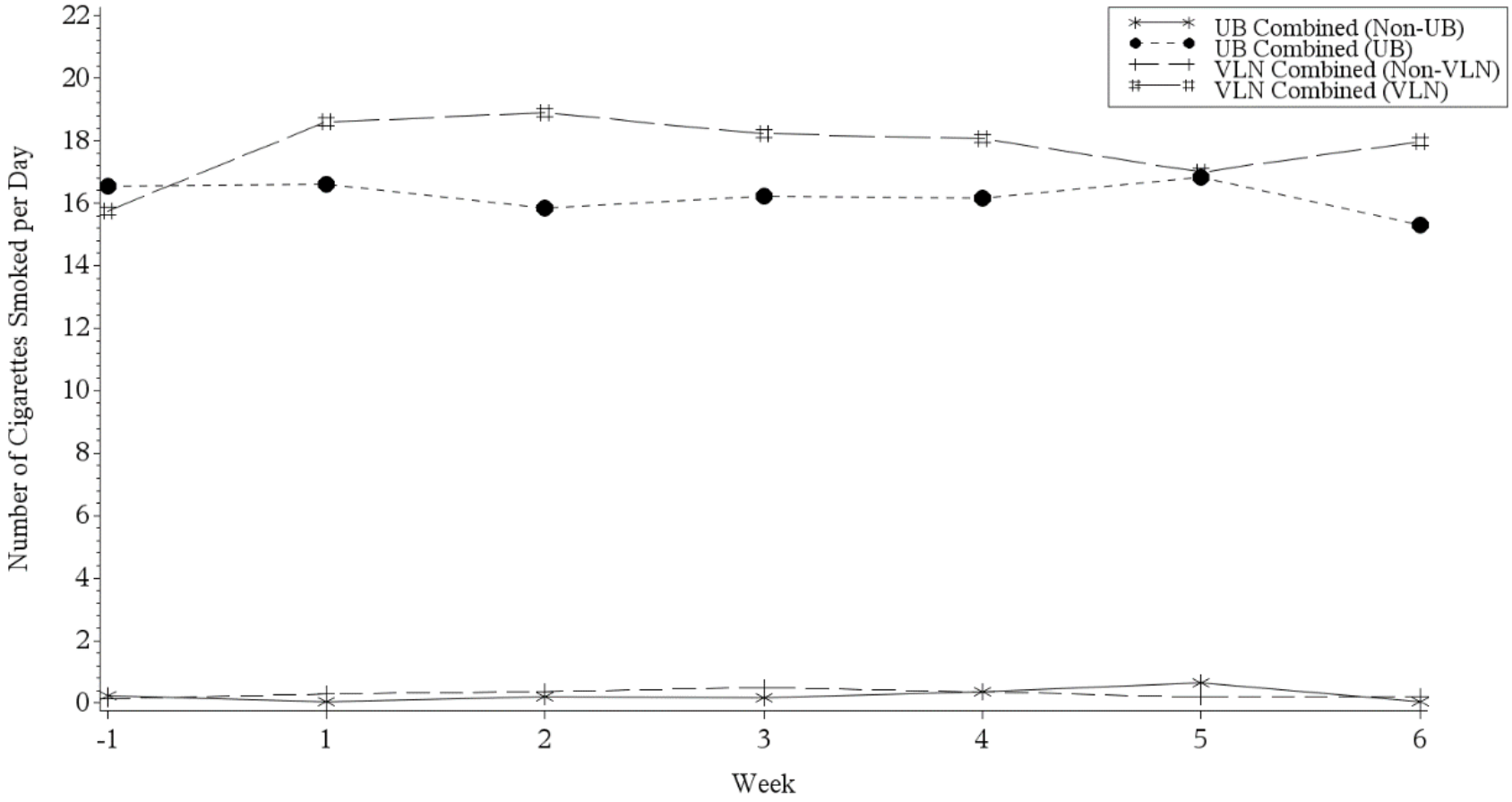


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Figure VIII.D-103. Mean Number of Cigarettes Smoked per Day by Study Product Group and Study Week (Combined) (ITT Population)

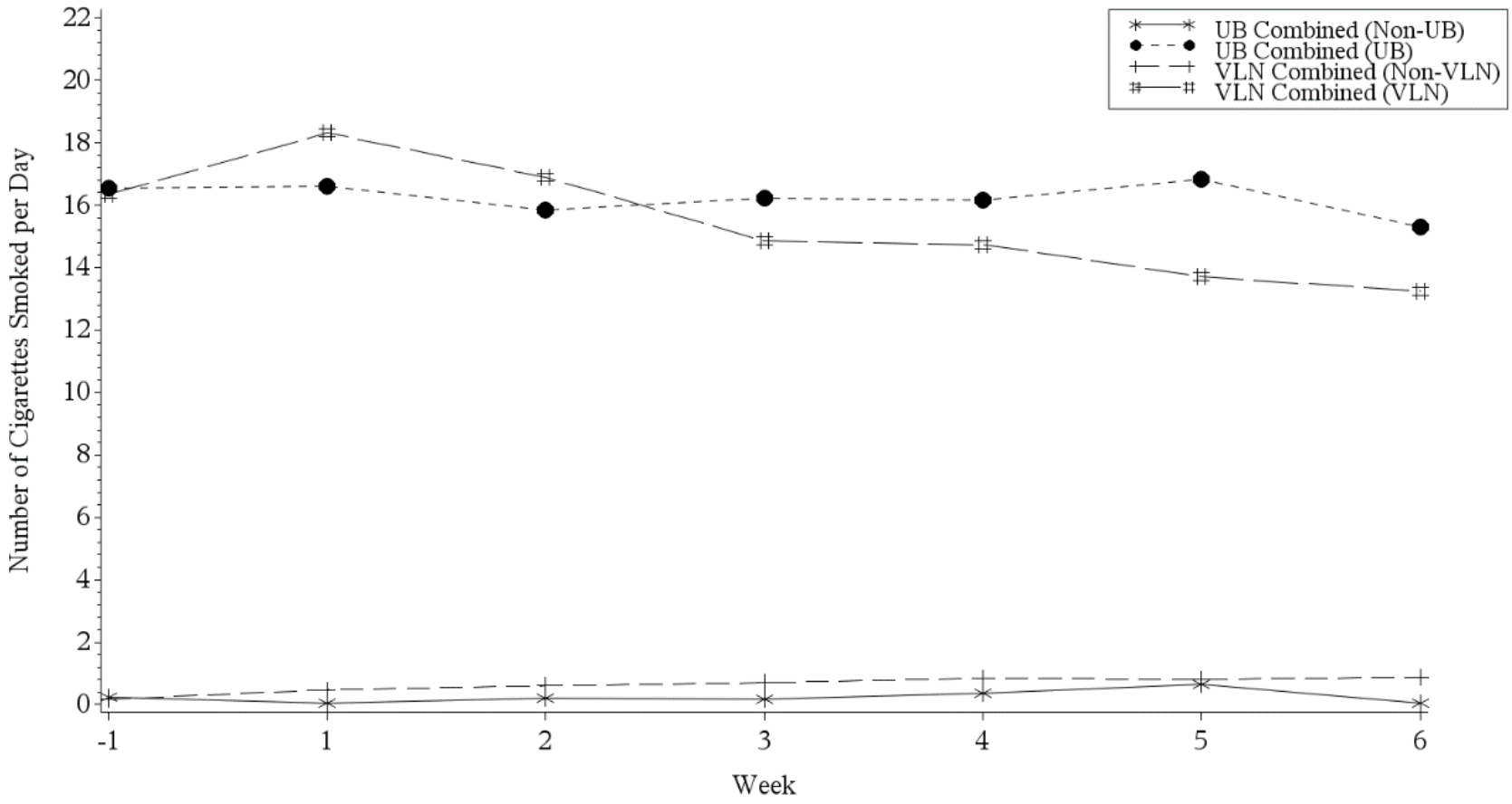


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Figure VIII.D-104. Results from Donny et al. (2015) showing CPD. 0.4 mg/g is the VLN™ product.

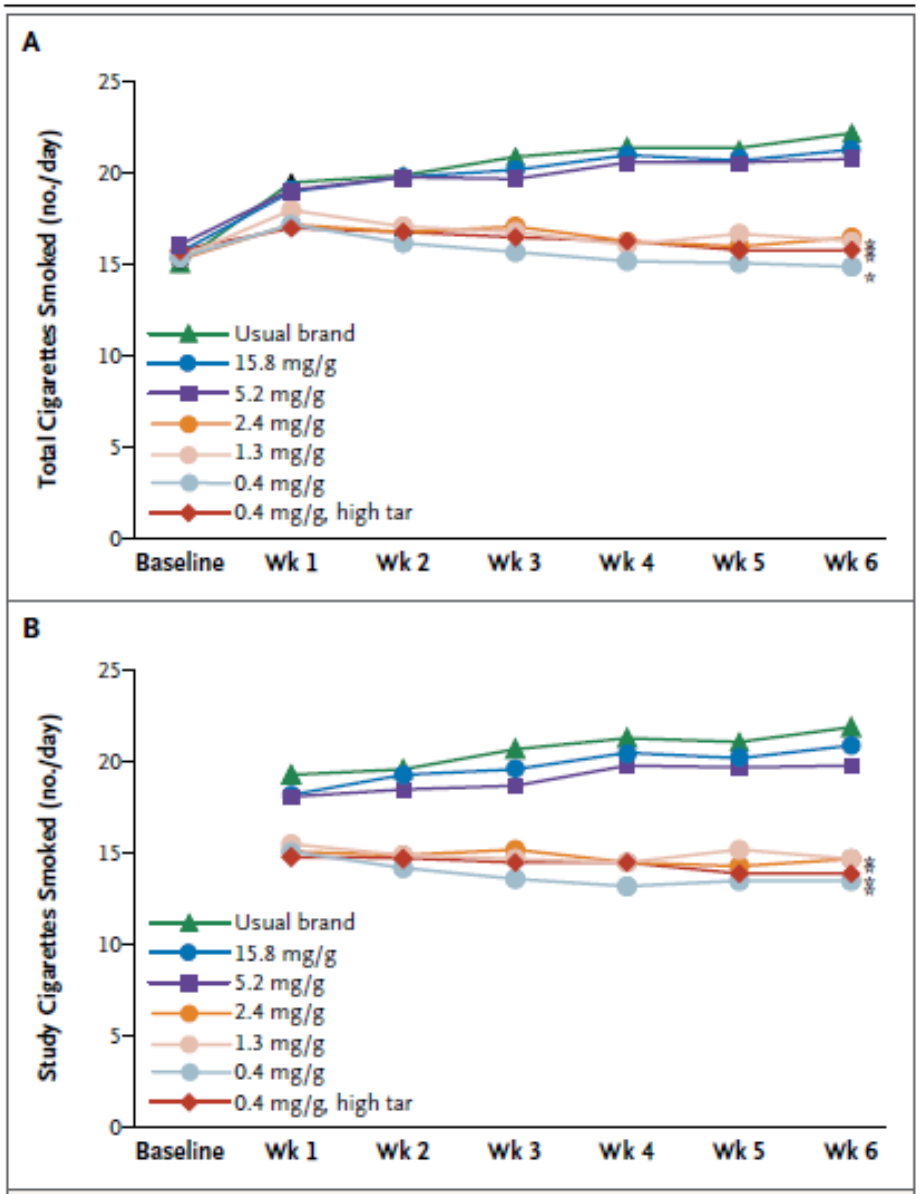


**Figure 1. Number of Cigarettes Smoked per Day According to Nicotine Content.**

The mean number of cigarettes smoked per day was based on the number reported by participants with the use of an interactive voice-response system. Panel A shows the mean total number of cigarettes smoked per day, including both study and nonstudy cigarettes. Panel B shows the mean number of study cigarettes smoked per day. All analyses were adjusted for the baseline number of cigarettes smoked per day. An asterisk indicates $P<0.001$ for the comparison at week 6 with the primary control cigarettes (those with 15.8 mg of nicotine per gram of tobacco).

Smoking topography was measured in a subset (intended 18 subjects per cigarette type) of the VLN™ smokers using a smoke puff analyzer from Sodim. The subjects were confined overnight and had no access to non-study products. From an analysis perspective the ITT population is reflective of smokers who switched completely to VLN™ cigarettes since non-study cigarettes were not available during the confined smoking period. VLN ™ smokers had significantly shorter total puff durations, significantly smaller total puff volumes, and significantly shorter inter-puff intervals observed at Weeks 2 and 6 following the switch from UB to VLN cigarettes. Average puff duration, average puff volume, and average peak puff flow rate and average flow rate were not significantly changed though were typically lower at Weeks 2 and 6 compared to baseline. A small but significant decrease in the average number of puffs taken was observed on Week 6 but not on Week 2 when compared to baseline (Table VIII.D-86). Taken together, these data indicate that the subjects did not compensate for the much smaller nicotine content of the VLN cigarettes by changing their puffing behavior in a compensatory manner with the exception of a slightly shorter inter-puff interval. This data is consistent with other publications on VLN™/SPECTRUM cigarettes (Denlinger et al. 2016; Donny et al. 2015; Hatsukami et al. 2013, 2018; Pacek et al. 2016).

Table VIII.D-86. Statistical Comparisons of Puffing Topography Parameters at Weeks 2 and 6 Versus Week -1 by Study Product Group (ITT Population)

| | | | Means | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Study Week** | **Product Group** | **Test Week** | **n** | **Baseline** | **n** | **Difference (Test Week - Baseline)** | **95% Confidence Interval** | **p-Value** |
| Average Puff Duration (sec) | Week 2 | VLN Non-Mentholated | 2.212 | 16 | 2.125 | 16 | 0.09 | -0.24 - 0.41 | 0.5745 |
| | | VLN Mentholated | 2.169 | 17 | 2.293 | 17 | -0.12 | -0.37 - 0.12 | 0.2937 |
| | | VLN Combined | 2.190 | 33 | 2.212 | 33 | -0.02 | -0.21 - 0.17 | 0.8207 |
| | Week 6 | VLN Non-Mentholated | 2.072 | 17 | 2.069 | 17 | 0.00 | -0.19 - 0.19 | 0.9817 |
| | | VLN Mentholated | 2.067 | 15 | 2.255 | 15 | -0.19 | -0.51 - 0.14 | 0.2327 |
| | | VLN Combined | 2.069 | 32 | 2.156 | 32 | -0.09 | -0.26 - 0.09 | 0.3163 |
| Average Total Puff Duration (sec) | Week 2 | VLN Non-Mentholated | 23.28 | 16 | 24.57 | 16 | -1.29 | -4.39 - 1.82 | 0.3917 |
| | | VLN Mentholated | 24.56 | 17 | 28.28 | 17 | -3.72 | -6.33 - -1.11 | 0.0082 |
| | | VLN Combined | 23.94 | 33 | 26.48 | 33 | -2.54 | -4.49 - -0.58 | 0.0125 |
| | Week 6 | VLN Non-Mentholated | 21.97 | 17 | 24.03 | 17 | -2.06 | -4.90 - 0.77 | 0.1429 |
| | | VLN Mentholated | 22.12 | 15 | 27.68 | 15 | -5.56 | -9.09 - -2.03 | 0.0045 |
| | | VLN Combined | 22.04 | 32 | 25.74 | 32 | -3.70 | -5.90 - -1.50 | 0.0017 |
| Average Puff Volume (mL) | Week 2 | VLN Non-Mentholated | 44.66 | 16 | 51.03 | 16 | -6.38 | -14.00 - 1.25 | 0.0951 |
| | | VLN Mentholated | 49.74 | 17 | 57.38 | 17 | -7.64 | -20.28 - 5.00 | 0.2183 |
| | | VLN Combined | 47.28 | 33 | 54.30 | 33 | -7.03 | -14.11 - 0.05 | 0.0516 |
| | Week 6 | VLN Non-Mentholated | 47.97 | 17 | 50.27 | 17 | -2.30 | -8.22 - 3.63 | 0.4232 |
| | | VLN Mentholated | 46.75 | 15 | 56.24 | 15 | -9.49 | -21.39 - 2.41 | 0.1092 |
| | | VLN Combined | 47.40 | 32 | 53.07 | 32 | -5.67 | -11.81 - 0.47 | 0.0692 |
| Average Total Puff Volume (mL) | Week 2 | VLN Non-Mentholated | 473.4 | 16 | 580.9 | 16 | -107.47 | -197.50 - -17.43 | 0.0225 |
| | | VLN Mentholated | 576.2 | 17 | 708.5 | 17 | -132.33 | -277.07 - 12.41 | 0.0705 |
| | | VLN Combined | 526.4 | 33 | 646.6 | 33 | -120.27 | -202.03 - -38.51 | 0.0052 |
| | Week 6 | VLN Non-Mentholated | 508.9 | 17 | 576.8 | 17 | -67.88 | -159.34 - 23.58 | 0.1352 |
| | | VLN Mentholated | 491.5 | 15 | 690.8 | 15 | -199.38 | -337.94 - -60.83 | 0.0080 |
| | | VLN Combined | 500.7 | 32 | 630.3 | 32 | -129.52 | -209.37 - -49.67 | 0.0024 |
| Average Inter-Puff Interval (sec) | Week 2 | VLN Non-Mentholated | 24.28 | 16 | 29.50 | 16 | -5.22 | -9.95 - -0.50 | 0.0325 |
| | | VLN Mentholated | 26.62 | 17 | 28.89 | 17 | -2.27 | -7.62 - 3.08 | 0.3824 |
| | | VLN Combined | 25.49 | 33 | 29.19 | 33 | -3.70 | -7.13 - -0.28 | 0.0351 |
| | Week 6 | VLN Non-Mentholated | 21.04 | 17 | 29.46 | 17 | -8.41 | -12.62 - -4.21 | 0.0006 |

