

Section VIII. Scientific Studies and Analyses

D. Clinical Studies

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VIII. Scientific Studies and Analyses

D. Clinical Studies

1. Background

As noted in Section VIII. A. Product Analysis, the SPECTRUM® NRC 102 and NRC103 cigarettes, PARE® cigarettes and VLN™ cigarettes are the same cigarette. These products are made to the same specifications, use the same materials and ingredients, use the same blend and have the same smoke chemistry. As noted elsewhere, SPECTRUM® is a research cigarette made by 22nd Century for NIDA. The results of SPECTRUM® studies come from published articles. Prior to the production of SPECTRUM® cigarettes, NIDA contracted with Ultratech to produce low nicotine cigarettes. The tobacco in these cigarettes was extracted to remove the nicotine. Xodus was a VLN™ product sold by 22nd Century in 2010. Xodus used VLN™ tobacco but had a nicotine in filler level of about 1.8 mg/g tobacco dry weight. PARE® was the subject of a 2015 MRTP application by 22nd Century. There are no published or 22nd Century-sponsored clinical studies

with PARE®. VLN™ is the subject of this application. These studies on VLN™ and SPECTRUM® serve as the primary basis for supporting the claims on VLN™. There are additional studies on Quest 3, X-22, Ultratech, and Magic VLNC cigarettes. As shown by the nicotine in filler and HPHC data, these products are substantially similar to VLN™ but not exactly the same. The results from these products are supportive of the primary studies with SPECTRUM® and VLN™ cigarettes. X-22 was the subject of an IND for cessation conducted by 22nd Century. Quest was the subject of an IND submission by Vector Tobacco, Inc. SPECTRUM® is a brand family of cigarettes with varying nicotine and tar levels. The SPECTRUM® cigarettes that are the same as VLN™ are identified as NRC 102 (regular king) and NRC 103 (menthol king). These cigarettes are sometimes identified by their nicotine in tobacco content levels nominally reported as 0.4 mg/g. They are also reported with their nicotine in smoke yields of 0.05 mg/cig. There is an additional set of studies conducted using cigarettes that have had the nicotine removed by chemical extraction processes. The most prominent product was Philip Morris' Next product made with de-nicotinized tobacco. Philip Morris also made test cigarettes for research purposes (Coffa *et al.* 2016 [pg [298](#)]). These cigarettes were provided principally to Dr. Neil Benowitz and are the subject of many of his publications on VLNC cigarettes. These studies are generally excluded from this discussion because they are made using tobacco that has been processed in a completely different manner (extraction with super critical CO₂) as compared to the naturally produced VLN™ tobacco and the products appear to perform differently. Table VIII.D-1. *Smoke chemistry (HPHC) comparison of VLN™ to Philip Morris' denicotinized research (de-nic) cigarettes under ISO smoking conditions.*, shows a comparison of the smoke chemistry of VLN™ to the king size denicotinized (de-nic) research cigarettes (Coffa *et al.* 2016 [pg [298](#)]). The most important difference between the two cigarettes is the nicotine in smoke

yield. The de-nic product yielded almost 6 times more nicotine (0.12 mg/cig as compared to 0.0246 for VLN™). The de-nic product had 9.94 