| | | | Means | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Study Week** | **Product Group** | **Test Week** | **n** | **Baseline** | **n** | **Difference (Test Week - Baseline)** | **95% Confidence Interval** | **p-Value** |
| | | VLN Mentholated | 27.22 | 15 | 29.31 | 15 | -2.09 | -7.90 - 3.71 | 0.4516 |
| | | VLN Combined | 23.94 | 32 | 29.39 | 32 | -5.45 | -8.95 - -1.95 | 0.0034 |
| Average Peak Puff Flow Rate (mL/sec) | Week 2 | VLN Non-Mentholated | 39.70 | 16 | 42.89 | 16 | -3.19 | -10.03 - 3.66 | 0.3370 |
| | | VLN Mentholated | 41.44 | 17 | 44.02 | 17 | -2.58 | -13.49 - 8.33 | 0.6235 |
| | | VLN Combined | 40.60 | 33 | 43.47 | 33 | -2.87 | -9.04 - 3.30 | 0.3500 |
| | Week 6 | VLN Non-Mentholated | 43.43 | 17 | 43.73 | 17 | -0.30 | -5.32 - 4.71 | 0.8992 |
| | | VLN Mentholated | 40.02 | 15 | 43.95 | 15 | -3.93 | -14.74 - 6.88 | 0.4484 |
| | | VLN Combined | 41.83 | 32 | 43.83 | 32 | -2.00 | -7.41 - 3.40 | 0.4549 |
| Average Flow Rate (mL/sec) | Week 2 | VLN Non-Mentholated | 23.63 | 16 | 26.65 | 16 | -3.02 | -6.60 - 0.56 | 0.0919 |
| | | VLN Mentholated | 25.45 | 17 | 27.62 | 17 | -2.17 | -9.11 - 4.77 | 0.5171 |
| | | VLN Combined | 24.57 | 33 | 27.15 | 33 | -2.58 | -6.34 - 1.18 | 0.1714 |
| | Week 6 | VLN Non-Mentholated | 26.72 | 17 | 27.08 | 17 | -0.37 | -3.58 - 2.85 | 0.8117 |
| | | VLN Mentholated | 24.12 | 15 | 27.62 | 15 | -3.49 | -10.39 - 3.40 | 0.2958 |
| | | VLN Combined | 25.50 | 32 | 27.33 | 32 | -1.83 | -5.31 - 1.64 | 0.2901 |
| Average Number of Puffs (N) | Week 2 | VLN Non-Mentholated | 11.08 | 16 | 11.70 | 16 | -0.62 | -1.91 - 0.67 | 0.3232 |
| | | VLN Mentholated | 11.85 | 17 | 12.60 | 17 | -0.75 | -2.15 - 0.66 | 0.2772 |
| | | VLN Combined | 11.48 | 33 | 12.16 | 33 | -0.68 | -1.59 - 0.22 | 0.1328 |
| | Week 6 | VLN Non-Mentholated | 11.06 | 17 | 11.77 | 17 | -0.72 | -2.32 - 0.89 | 0.3594 |
| | | VLN Mentholated | 10.90 | 15 | 12.58 | 15 | -1.68 | -2.79 - -0.57 | 0.0059 |
| | | VLN Combined | 10.98 | 32 | 12.15 | 32 | -1.17 | -2.13 - -0.21 | 0.0189 |

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN mentholated = Mentholated VLN cigarettes
VLN non-mentholated = Non-mentholated VLN cigarettes
Paired t-test method is used to perform analysis.

Source: Table 14.2.3.3
Program: /CA24914/sas_prg/pksas/pd_top/adam_intext_statsttest.sas 13JUN2019 5:32

Compared to the top 100 brand styles in the US, VLN™ cigarettes have at least a 95% reduction in reduction in the nicotine per cigarette and in the smoke. This data has been previously submitted and is shown in Figure VIII.D-107 below for illustrative purposes. Plasma nicotine pharmacokinetics was measured in a subset (intended 12 subjects per cigarette type)

of the VLN™ smokers. The amount of nicotine in the usual brand cigarettes is unknown but it is reasonable to expect that VLN™ contained and delivered at least 95% less nicotine. The subjects were confined overnight and had no access to non-study products. From an analysis perspective the ITT population is reflective of smokers who switched completely to VLN™ cigarettes since non-study cigarettes were not available during the confined smoking. For all subjects (smokers of non-mentholated and mentholated cigarettes combined), nicotine peak and overall exposures (as measured by geometric mean Cmax and geometric mean AUC0-180) were significantly lower following the switch to VLN cigarettes. The decrease was over 98% for AUC0-180 on Weeks 2 and 6. Cmax decreased >97%. Median Tmax values following use of VLN cigarettes were within the same range as those observed following UB cigarettes (Table VIII.D-87). Figure VIII.D-105 shows the nicotine concentrations versus time after smoking. These results are very similar to the PK data from the VLN™ menthol and regular cigarette abuse liability studies (Figure VIII.D-106) where a greater than 97% reduction in nicotine AUC0-180 compared to usual brand was observed.

Table VIII.D-87. Statistical Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters at Weeks 2 and 6 Versus Week -1 (Pharmacokinetic Population from ITT)

| | | | Geometric Means | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter (Unit)** | **Study Week** | **Product Groups** | **Test Week (VLN)** | **(n)** | **Baseline (UB)** | **(n)** | **GMR (Test Week /Baseline)** | **% Reduction** | **95% Confidence Interval** | **p-Value** |
| Cmax (ng/mL) | Week 2 | Non-mentholated | 0.2974 | (12) | 12.18 | (12) | 0.024 | 97.6 | 0.017 - 0.035 | <.0001 |
| | | Mentholated | 0.3029 | (10) | 12.27 | (10) | 0.025 | 97.5 | 0.017 - 0.037 | <.0001 |
| | | Combined | 0.2999 | (22) | 12.22 | (22) | 0.025 | 97.5 | 0.019 - 0.031 | <.0001 |
| | Week 6 | Non-mentholated | 0.3770 | (12) | 12.18 | (12) | 0.031 | 96.9 | 0.023 - 0.041 | <.0001 |
| | | Mentholated | 0.2947 | (10) | 12.67 | (10) | 0.023 | 97.7 | 0.017 - 0.032 | <.0001 |
| | | Combined | 0.3371 | (22) | 12.40 | (22) | 0.027 | 97.3 | 0.022 - 0.033 | <.0001 |
| AUC0-180 (hr*ng/mL) | Week 2 | Non-mentholated | 0.1213 | (12) | 12.56 | (12) | 0.010 | 99.0 | 0.005 - 0.018 | <.0001 |

| | | | Geometric Means | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter (Unit)** | **Study Week** | **Product Groups** | **Test Week (VLN)** | **(n)** | **Baseline (UB)** | **(n)** | **GMR (Test Week /Baseline)** | **% Reduction** | **95% Confidence Interval** | **p-Value** |
| | | Mentholated | 0.1584 | (10) | 13.29 | (10) | 0.012 | 98.8 | 0.007 - 0.020 | <.0001 |
| | | Combined | 0.1370 | (22) | 12.88 | (22) | 0.011 | 98.9 | 0.007 - 0.016 | <.0001 |
| | Week 6 | Non-mentholated | 0.1956 | (12) | 12.56 | (12) | 0.016 | 98.4 | 0.009 - 0.026 | <.0001 |
| | | Mentholated | 0.1545 | (10) | 13.53 | (10) | 0.011 | 98.9 | 0.006 - 0.021 | <.0001 |
| | | Combined | 0.1757 | (22) | 12.99 | (22) | 0.014 | 98.6 | 0.009 - 0.020 | <.0001 |

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Analysis is based on the log-transformed data.
Paired t-test method is used to perform the analysis.
Geometric means are calculated by exponentiating the means.
Geometric Mean Ratios (GMR) are calculated by exponentiating the mean of difference from paired t-test.
95% Confidence Intervals are calculated by exponentiating the 95% Confidence Intervals of the mean difference from paired t-test.
Source: Table 14.2.7.12
Program: /CA24914/sas_prg/pksas/adam_intext_statsmixed.sas 12JUN2019 15:21

Figure VIII.D-105. Mean Baseline Adjusted Plasma Nicotine Concentrations Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Linear Scale) (Pharmacokinetic Population from PP).

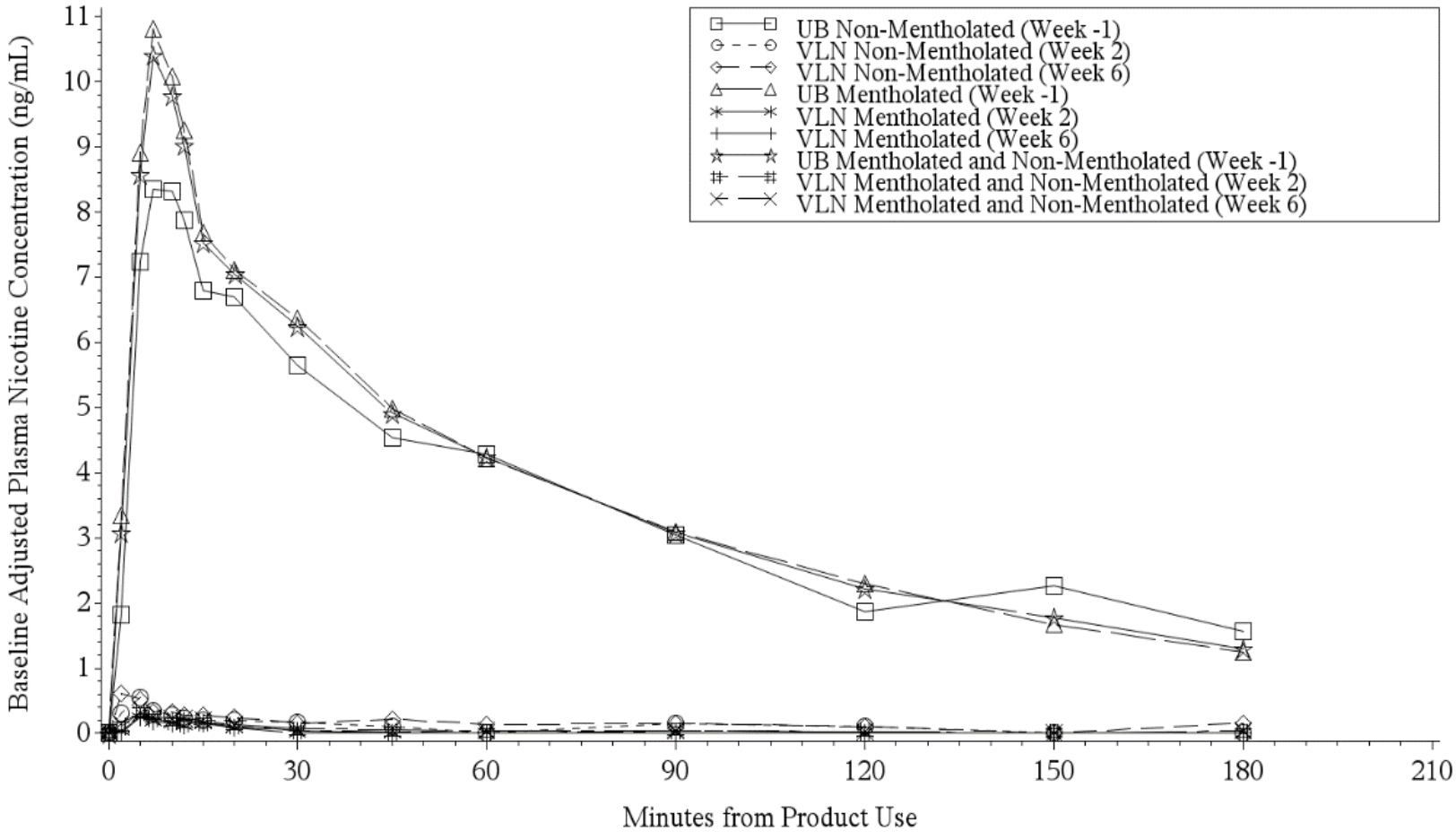


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Figure VIII.D-106. Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum) (From VLN™ Regular Abuse Liability study).

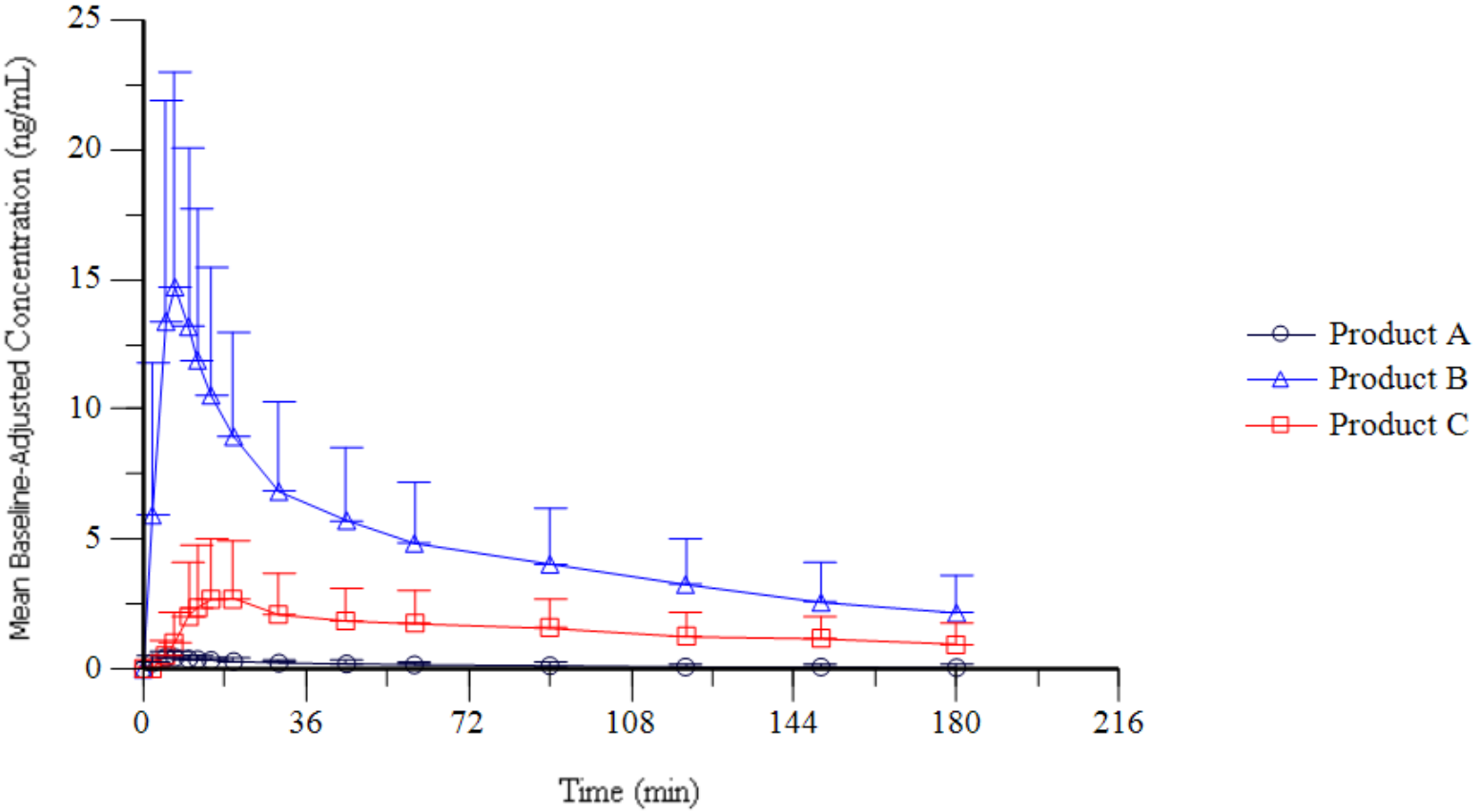
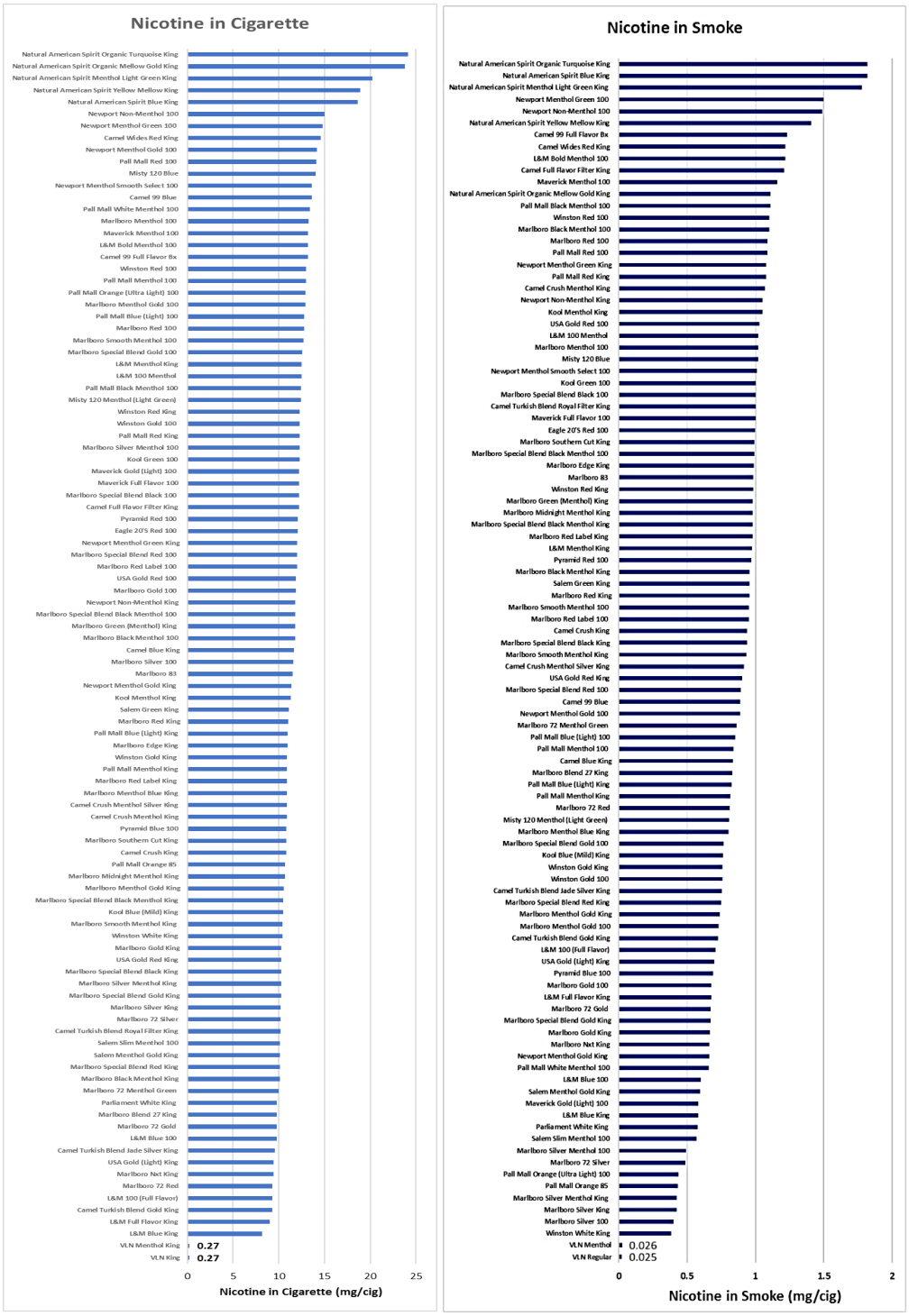


Figure VIII.D-107. Amount of nicotine in tobacco and in smoke for VLN and the top 100 cigarette brand styles in the US.



Total nicotine equivalents (Tneq) were measured in the 24-hour urine of the VLN™ smokers during confinement. Creatine concentrations were used to adjust the concentrations of the urine biomarkers. Significant decreases in urinary Tneq were observed in subjects who switched to VLN cigarettes in the PP population (approximately 93% decrease at Weeks 2 and 6) and in the ITT population (69% to 73% at Week 2 and 48% to 58% and Week 6) (Table VIII.D-88). Donny (Donny et al. 2015) observed an approximate 60% reduction in Tneq after 6-weeks. These results are consistent with expected results. The compliant (PP) subjects should have higher reductions in Tneq than the less compliant (ITT).

Table VIII.D-88. Summary of Comparisons of BoE at Weeks 2 and 6 Versus Week -1 by Study Product Group

| | | ITT Population | | PP Population | |
|---|---|---|---|---|---|
| | | LS Mean Difference (p-Value) | | LS Mean Difference (p-Value) | |
| **Biomarker** | **Comparison** | **Week 2** | **Week 6** | **Week 2** | **Week 6** |
| Urine NNAL (ng/24 hour) | Non-Mentholated | -233.388 (<.0001) | -203.034 (<.0001) | -286.350 (<.0001) | -352.687 (<.0001) |
| | Mentholated | -182.927 (<.0001) | -152.537 (0.0008) | -177.963 (0.0008) | -189.781 (0.0014) |
| | Combined | -208.157 (<.0001) | -177.785 (<.0001) | -232.157 (<.0001) | -271.234 (<.0001) |
| Urine NNN (ng/24 hour) | Non-Mentholated | -4.519 (0.0690) | -4.714 (0.0992) | -10.076 (0.0199) | -13.736 (0.0030) |
| | Mentholated | -1.827 (0.4645) | -1.497 (0.5926) | 3.345 (0.4174) | 3.322 (0.4434) |
| | Combined | -3.173 (0.0724) | -3.106 (0.1213) | -3.366 (0.2565) | -5.207 (0.0964) |
| Urine 3-HPMA (µg/24 hour) | Non-Mentholated | 115.922 (0.3193) | -235.818 (0.0811) | 162.276 (0.2032) | -154.535 (0.3891) |
| | Mentholated | -233.965 (0.0484) | -455.443 (0.0006) | -159.848 (0.1977) | -444.949 (0.0141) |
| | Combined | -59.022 (0.4756) | -345.631 (0.0003) | 1.214 (0.9890) | -299.742 (0.0199) |
| Urine S-PMA (µg/24 hour) | Non-Mentholated | 1.579 (0.0365) | 0.367 (0.6093) | 2.756 (0.0013) | 1.244 (0.1976) |
| | Mentholated | 0.356 (0.6386) | -0.992 (0.1509) | 0.464 (0.5614) | -1.150 (0.2302) |
| | Combined | 0.967 (0.0711) | -0.312 (0.5302) | 1.610 (0.0064) | 0.047 (0.9448) |
| Urine 1-OHP (ng/24 hour) | Non-Mentholated | -46.405 (0.0337) | -65.665 (0.0131) | -69.511 (0.0188) | -103.050 (0.0016) |
| | Mentholated | -32.365 (0.1415) | -62.452 (0.0145) | -23.356 (0.4073) | -82.147 (0.0099) |
| | Combined | -39.385 (0.0116) | -64.058 (0.0006) | -46.434 (0.0242) | -92.599 (<.0001) |
| Urine Tneq (mg/24 hour) | Non-Mentholated | -11.251 (<.0001) | -8.446 (<.0001) | -14.398 (<.0001) | -15.394 (<.0001) |
| | Mentholated | -11.704 (<.0001) | -8.078 (<.0001) | -13.920 (<.0001) | -12.963 (<.0001) |
| | Combined | -11.478 (<.0001) | -8.262 (<.0001) | -14.159 (<.0001) | -14.178 (<.0001) |
| Blood COHb (% Saturation) | Non-Mentholated | 0.870 (0.0373) | -0.745 (0.0515) | 0.706 (0.1969) | -0.797 (0.0703) |
| | Mentholated | -0.348 (0.4152) | -0.335 (0.3771) | -0.358 (0.5023) | 0.040 (0.9271) |
| | Combined | 0.261 (0.3813) | -0.540 (0.0457) | 0.174 (0.6481) | -0.379 (0.2247) |

| | | ITT Population | | PP Population | |
|---|---|---|---|---|---|
| | | LS Mean Difference (p-Value) | | LS Mean Difference (p-Value) | |
| **Biomarker** | **Comparison** | **Week 2** | **Week 6** | **Week 2** | **Week 6** |
| Baseline = Week -1<br>Subjects used their own usual brand cigarettes at Week -1.<br>LS mean difference = LS mean VLN cigarette group - LS mean UB cigarette group<br>Non-Mentholated = VLN Non-mentholated vs UB Non-mentholated<br>Mentholated = VLN Mentholated vs UB Mentholated<br>Combined = VLN Combined vs UB Combined<br>Source: Tables 14.2.5.1.3.1, 14.2.5.1.3.2, 14.2.5.2.3.1, 14.2.5.2.3.2, 14.2.5.3.3.1, 14.2.5.3.3.2, 14.2.5.4.3.1, 14.2.5.4.3.2, 14.2.5.5.3.1, 14.2.5.5.3.2, 14.2.5.6.3.1, 14.2.5.6.3.2, 14.2.5.7.3, 14.2.5.7.5<br>Program: /CA24914/sas_prg/pksas/pdurine/adam_intext_urinestatsmixed.sas 12JUN2019 10:42 | | | | | |

Additional biomarkers of exposure were measured in the VLN™ subjects and compared to their baseline values. It is not possible to know what the subject's exposure to the various HPHC's from their usual brand were. Comparing each subject to their baseline before the switch at least tells what the change was. The HPHC's from VLN™ cigarettes were compared to the top six market leading brands. The results have been previously submitted and are shown in Table VIII.D-89. Figure VIII.D-108 shows the relationship of VLN to the leading brands. Compared to the leading brands, VLN™ appears to have less benzo[a]pyrene, NNK, acrolein, and nicotine. NNN appears to be slightly decreased. Benzene and CO do not appear to be different. Biomarkers of these HPHC's were measured in this study.

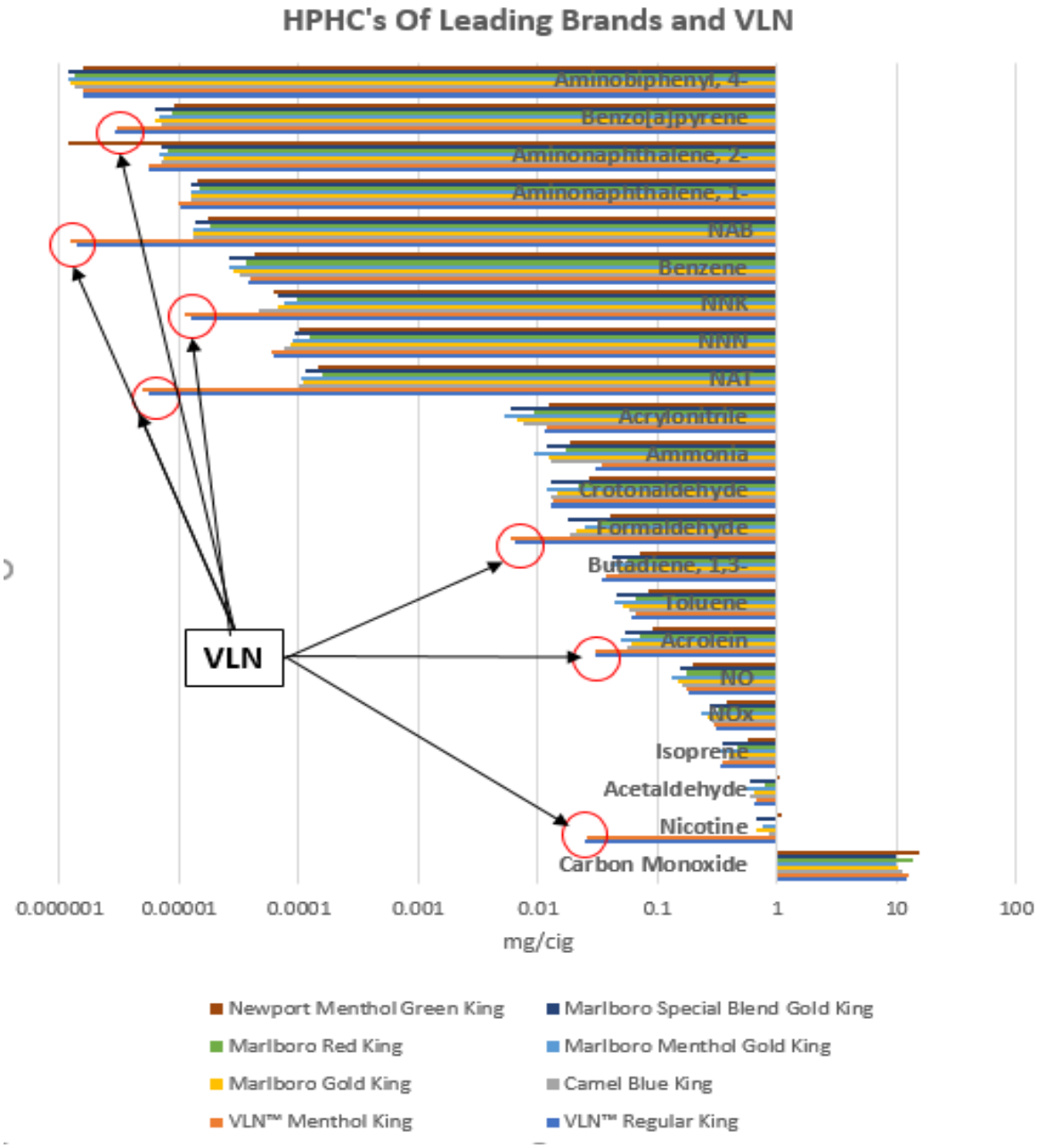
Table VIII.D-89. Summary of HPHC results of VLN™ and market leading brands.

| **ISO Smoking Conditions** | | **VLN™ King** | **VLN™ Menthol King** | **Camel Blue King** | **Marlboro Gold King** | **Marlboro Menthol Gold King** | **Marlboro Red King** | **Marlboro Special Blend Gold King** | **Newport Menthol Green King** |
|---|---|---|---|---|---|---|---|---|---|
| **Constituent** | **Unit** | | | | | | | | |
| Acetaldehyde | (µg/cig) | 647 (56) | 678 (62) | 597 (51.2) | 649 (35.5) | 547 (33.4) | 783 (40.3) | 595 (29.0) | 1005 (29.1) |
| Acrolein | (µg/cig) | 29.6 (3.3) | 30.1 (2.8) | 55.7 (5.13) | 59.7 (3.35) | 48.9 (3.46) | 69.8 (4.56) | 54 (3.41) | 92 (3.59) |
| Acrylonitrile | (µg/cig) | 11.5 (0.8) | 12.0 (0.5) | 7.46 (0.716) | 6.55 (0.493) | 5.23 (0.605) | 9.24 (0.800) | 5.79 (0.924) | 12.1 (0.908) |
| Aminobiphenyl, 4- | (ng/cig) | 1.57 (0.11) | 1.55 (0.06) | 1.33 (0.08) | 1.23 (0.5) | 1.19 (0.06) | 1.34 (0.05) | 1.17 (0.07) | 1.55 (0.06) |
| Aminonaphthalene, 1- | (ng/cig) | 10.1 (1) | 9.71 (0.78) | 12.4 (0.3) | 12.5 (0.7) | 12.3 (0.5) | 14.6 (0.6) | 12.4 (0.2) | 14.3 (0.2) |

| ISO Smoking Conditions | | VLN™ King | VLN™ Menthol King | Camel Blue King | Marlboro Gold King | Marlboro Menthol Gold King | Marlboro Red King | Marlboro Special Blend Gold King | Newport Menthol Green King |
|---|---|---|---|---|---|---|---|---|---|
| Aminonaphthalene, 2- | (ng/cig) | 5.63 (0.44) | 5.54 (0.29) | 7.06 (0.25) | 7.26 (0.41) | 6.89 (0.24) | 7.87 (0.23) | 7.08 (0.27) | 1.17 (0.07) |
| Ammonia | (µg/cig) | 30.1 (5.0) | 34.3 (3.4) | 12.7 (0.788) | 12.3 (0.691) | 9.15 (0.684) | 17.3 (0.838) | 12.0 (0.89) | 18.8 (1.27) |
| Benzene | (µg/cig) | 37.8 (2.2) | 39.2 (1.7) | 31.9 (2.88) | 28.6 (2.65) | 26.0 (3.0) | 35.7 (2.71) | 25.6 (2.99) | 43.3 (2.86) |
| Benzo[a]pyrene | (ng/cig) | 2.84 (0.15) | 2.97 (0.27) | 7.07 (0.39) | 6.26 (0.29) | 6.8 (0.30) | 8.70 (0.65) | 6.19 (0.51) | 9.10 (0.77) |
| Butadiene, 1,3- | (µg/cig) | 34.5 (1.3) | 36.3 (1.7) | 46.6 (4.27) | 46.4 (4.84) | 40.3 (2.69) | 54.7 (5.02) | 41.3 (5.08) | 69.9 (6.58) |
| Carbon Monoxide | (mg/cig) | 11.8 (0.6) | 12.3 (0.7) | 10.9 (0.7) | 10.2 (0.6) | 9.90 (0.54) | 13.3 (0.90) | 9.92 (0.64) | 15.1 (1.1) |
| Crotonaldehyde | (µg/cig) | 12.6 (1.5) | 13.4 (1.3) | 13.0 (1.59) | 14.7 (1.62) | 12 (1.17) | 21.9 (1.89) | 12.8 (0.891) | 26.9 (0.76) |
| Formaldehyde | (µg/cig) | 6.32 (0.45) | 5.93 (0.6) | 18.6 (2.71) | 20.7 (2.76) | 24.6 (2.15) | 30.7 (4.84) | 18.0 (1.79) | 40.2 (4.01) |
| Isoprene | (µg/cig) | 332 (15) | 347 (12) | 393 (35.2) | 395 (34.2) | 334 (28.8) | 468 (21.1) | 345 (40.5) | 570 (49.1) |
| Nicotine | (mg/cig) | 0.0246 (0.0015) | 0.0257 (0.0012) | 0.837 (0.028) | 0.670 (0.026) | 0.741 (0.036) | 0.956 (0.055) | 0.675 (0.039) | 1.08 (0.05) |
| NNK | (ng/cig) | 12.5 (1.2) | 11 (0.8) | 46.1 (1.29) | 67.0 (3.6) | 76.2 (3.83) | 96.8 (6.97) | 66.4 (2.53) | 62.1 (4.29) |
| NNN | (ng/cig) | 62 (2.2) | 58.2 (1.9) | 74.0 (3.60) | 86.2 (4.31) | 87.7 (8.48) | 125 (4.85) | 91.4 (6.02) | 102 (10.5) |
| NAB | (ng/cig) | 1.39 (0.11) | 1.24 (0.13) | 12.8 (0.592) | 13.2 (0.404) | 12.9 (0.556) | 17.9 (0.485) | 13.8 (0.402) | 17.1 (0.929) |
| NAT | (ng/cig) | 5.48 (0.46) | 5.0 (0.33) | 101 (4.13) | 107 (3.66) | 104 (4.79) | 158 (4.24) | 111 (3.39) | 145 (8.95) |
| NO | (µg/cig) | 179 (7) | 176 (12) | 163 (31) | 148 (26) | 131 (21) | 173 (26) | 155 (22) | 195 (28) |
| NOx | (µg/cig) | 301 (12) | 296 (24) | 288 (53) | 260 (45) | 226 (25) | 322 (54) | 270 (34) | 383 (63) |
| Toluene | (µg/cig) | 60.3 (4.5) | 64.6 (3.0) | 57.2 (4.87) | 50.6 (4.03) | 44.0 (4.66) | 64.9 (4.12) | 44.5 (4.71) | 82.7 (4.87) |
| Tar | (mg/cig) | 6.98 (0.4) | 7.37 (0.39) | 9.84 (0.53) | 8.97 (0.55) | 9.44 (0.55) | 14.0 (1.0) | 8.87 (0.55) | 15.4 (1.0) |
| Water | (mg/cig) | 0.466 (0.146) | 0.490 (0.114) | 0.997 (0.159) | 0.751 (0.145) | 0.779 (0.182) | 1.96 (0.37) | 0.747 (0.131) | 3.17 (0.76) |
| Puffs | (#/cig) | 5.76 (0.17) | 5.85 (0.17) | 8.14 (0.21) | 7.29 (0.21) | 7.48 (0.25) | 7.30 (0.29) | 7.43 (0.25) | 7.32 (0.31) |
| Menthol | (mg/cig) | Not Measured | 0.432 (0.027) | Not Measured | Not Measured | 0.376 (0.0268) | Not Measured | Not Measured | 0.481 (0.0194) |
| Date of testing | | 5/30/2018 | 5/30/2018 | 9/5/18 | 9/5/18 | 9/5/18 | 9/5/18 | 9/5/18 | 9/5/18 |
| Laboratory | | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical | Enthalpy Analytical |

| ISO Smoking Conditions | VLN™ King | VLN™ Menthol King | Camel Blue King | Marlboro Gold King | Marlboro Menthol Gold King | Marlboro Red King | Marlboro Special Blend Gold King | Newport Menthol Green King |
|---|---|---|---|---|---|---|---|---|
| Publication/ Report No. | Project Code: 0318-026 | Project Code: 0318-026 | Project Code: 0718-022 | Project Code: 0718-022 | Project Code: 0718-022 | Project Code: 0718-022 | Project Code: 0718-022 | Project Code: 0718-022 |

Figure VIII.D-108 HPHC's of Leading Brands and VLN™.



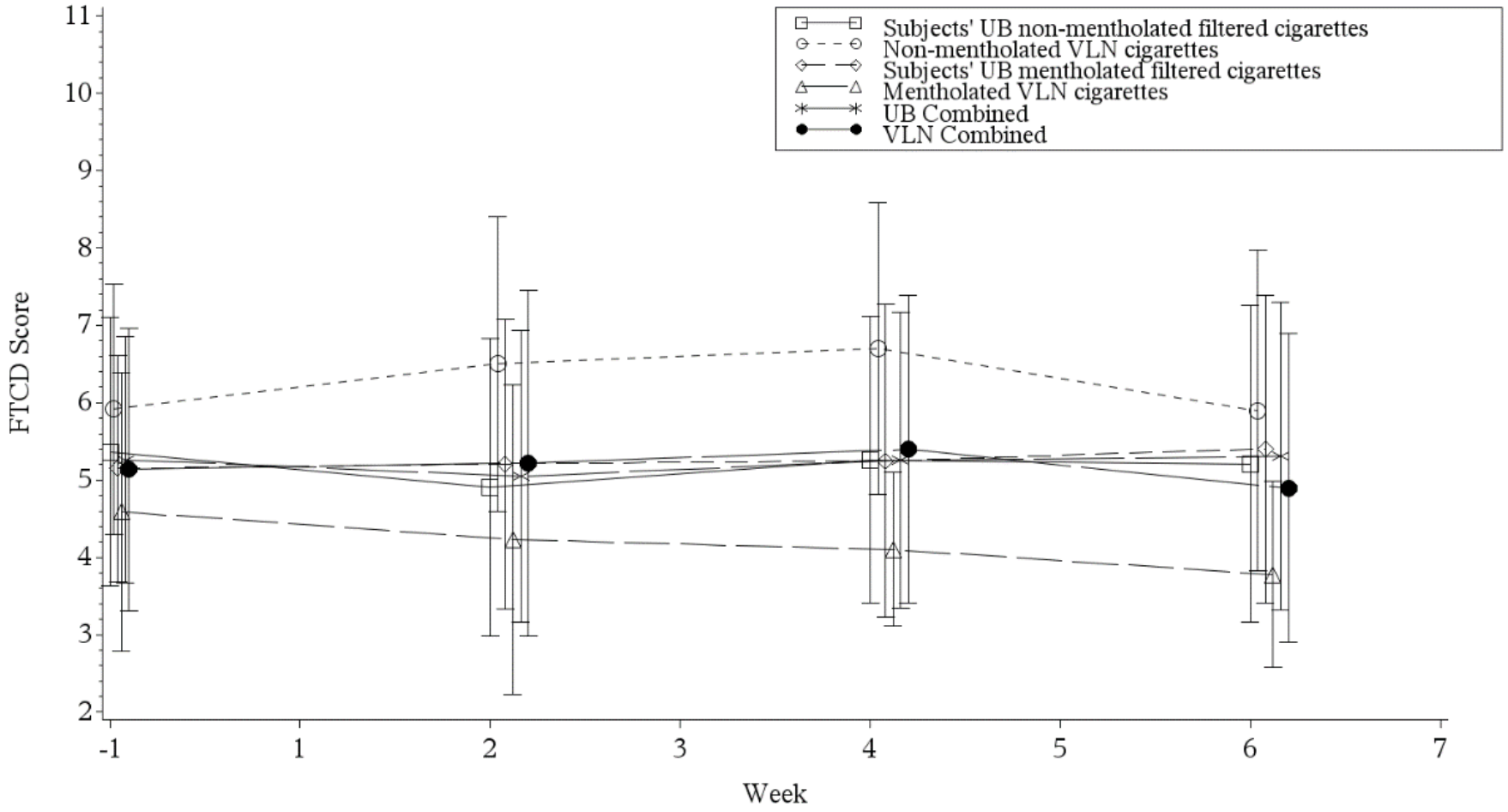
NNAL (NNK biomarker) was significantly reduced in the compliant subjects (PP) and non-compliant subjects (ITT) at Weeks 2 and 6 (56% to 70% in the PP population and 38% to 49% in the ITT population) (Table VIII.D-88). Donny (Donny et al. 2015) observed a non-significant reduction in NNAL after 6 weeks. These results are consistent with the reduced levels of NNK in the HPHC's. NNN does not appear to be significantly reduced in the HPHC of VLN™ Cigarettes. NNN was non-significantly decreased in the urine of VLN™ smokers (Table VIII.D-88). Acrolein appears to be decreased in the smoke of VLN™ cigarettes. 3-HPMA is a biomarker of acrolein exposure. At Week 6, decreases in urinary 3-HPMA were only significant in subject groups who switched to VLN cigarettes (smokers in PP and ITT populations showing a 26% decrease)(Table VIII.D-88). Hatsukami (Hatsukami et al. 2018) observed a decrease after 20-weeks. S-PMA is a biomarker of benzene exposure. Benzene HPHC levels from VLN™ cigarettes do not appear to be different from other cigarettes on the market. S-PMA was not affected in the ITT population but decreased at 6 Weeks in the PP (Table VIII.D-88). Hatsukami (Hatsukami et al. 2018) observed a decrease after 20-weeks. 1-OHP is a biomarker for polycyclic aromatic hydrocarbons (PAH) exposure. Benzo[a]pyrene is reduced in the smoke of VLN™ cigarettes. At Week 6 significant decreases in urinary 1-OHP were seen in subjects who switched to VLN cigarettes with 33% decreases in the PP population and 25% decreases in the ITT population (Table VIII.D-88). Hatsukami did not measure 1-OHP but did measure urinary phenanthrene tetraol (PheT), an indicator of exposure to polycyclic aromatic hydrocarbons. PheT was reduced after 20 weeks (Hatsukami et al. 2018). The amount of CO in smoke from VLN™ cigarettes is not considered different from usual brands. Carboxyhemoglobin was measured and found to be reduced at 6 weeks

in the non-compliant population (ITT) but not be affected in the compliant population (PP) (Table VIII.D-88). Hatsukami (Hatsukami et al. 2018) observed a decrease after 20-weeks. In summary the reduced biomarkers of exposure are consistent with the reduced levels of specific constituents in the smoke of VLN™ cigarettes. Some reductions also may be due to slight reduced cigarette consumption in individual subjects.

The subjects were evaluated for degree of addiction (Fagerstrom Test for Cigarette Dependence, FTCD), smoking urges (Questionnaire on Smoking Urges – Brief, QSU), withdrawal (Minnesota Nicotine Withdrawal Scale, MNWS) and their perception of the addiction risks of smoking the product at Weeks -1, 2, 4, and 6. There was no difference in the level of addiction as measured by the FTCD in the compliant (PP) (Figure VIII.D-109) or non-compliant subjects (ITT) (Figure VIII.D-110). Donny (Donny et al. 2015) observed a slight statistically significant reduction in dependence after 6-weeks. The results of the QSU can be broken down into two factors: Factor 1 representing anticipation of pleasure from smoking and Factor 2 representing relief from nicotine withdrawal. In the compliant population (PP) there appeared to be a slight reduction in the pleasure from smoking (Factor 1) for the VLN™ Menthol smokers (Figure VIII.D-111) after 6 weeks. There were no effects in the non-complaint subjects (ITT) (Figure VIII.D-112). Relief from withdrawal (Factor 2) was reduced at 6 Weeks in the compliant population (PP) (Figure VIII.D-113) but not in the non-complaint population (ITT) (Figure VIII.D-114). Hatsukami (Hatsukami et al. 2018) observed a reduction in Factor 1 and 2 at 6 weeks in the 20-week study. Withdrawal as measured by the MNWS-R total score was reduced at 6 weeks in the compliant population (PP) but not in the non-compliant population (ITT) (Figure VIII.D-115 and Figure VIII.D-116, respectively). Hatsukami

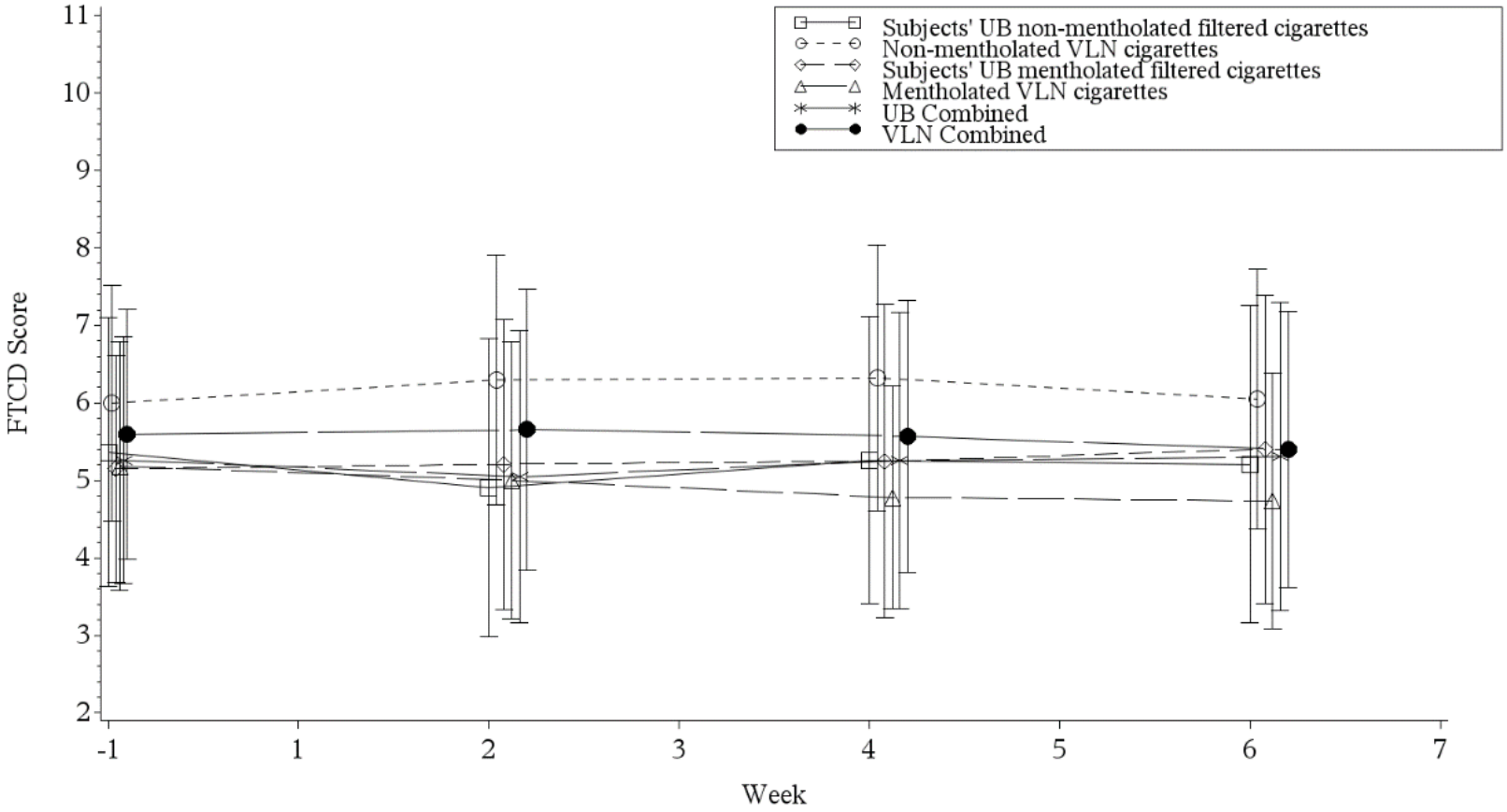
(Hatsukami et al. 2018) did not observe an effect on MNWS at 6 weeks in the 20-week study. The perceived health risks questionnaire asked the smokers their perception of the risk of becoming addicted to the product. The smokers perception of becoming addicted to VLN decreased by 6 Weeks in the compliant (PP) (Figure VIII.D-117) and non-complaint populations (Figure VIII.D-118).

Figure VIII.D-109. Mean (±SD) of FTCD Score by Study Product Group and Study Week (PP Population).



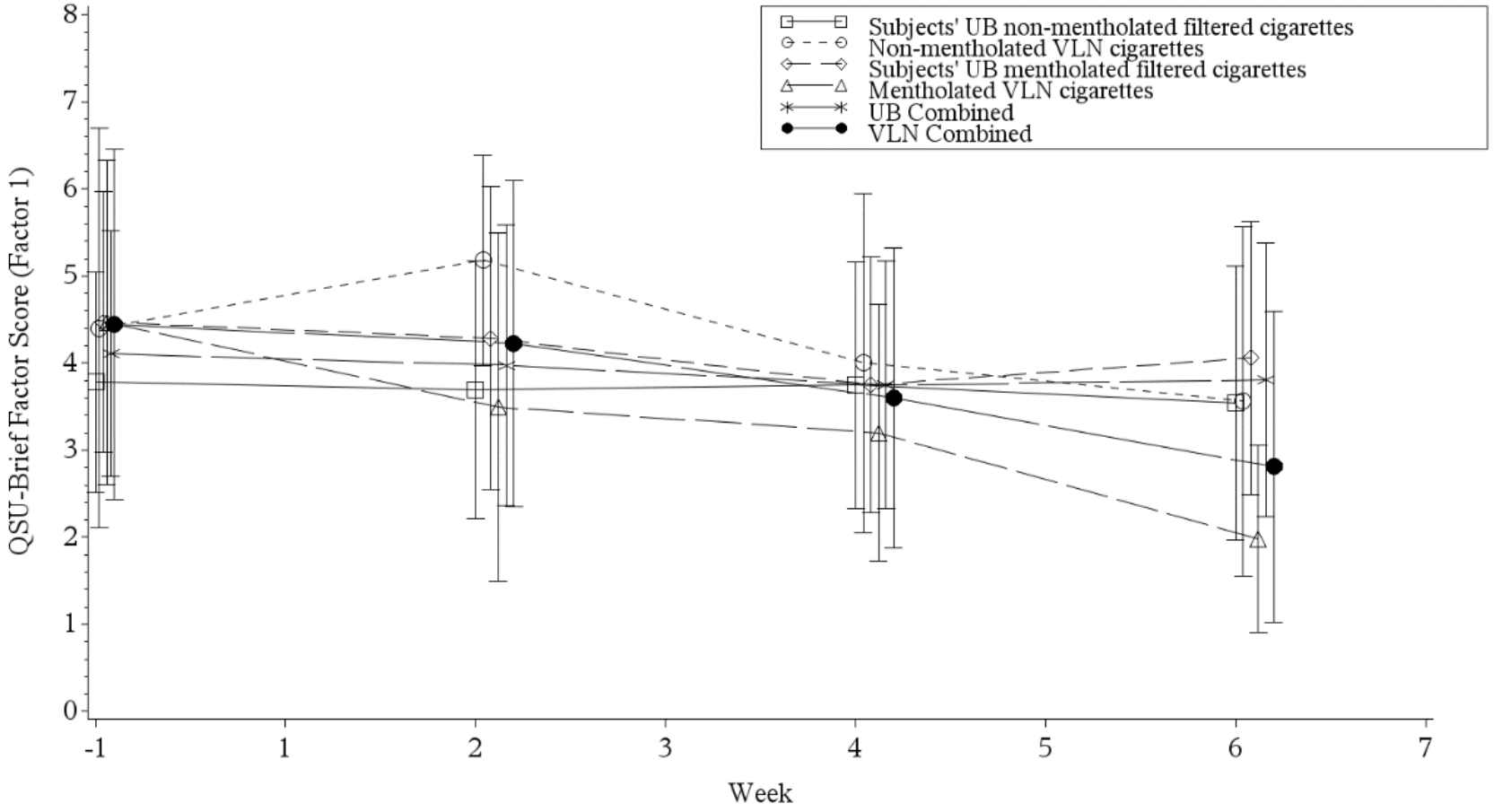

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-110. Mean (±SD) of FTCD Score by Study Product Group and Study Week (ITT Population)



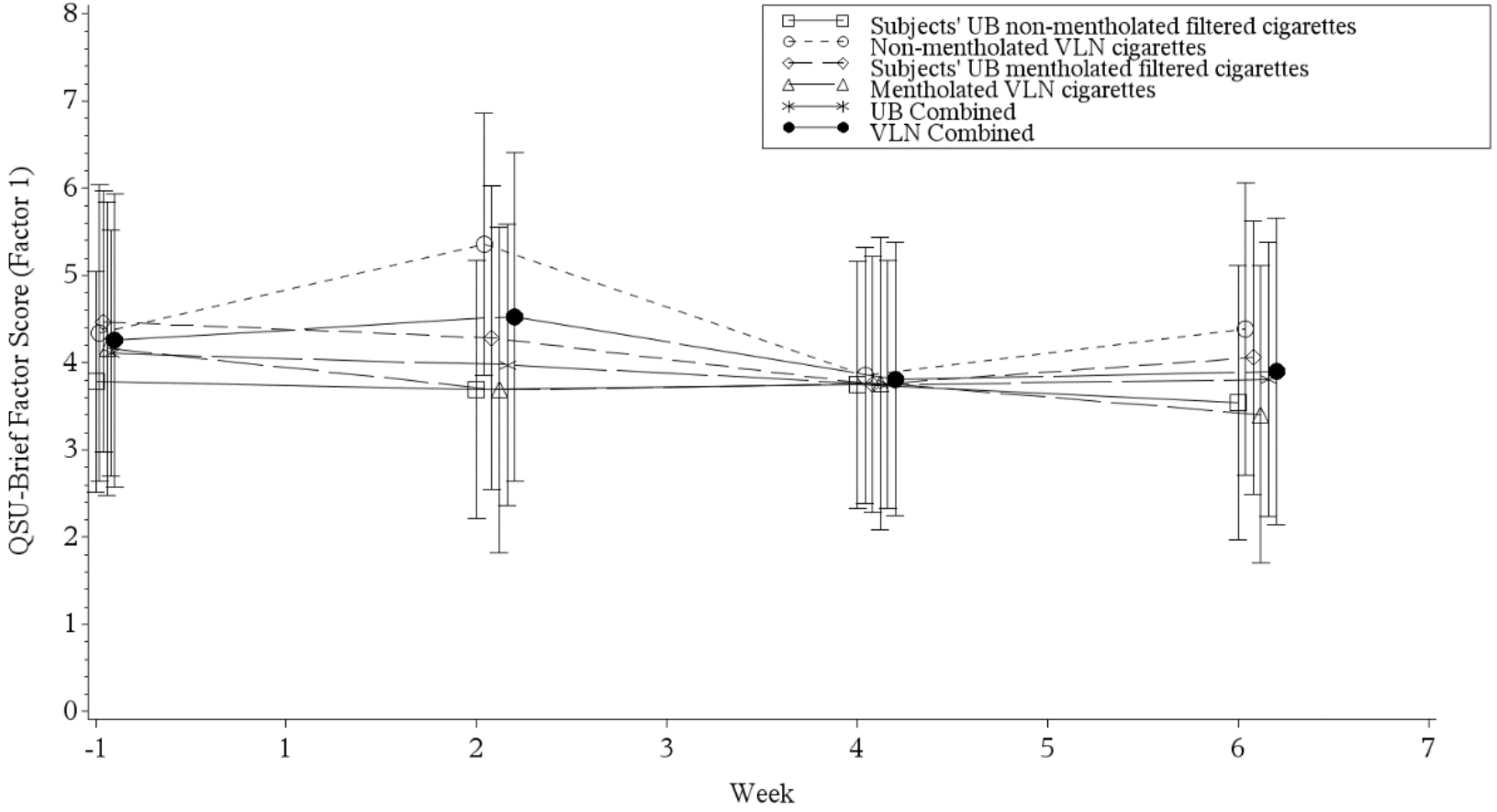

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-111. Mean (±SD) of QSU-Brief Factor Score (Factor 1) by Study Product Group and Study Week (PP Population).



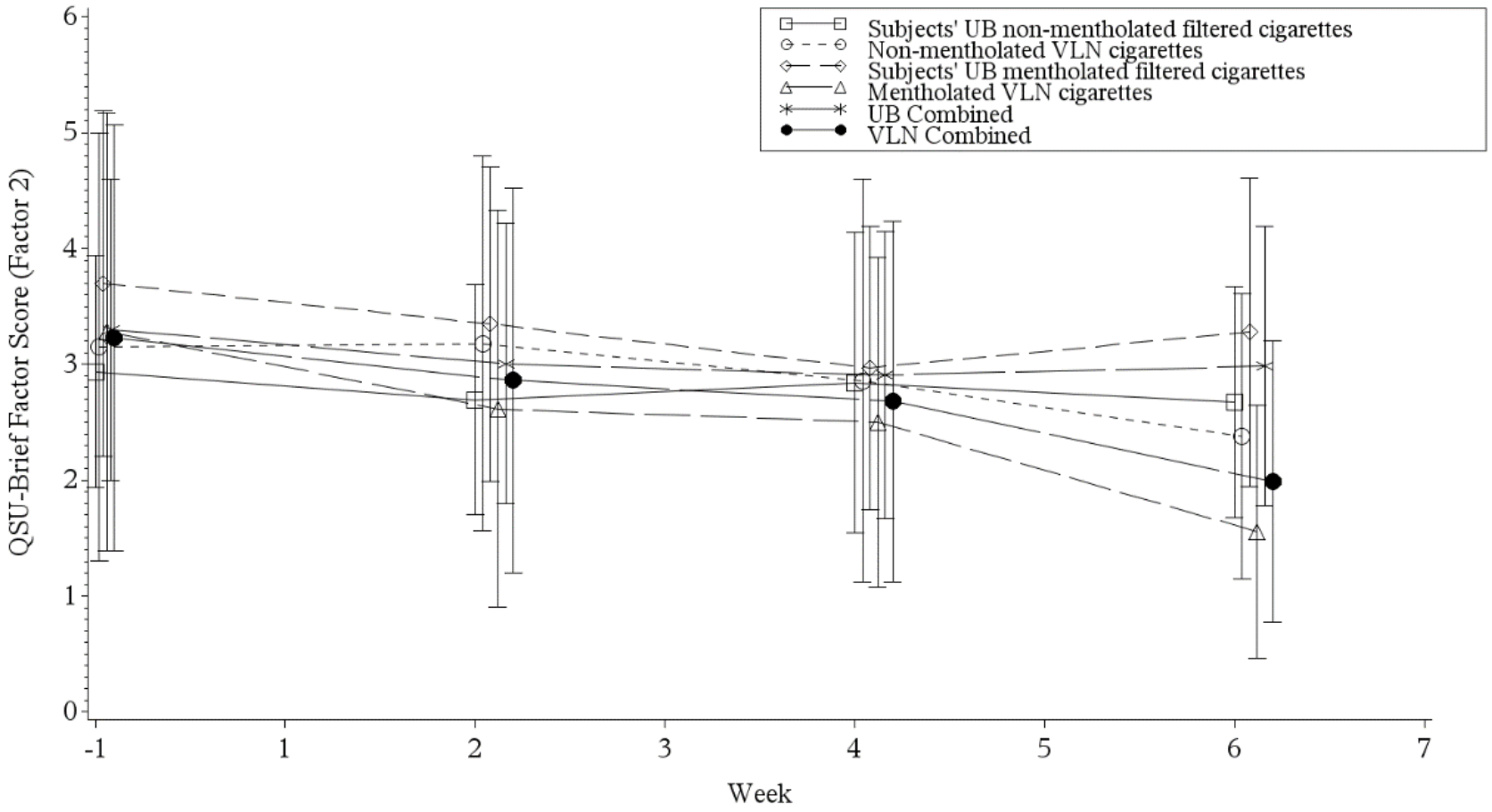

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-112. Mean (±SD) of QSU-Brief Factor Score (Factor 1) by Study Product Group and Study Week (ITT Population).



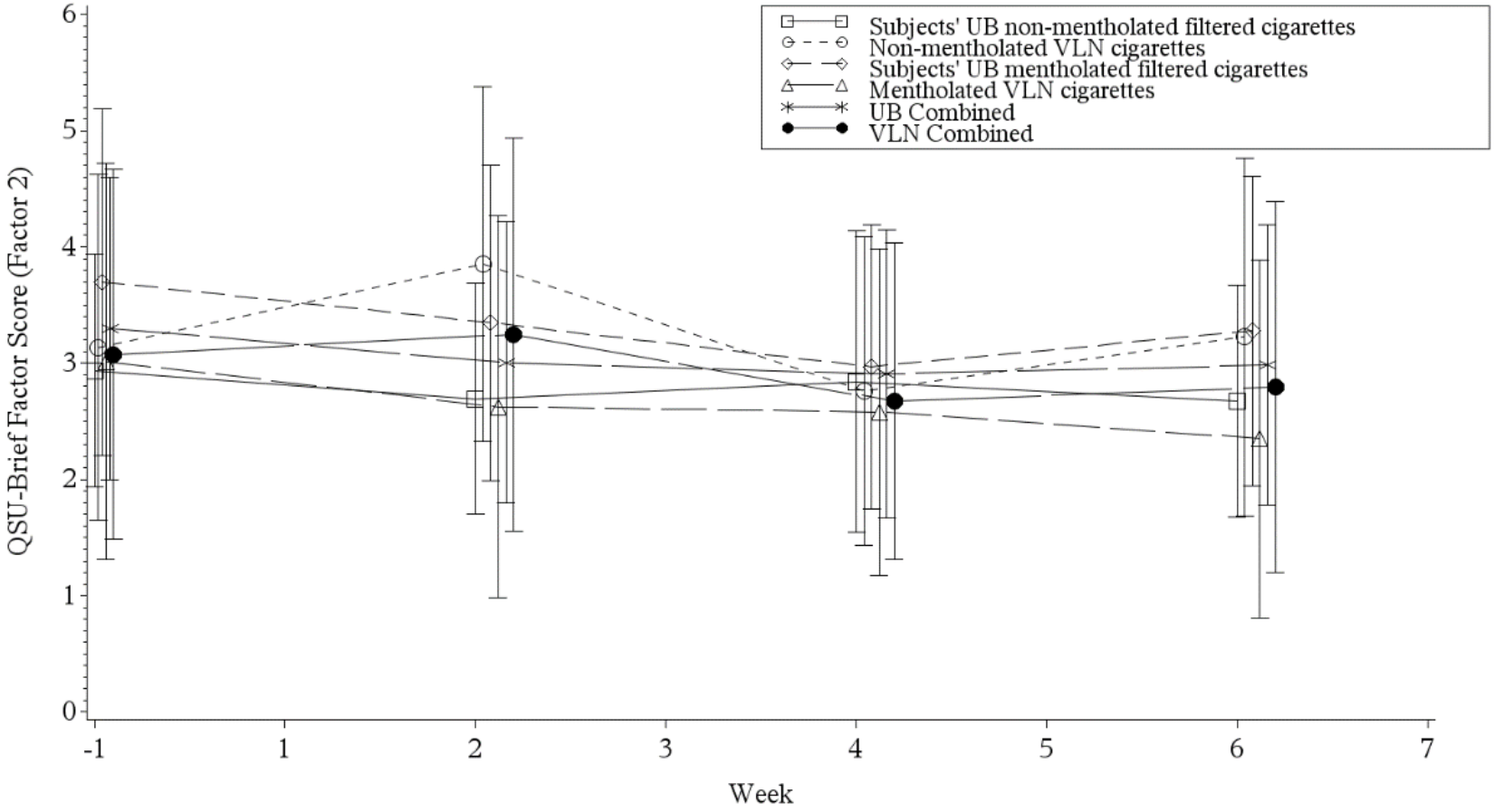

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-113. Mean (±SD) of QSU-Brief Factor Score (Factor 2) by Study Product Group and Study Week (PP Population).



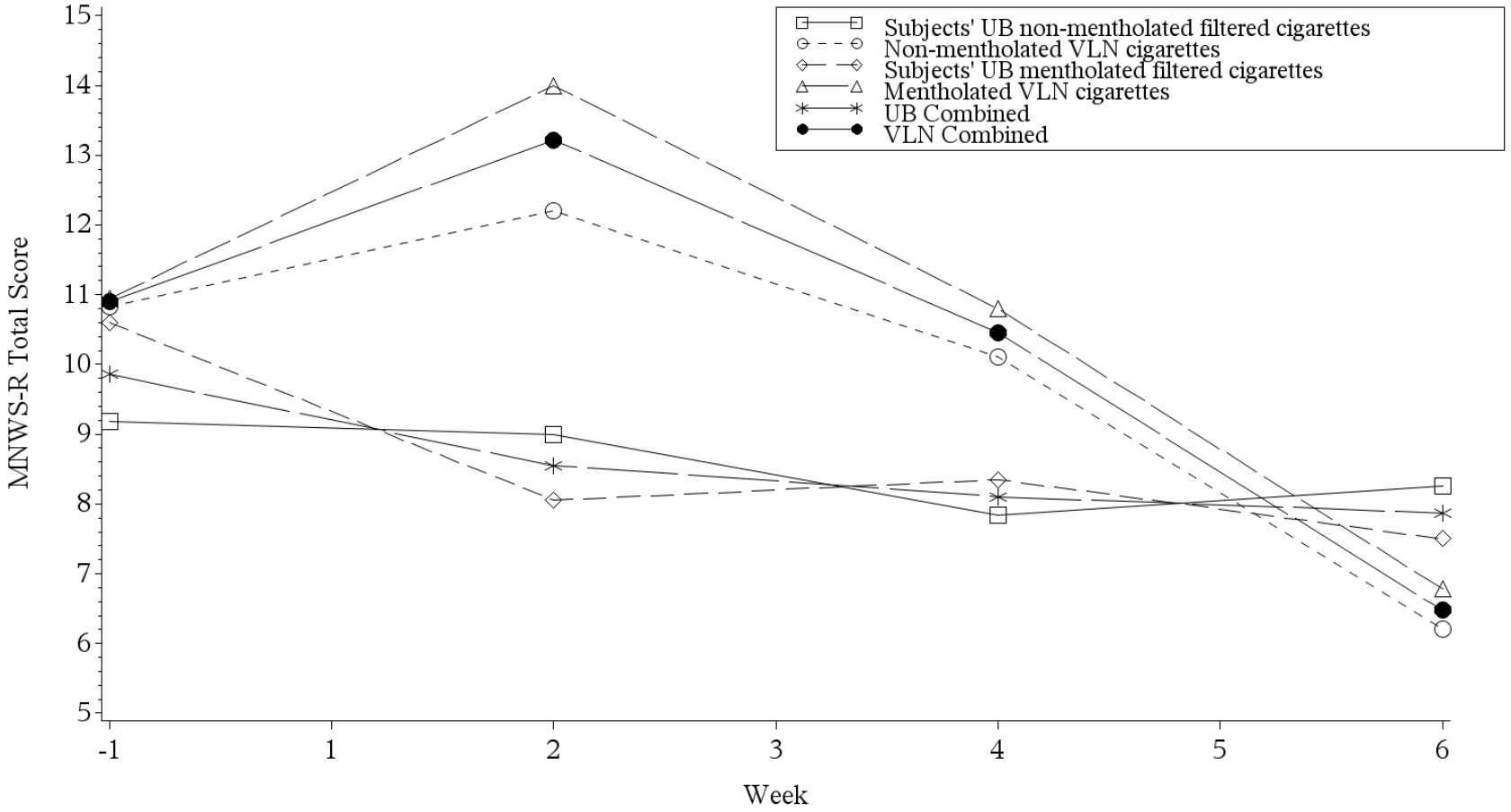

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-114. Mean (±SD) of QSU-Brief Factor Score (Factor 2) by Study Product Group and Study Week (ITT Population).



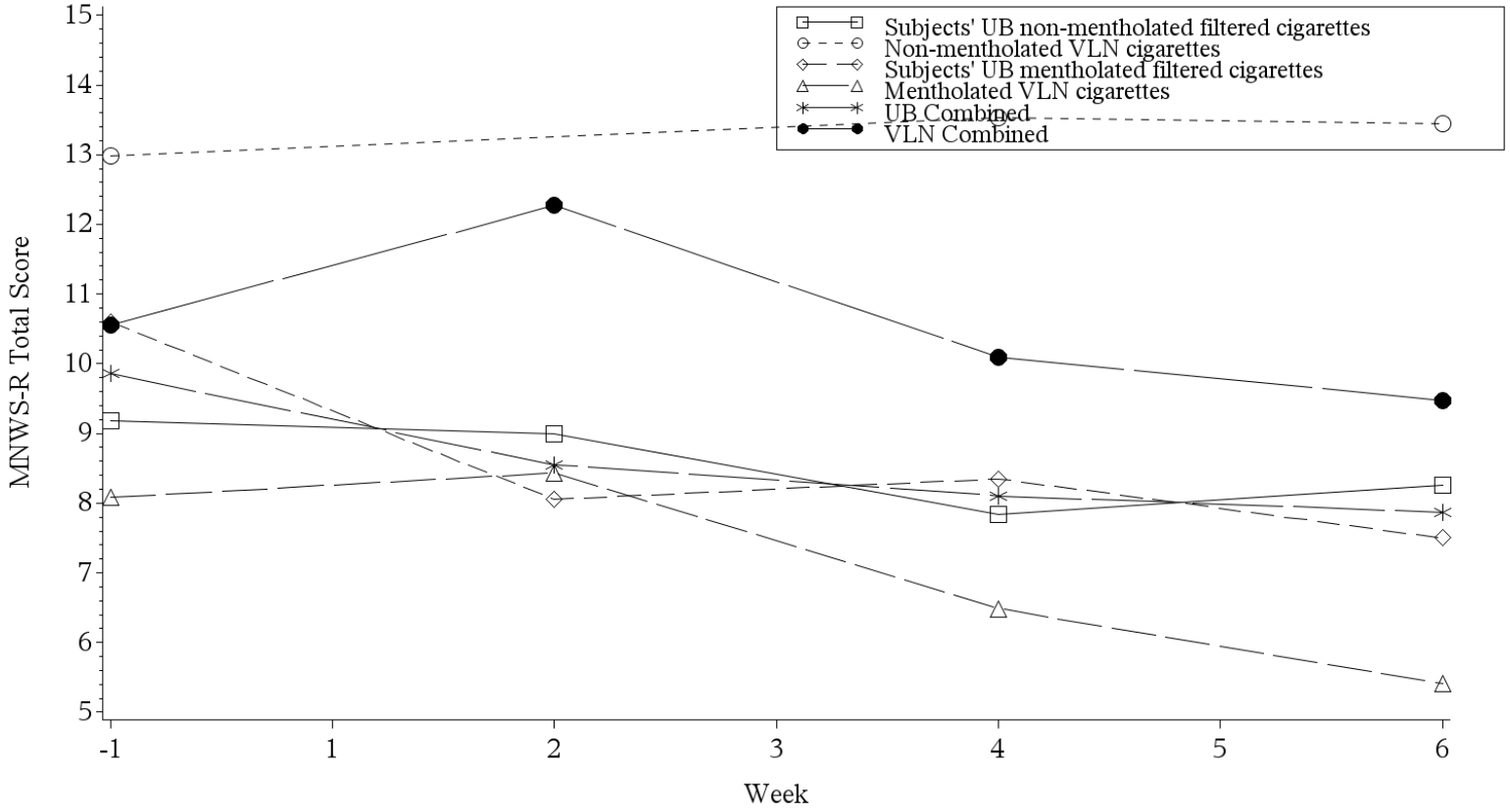

All products except Subjects' UB non-mentholated filtered cigarettes are shifted to the right for ease of reading.
Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-115. Mean MNWS-R Total Score by Study Product Group and Study Week (PP Population).



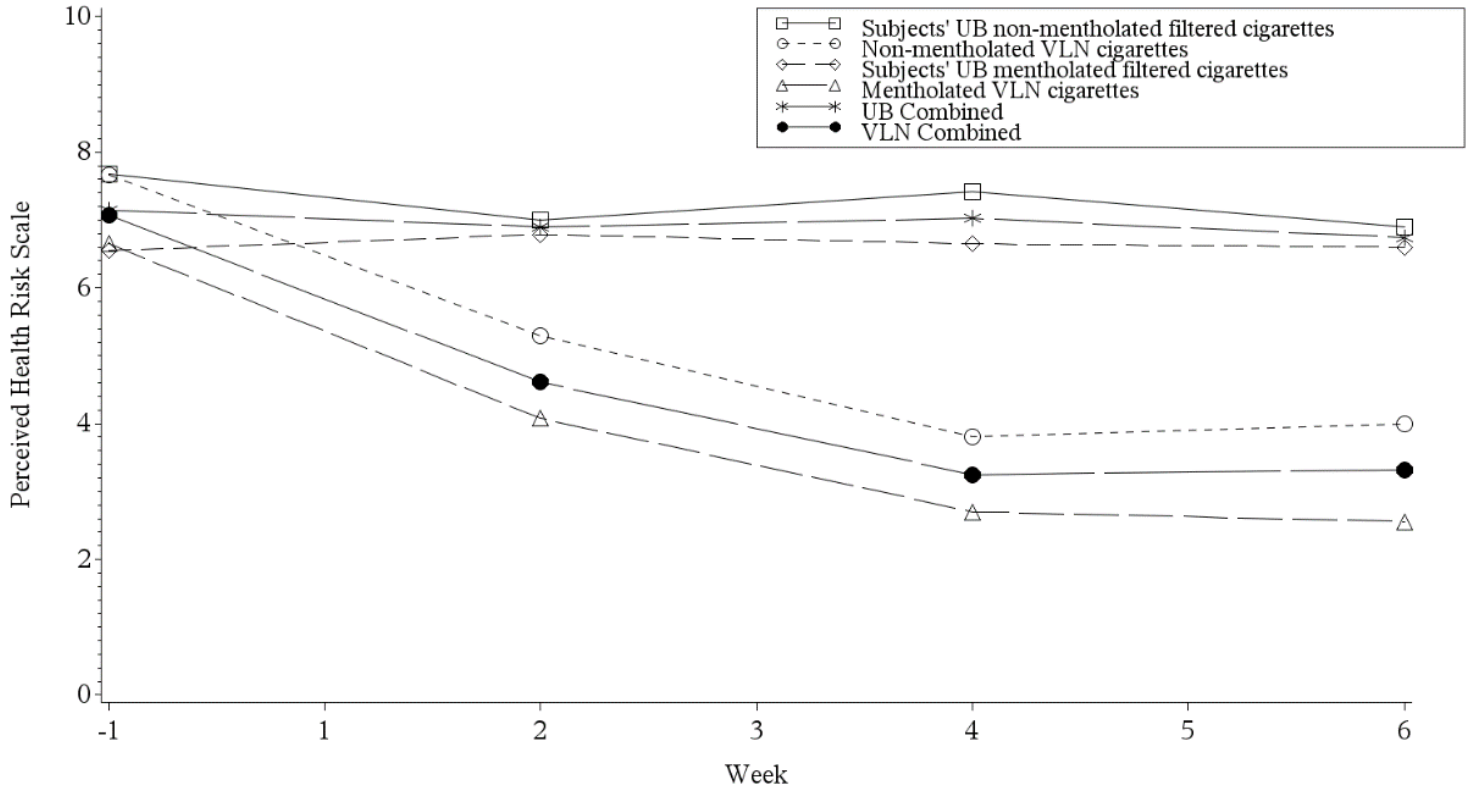

Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 02JUL2019 5:31

Figure VIII.D-116. Mean MNWS-R Total Score by Study Product Group and Study Week (ITT Population).



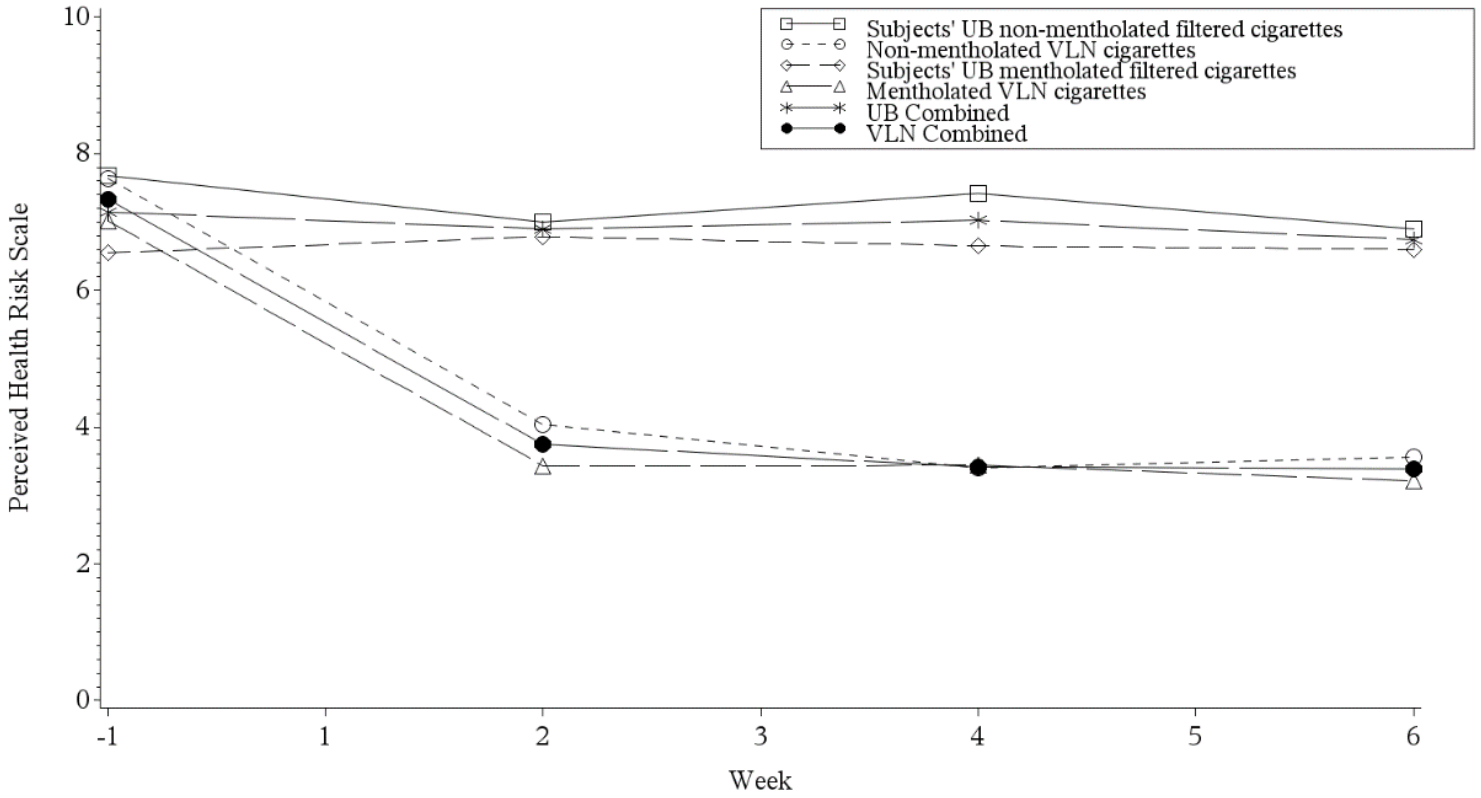

Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 02JUL2019 5:31

Figure VIII.D-117. Mean Perceived Health Risk Scale by Study Product Group and Study Week (PP Population).




Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

Figure VIII.D-118. Mean Perceived Health Risk Scale by Study Product Group and Study Week (ITT Population).




Program: /CA24914/sas_prg/pksas/pd_cpd_qs/adam_meangraph_qs.sas 13JUN2019 5:04

#### (c) Conclusion

Overall the results of the CPD data are consistent with that observed by Donny after use of SPECTRUM research cigarettes (same as VLN™) for 6 weeks (Donny et al. 2015). Smoking topography was not affected by switching to VLN™ cigarettes. There was no compensation. Nicotine exposure as measured by nicotine blood levels was reduced >98%. Urinary analysis for total nicotine confirmed reduced exposure to nicotine. Compared to the leading brands, VLN™ appears to have less benzo[a]pyrene, NNK, acrolein, and nicotine. Biomarkers of these smoke constituents were reduced in the VLN™ smokers. There was no difference in the level of addiction as measured by the FTCD. In compliant subjects (PP) there was a slight reduction in the pleasure from smoking and also withdrawal as measured by QSU. Withdrawal was also reduced in the MNWS-R in the compliant population (PP). There were no clear effects on the non-compliant subjects after 6 weeks of use. Both compliant (PP) and non-compliant subjects (ITT) perceived the risk of addiction as being less for VLN™ cigarettes.

### *lxix.* Effects of immediate versus gradual nicotine reduction in cigarettes on biomarkers of biological effects. (NCT: 02139930)

#### (a) Study Design

This study (Hatsukami et al. 2019) was a randomized, parallel, double-blind trial conducted at 10 sites throughout the United States. Participants (N = 1250) who had no desire to quit within the next 30 days were randomly assigned to 1 of 3 experimental conditions in a 2:2:1 ratio: (1) immediate nicotine reduction, (2) gradual nicotine reduction, or (3) usual nicotine content control. Participants underwent a 2-week baseline period during which they smoked their usual brand cigarettes and then were assigned to their experimental condition for 20 weeks. While on study cigarettes (SPECTRUM® 0.4 mg nicotine/g tobacco), participants attended a weekly clinic visit for the first 4 weeks and then

biweekly visits for the next 16 weeks. In the gradual reduction group, levels of nicotine content were decreased every 4 weeks (weeks 4, 8, 12, and 16).

The primary end points related to biomarkers of exposure have been previously reported (Hatsukami et al. 2018). This study examined secondary effects of gradual or immediate switching to Spectrum 0.4 mg nicotine cigarettes on selected biomarkers associated with harmful biological effects (biomarkers of harm). Biomarkers of inflammation, oxidative stress and hematological parameters were measured over time and the area under the curves compared.

### (b) Results

This study was primarily focused on biomarkers of exposure and these results were summarized in the original applications. The biomarkers and cigarette per day data are shown in Table VIII.D-90. Study cigarettes per day were reduced by 10.62. The pre-study cigarette consumption was 15.6 in the immediate group. CO, 3-HMPA and PheT were significantly reduced. Total nicotine equivalents and total NNAL were also reduced. Figure VIII.D-119 shows the time course for the development of the reductions.

Table VIII.D-91 shows the effects on the various biomarkers of harm. Few biomarkers associated with adverse health effects showed differences across the experimental groups. A biomarker that was consistently significant across primary and sensitivity analysis was RDW% (Red Blood Cell Size and Volume Variability), which followed the pattern that was observed with biomarkers of exposures; that is, lower levels in the immediate versus gradual nicotine reduction and control groups. The findings of the other studied biomarkers were either inconclusive or showed no difference based on the Bayes factors analysis.

### (c) Conclusion

This study does not indicate that reduction in any of the biomarkers of exposure are large enough to produce reductions in know biomarkers of harm associated with smoking over the 20-week period.

Table VIII.D-90. BOE (From Hatsukami *et al.* 2018) (eSupplement).

| Measures | Immediate vs. Gradual | | Immediate vs. Control | | Gradual vs. Control | |
|---|---|---|---|---|---|---|
| | Mean Difference/Ratio of Geometric Means[b] (95% CI) | *P* Value | Mean Difference/Ratio of Geometric Means[b] (95% CI) | *P* Value | Mean Difference/Ratio of Geometric Means[b] (95% CI) | *P* Value |
| **Measures at Week 20, Multiple Imputation[c], Unadjusted[d]** | | | | | | |
| CO (ppm) | -3.27 (-4.48, -2.07) | <.001 | -5.31 (-6.77, -3.85) | <.001 | -2.03 (-3.45, -0.61) | .005 |
| 3-HPMA (nmol/mg) | 0.83 (0.74, 0.94) | .003 | 0.69 (0.60, 0.79) | <.001 | 0.83 (0.73, 0.95) | .005 |
| PheT (pmolmgl) | 0.90 (0.81, 0.99) | .034 | 0.78 (0.69, 0.87) | <.001 | 0.87 (0.78, 0.96) | .009 |
| TNE (nmol/mg) | 1.81 (1.41, 2.32) | <.001 | 0.21 (0.15, 0.28) | <.001 | 0.11 (0.09, 0.15) | <.001 |
| Total NNAL (pmol/mg) | 1.02 (0.86, 1.21) | .80 | 0.48 (0.39, 0.59) | <.001 | 0.47 (0.39, 0.57) | <.001 |
| CEMA (nmol/mg) | 0.60 (0.50, 0.71) | <.001 | 0.48 (0.40, 0.59) | <.001 | 0.81 (0.67, 0.97) | .022 |
| HMPMA (nmol/mg) | 0.84 (0.76, 0.94) | .002 | 0.68 (0.59, 0.77) | <.001 | 0.80 (0.70, 0.91) | <.001 |
| SPMA (pmol/mg) | 0.72 (0.61, 0.86) | <.001 | 0.61 (0.50, 0.73) | <.001 | 0.84 (0.69, 1.02) | .070 |
| 2-HPMA (nmol/mg) | 0.91 (0.80, 1.04) | .16 | 0.76 (0.65, 0.88) | <.001 | 0.83 (0.72, 0.97) | .017 |
| Cigarettes/day total | -6.40 (-7.54, -5.26) | <.001 | -8.77 (-10.16, -7.37) | <.001 | -2.37 (-3.75, -0.99) | <.001 |
| Cigarettes/day study | -7.99 (-9.24, -6.75) | <.001 | -10.62 (-12.14, -9.09) | <.001 | -2.62 (-4.11, -1.14) | <.001 |
| Cigarettes/day non-study | 1.68 (0.99, 2.38) | <.001 | 1.86 (0.89, 2.83) | <.001 | 0.18 (-0.79, 1.14) | .72 |

Figure VIII.D-119. BOE (From Hatsukami *et al.* 2018).

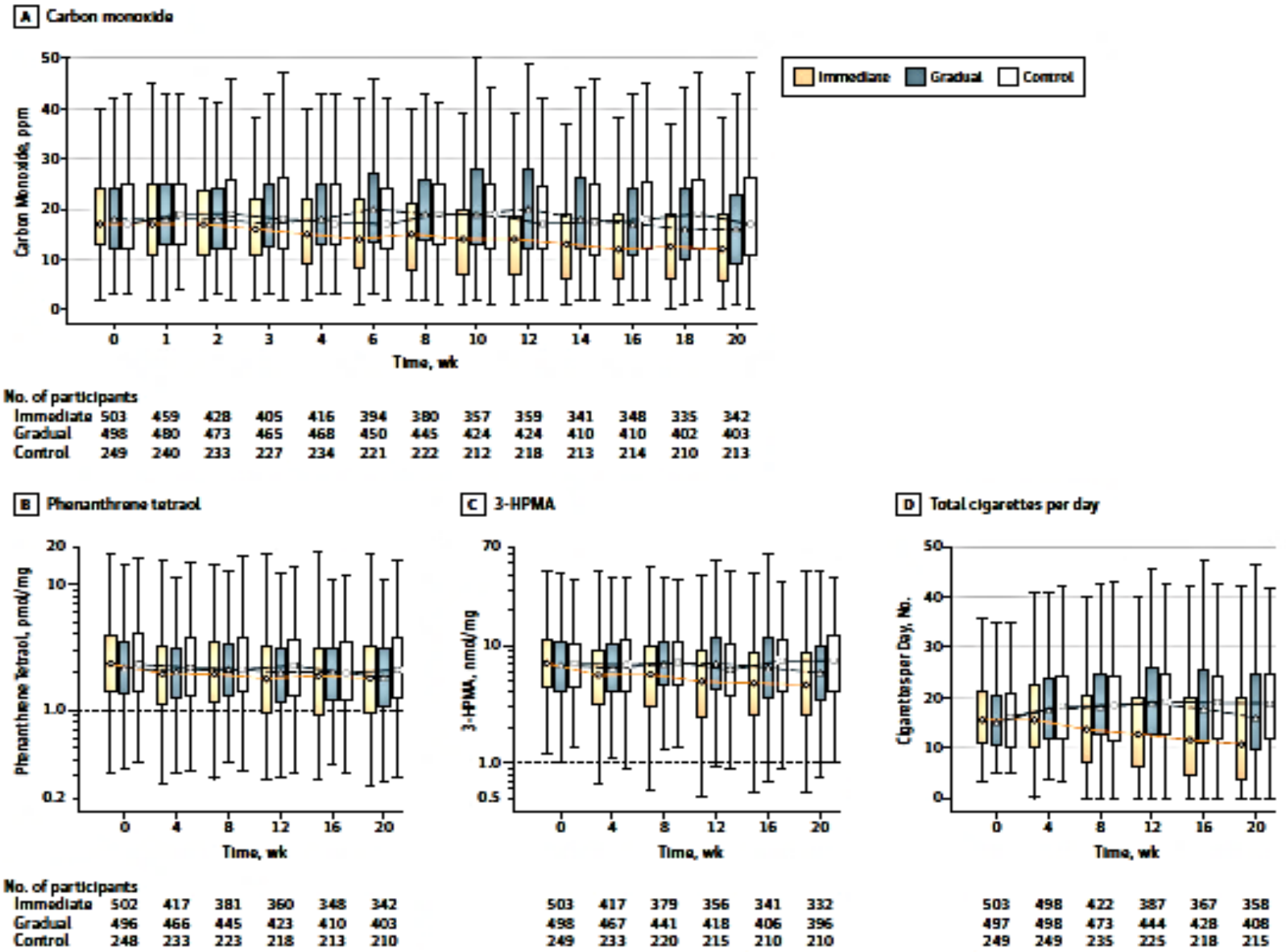


Table VIII.D-91. Analysis of Biomarkers (From Hatsukami et al 2019)

**Table 2** Analysis of area under the curve (AUC)[a] of biomarkers across interventions.

| | *Immediate versus gradual* | | *Immediate versus control* | | *Gradual versus control* | |
|---|---|---|---|---|---|---|
| *Measures* | *Mean difference/ratio of geometric means[b] (95% CI)* | *P-value[c]* | *Mean difference/ratio of geometric means[b] (95% CI)* | *P-value[c]* | *Mean difference/ratio of geometric means[b] (95% CI)* | *P-value[c]* |
| Linear regression of AUC, adjusted for baseline[d] | | | | | | |
| 8-*iso*-$PGF_{2\alpha}$ (pmol/mg creatinine) | 0.99 (0.95, 1.04) | 0.69 | 0.96 (0.92, 1.01) | 0.14 | 0.97 (0.92, 1.02) | 0.28 |
| hs-CRP (mg/l) | 0.98 (0.91, 1.06) | 0.61 | 1.06 (0.97, 1.17) | 0.17 | 1.09 (0.99, 1.19) | 0.078 |
| hs-CRP (mg/l), ≤ 10 values only[f] | 0.97 (0.91, 1.03) | 0.27 | 1.04 (0.96, 1.13) | 0.29 | 1.08 (1.00, 1.16) | 0.045 |
| WBC ($10^3$/µl) | −0.26 (−0.40, −0.12) | 0.0004 | −0.10 (−0.26, 0.07) | 0.27 | 0.17 (0.00, 0.33) | 0.056 |
| WBC ($10^3$/µl), ≤14 values only[f] | −0.19 (−0.34, −0.05) | 0.008 | −0.13 (−0.29, 0.03) | 0.10 | 0.06 (−0.10, 0.22) | 0.45 |
| PGEM (pmol/mg creatinine) | 0.99 (0.92, 1.06) | 0.73 | 0.94 (0.86, 1.02) | 0.14 | 0.95 (0.87, 1.03) | 0.23 |
| Red cell count ($10^6$/µl) | −0.01 (−0.04, 0.01) | 0.28 | −0.01 (−0.04, 0.02) | 0.52 | 0.00 (−0.02, 0.03) | 0.78 |
| Hemoglobin (g/dl) | −0.04 (−0.11, 0.04) | 0.32 | −0.06 (−0.15, 0.02) | 0.14 | −0.03 (−0.11, 0.06) | 0.51 |
| Hematocrit (%) | −0.12 (−0.34, 0.10) | 0.27 | −0.20 (−0.46, 0.06) | 0.13 | −0.08 (−0.33, 0.17) | 0.54 |
| MCV (fl) | −0.07 (−0.28, 0.14) | 0.52 | −0.23 (−0.48, 0.01) | 0.061 | −0.17 (−0.40, 0.07) | 0.17 |
| MCH (pg) | −0.01 (−0.09, 0.07) | 0.79 | −0.07 (−0.16, 0.02) | 0.13 | −0.06 (−0.15, 0.03) | 0.21 |
| MCHC (g/dl) | 0.04 (−0.04, 0.11) | 0.32 | 0.02 (−0.06, 0.10) | 0.62 | −0.02 (−0.10, 0.07) | 0.71 |
| RDW (%) | −0.11 (−0.18, −0.04) | 0.004 | −0.15 (−0.23, −0.06) | 0.001 | −0.04 (−0.12, 0.05) | 0.43 |
| Platelet count ($10^3$/µl) | −1.58 (−5.06, 1.89) | 0.37 | 3.03 (−1.08, 7.14) | 0.15 | 4.61 (0.61, 8.61) | 0.024 |
| MPV (fl) | 0.07 (−0.08, 0.21) | 0.36 | 0.02 (−0.09, 0.13) | 0.74 | −0.05 (−0.18, 0.09) | 0.50 |
| Linear regression of AUC, adjusted for baseline and other covariates[e] | | | | | | |
| 8-*iso*-$PGF_{2\alpha}$ (pmol/mg creatinine) | 0.99 (0.95, 1.03) | 0.60 | 0.96 (0.92, 1.01) | 0.13 | 0.97 (0.93, 1.03) | 0.32 |
| hs-CRP (mg/l) | 0.98 (0.91, 1.06) | 0.66 | 1.07 (0.97, 1.17) | 0.16 | 1.08 (0.99, 1.19) | 0.083 |
| hs-CRP (mg/l), ≤ 10 values only[f] | 0.97 (0.91, 1.03) | 0.31 | 1.04 (0.97, 1.13) | 0.28 | 1.08 (1.00, 1.16) | 0.050 |
| WBC ($10^3$/µl) | −0.27 (−0.41, −0.13) | 0.0002 | −0.10 (−0.27, 0.07) | 0.24 | 0.17 (0.00, 0.34) | 0.049 |
| WBC ($10^3$/µl), ≤14 values only[f] | −0.21 (−0.35, −0.06) | 0.005 | −0.14 (−0.30, 0.02) | 0.089 | 0.07 (−0.09, 0.23) | 0.40 |
| PGEM (pmol/mg creatinine) | 0.98 (0.92, 1.05) | 0.65 | 0.94 (0.86, 1.02) | 0.16 | 0.96 (0.88, 1.04) | 0.29 |
| Red cell count ($10^6$/µl) | −0.01 (−0.04, 0.01) | 0.32 | −0.01 (−0.04, 0.02) | 0.47 | 0.00 (−0.02, 0.03) | 0.89 |
| Hemoglobin (g/dl) | −0.04 (−0.11, 0.04) | 0.32 | −0.07 (−0.16, 0.01) | 0.10 | −0.04 (−0.12, 0.05) | 0.41 |
| Hematocrit (%) | −0.12 (−0.34, 0.10) | 0.27 | −0.22 (−0.47, 0.04) | 0.097 | −0.09 (−0.34, 0.16) | 0.46 |
| MCV (fl) | −0.08 (−0.29, 0.12) | 0.43 | −0.24 (−0.49, 0.00) | 0.049 | −0.16 (−0.40, 0.08) | 0.18 |
| MCH (pg) | −0.01 (−0.10, 0.07) | 0.73 | −0.08 (−0.17, 0.02) | 0.11 | −0.06 (−0.16, 0.03) | 0.20 |
| MCHC (g/dl) | 0.04 (−0.03, 0.11) | 0.29 | 0.01 (−0.07, 0.09) | 0.78 | −0.03 (−0.11, 0.05) | 0.52 |
| RDW (%) | −0.11 (−0.18, −0.04) | 0.003 | −0.14 (−0.23, −0.06) | 0.001 | −0.03 (−0.12, 0.05) | 0.45 |
| Platelet count ($10^3$/µl) | −1.15 (−4.64, 2.33) | 0.52 | 3.24 (−0.87, 7.36) | 0.12 | 4.39 (0.37, 8.41) | 0.032 |
| MPV (fl) | 0.06 (−0.08, 0.21) | 0.37 | 0.02 (−0.09, 0.14) | 0.67 | −0.04 (−0.18, 0.10) | 0.57 |

[a]Area under the curve (AUC) scaled by time (i.e. time-weighted average); the unit is the same as its original variable. [b]Mean difference for WBC, red cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelet count and MPV; ratio of geometric means for 8-*iso*-$PGF_{2\alpha}$, PGEM and hs-CRP. [c]$P < 0.00057$ were considered statistically significant for secondary end-points (8-*iso*-$PGF_{2\alpha}$, hs-CRP and WBC); hs-CRP (≤ 10 values only) and WBC (≤ 14 values only) were analyzed as a sensitivity analysis for their respective non-restricted counterparts, hence the same *P*-value cut-off points were applied; $P < 0.0167$ were considered statistically significant for all the other biomarkers, which are exploratory end-points. [d]Linear regression of the AUC adjusted for the corresponding baseline measure of the biomarker; log-transformation was used for the AUC of 8-*iso*-$PGF_{2\alpha}$, PGEM and hs-CRP and their baseline measure. [e]Linear regression of the AUC adjusted for the corresponding baseline measure of the biomarker study site, together with any baseline variables which were different between treatment arms at $P < 0.20$ (employment, Fagerström Test for Nicotine Dependence and serum nicotine metabolic ratio); log-transformation was used for the AUC of 8-*iso*-$PGF_{2\alpha}$, PGEM, and hs-CRP. CI = confidence interval. [f]Analysis conducted excluding out-of-range values. 8-*iso*-$PGF_{2\alpha}$ (pmol/mg) = (Z)-7-[1*R*,2*R*,3*R*,5*S*]-3,5-dihydroxy-2-[(*E*,3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid) or 8-iso-prostaglandin $F_{2\alpha}$; hs-CRP = high-sensitivity C-reactive protein; WBC ($10^3/\mu l$) = white cell count; PGEM (pmol/ml) = prostaglandin E metabolite; MCV (fl) = mean corpuscular volume (measure of size of red blood cells); MCH (pg) = mean corpuscular hemoglobin (quantity of hemoglobin in red blood cell), MCHC (g/dl) = mean corpuscular hemoglobin concentration (concentration of hemoglobin in red blood cells); RDW (%) = red blood cell distribution (variation in size and volume of red blood cells); MPV (fl) = mean platelet volume (size of platelet).

## 4. Adverse Events

### *vii. A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes (NCT03571724).*

There were no deaths reported in this study. One subject experienced an SAE (subarachnoid hemorrhage) after study completion that was not product related. The subject made a complete recovery. One subject was discontinued by the PI due to experiencing several AEs.

During the Baseline period (Week -1), in which subjects smoked their usual brand cigarettes, 19 (13.4%) subjects experienced a total of 30 AEs; with headache being the most frequent event, reported by 12 (8.5%) subjects. The majority (16) of subjects experienced events that were mild in severity and three subjects experienced moderate events (migraine, presyncope, and vomiting). The PI considered two events (dyspepsia and headache) in the same subject to be possibly related to study product and the events in the remaining subjects unlikely/not related.

After study product group randomization, 45 of 142 (31.7%) subjects across study groups experienced a total of 83 AEs (Table VIII.D-92). There was no apparent difference in the percentages between UB and VLN™ cigarettes. Headache was the most frequently reported AE, experienced 24 times by a total of 22 (15.5%) subjects; all remaining AEs were experienced by seven or fewer (< 5%) subjects each (Table VIII.D-93). Regarding maximum severity, one subject experienced a severe AE (subarachnoid hemorrhage), nine subjects experienced moderate AEs (including five subjects with

headache), and the remaining 35 subjects experienced only mild AEs (Table VIII.D-94). The PI considered an AE in one subject (nausea [VLN non-mentholated]) to be likely related to study product, AEs in 12 subjects to be possibly related to study product, and the remaining 32 subjects only experienced events considered unlikely/not related to study product.

Overall, the use of the VLN™ products under the study conditions appeared to be well tolerated by the healthy adult smokers in this study.

Table VIII.D-92 AE Incidence by Study Product and Group

| Study Product | Number (%) of Subjects Reporting AEs | Number of AEs Reported |
|---|---|---|
| | | |
| Baseline Period* (n = 142) | 19 (13.4%) | 30 |
| | | |
| Randomized Study Product Groups | | |
| UB non-mentholated (n = 22) | 9 (40.9%) | 13 |
| VLN non-mentholated (n = 50) | 16 (32.0%) | 22 |
| UB mentholated (n = 20) | 5 (25.0%) | 6 |
| VLN mentholated (n = 50) | 15 (30.0%) | 42 |
| Overall (n = 142)# | 45 (31.7%) | 83 |

n = Number of Subjects
*Subjects used their usual brand cigarette at Baseline (Week -1).
#Overall includes AEs after the start of Week 1 product use.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Tables 14.3.1.1 and 14.3.1.2

Table VIII.D-93. Adverse Event Frequency - Number of Subjects Reporting the Event (% of Subjects Used Product) (Safety Population).

| | | Treatment | | | | |
|---|---|---|---|---|---|---|
| **Adverse Events*** | **Baseline** | **UB Non-Mentholated** | **VLN Non-Mentholated** | **UB Mentholated** | **VLN Mentholated** | **Overall#** |
| Number of Subjects Use Study Product | 142 (100%) | 22 (100%) | 50 (100%) | 20 (100%) | 50 (100%) | 142 (100%) |
| Number of Subjects With Adverse Events | 19 (13%) | 9 (41%) | 16 (32%) | 5 (25%) | 15 (30%) | 45 (32%) |
| Number of Subjects Without Adverse Events | 123 (87%) | 13 (59%) | 34 (68%) | 15 (75%) | 35 (70%) | 97 (68%) |
| **Eye disorders** | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Erythema of eyelid | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Eye pruritus | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Lacrimation increased | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

| | | Treatment | | | | |
|---|---|---|---|---|---|---|
| **Adverse Events*** | **Baseline** | **UB Non-Mentholated** | **VLN Non-Mentholated** | **UB Mentholated** | **VLN Mentholated** | **Overall#** |
| Ocular hyperaemia | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Gastrointestinal disorders** | 5 (4%) | 2 (9%) | 2 (4%) | 0 (0%) | 4 (8%) | 8 (6%) |
| Abdominal discomfort | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Constipation | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Diarrhoea | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 1 (2%) | 2 (1%) |
| Dyspepsia | 2 (1%) | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Gastrooesophageal reflux disease | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nausea | 0 (0%) | 1 (5%) | 1 (2%) | 0 (0%) | 1 (2%) | 3 (2%) |
| Oral discomfort | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Toothache | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Vomiting | 1 (1%) | 2 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (1%) |
| **General disorders and administration site conditions** | 1 (1%) | 0 (0%) | 2 (4%) | 0 (0%) | 4 (8%) | 6 (4%) |
| Chest discomfort | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Fatigue | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |
| Pain | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Vessel puncture site pain | 1 (1%) | 0 (0%) | 2 (4%) | 0 (0%) | 2 (4%) | 4 (3%) |
| **Infections and infestations** | 0 (0%) | 1 (5%) | 2 (4%) | 1 (5%) | 0 (0%) | 4 (3%) |
| Nasal abscess | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 0 (0%) | 1 (1%) |
| Tooth infection | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Upper respiratory tract infection | 0 (0%) | 1 (5%) | 1 (2%) | 0 (0%) | 0 (0%) | 2 (1%) |
| **Injury, poisoning and procedural complications** | 1 (1%) | 1 (5%) | 1 (2%) | 1 (5%) | 2 (4%) | 5 (4%) |
| Arthropod bite | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |
| Contusion | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Laceration | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Meniscus injury | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 0 (0%) | 1 (1%) |
| Subarachnoid hemorrhage | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Metabolism and nutrition disorders** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Increased appetite | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| **Musculoskeletal and connective tissue disorders** | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 2 (4%) | 3 (2%) |
| Back pain | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Neck pain | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 1 (2%) | 2 (1%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Skin papilloma | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Nervous system disorders** | 13 (9%) | 5 (23%) | 10 (20%) | 3 (15%) | 6 (12%) | 24 (17%) |
| Dizziness | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 1 (2%) | 2 (1%) |
| Headache | 12 (8%) | 5 (23%) | 8 (16%) | 3 (15%) | 6 (12%) | 22 (15%) |
| Lethargy | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Migraine | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Presyncope | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Tremor | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |

| | | Treatment | | | | |
|---|---|---|---|---|---|---|
| **Adverse Events*** | **Baseline** | **UB Non-Mentholated** | **VLN Non-Mentholated** | **UB Mentholated** | **VLN Mentholated** | **Overall#** |
| **Psychiatric disorders** | 0 (0%) | 0 (0%) | 3 (6%) | 1 (5%) | 5 (10%) | 9 (6%) |
| Anxiety | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Depressed mood | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Insomnia | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 1 (2%) | 2 (1%) |
| Irritability | 0 (0%) | 0 (0%) | 3 (6%) | 0 (0%) | 4 (8%) | 7 (5%) |
| Nightmare | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Stress | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 0 (0%) | 1 (1%) |
| **Respiratory, thoracic and mediastinal disorders** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |
| Oropharyngeal pain | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| Throat irritation | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 1 (1%) |
| **Skin and subcutaneous tissue disorders** | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |
| Erythema | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Palmar erythema | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pruritus | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (1%) |
| **Vascular disorders** | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Presyncope | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
*Adverse events are classified according to MedDRA® Version 21.0
Subjects used their own usual brand cigarettes at Week -1.
Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
# Overall includes AEs after the start of Week1 product use.

Source: Table 14.3.1.1
Program: /CA24914/sas_prg/stsas/intext/t_ae.sas 02JUL2019 6:09

Table VIII.D-94. Product-Use-Emergent Adverse Event Frequency by Severity and Relationship to Study Product – Number of Subjects Reporting Adverse Events (Safety Population)

| Adverse Event* | Product | Number of Subjects with PUEAEs | Number of PUEAEs | Severity | | | Relationship to Study Product | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Mild | Moderate | Severe | Not Related | Unlikely | Possible | Likely |
| Presyncope | VLN Non Mentholated | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Pruritus | Baseline | 1 | 3 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| | VLN Mentholated | 2 | 3 | 2 | 0 | 0 | 1 | 1 | 0 | 0 |
| Skin papilloma | UB Non Mentholated | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Stress | UB Mentholated | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Subarachnoid haemorrhage | VLN Non Mentholated | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Throat irritation | VLN Mentholated | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Tooth infection | VLN Non Mentholated | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Toothache | VLN Mentholated | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Tremor | VLN Mentholated | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Upper respiratory tract infection | UB Non Mentholated | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| | VLN Non Mentholated | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Vessel puncture site pain | Baseline | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| | VLN Mentholated | 2 | 3 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| | VLN Non Mentholated | 2 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Vomiting | Baseline | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | UB Non Mentholated | 2 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Baseline | | 19 | 30 | 16 | 3 | 0 | 14 | 4 | 1 | 0 |
| UB Mentholated | | 5 | 6 | 3 | 2 | 0 | 5 | 0 | 0 | 0 |
| UB Non Mentholated | | 9 | 13 | 7 | 2 | 0 | 8 | 1 | 0 | 0 |
| VLN Mentholated | | 15 | 42 | 12 | 3 | 0 | 7 | 1 | 7 | 0 |
| VLN Non Mentholated | | 16 | 22 | 13 | 2 | 1 | 6 | 4 | 5 | 1 |

Note: * Adverse events are classified according to MedDRA Version 21.0.
When a subject experienced the same AE at more than one level of severity, only the most severe occurrence was counted.
When a subject experienced the same AE at more than one level of product relationship, only the the most closely related to study product was counted.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CA24914/sas prg/stsas/tab/adam tblae3a auto 2.sas 18JUN2019 11:12

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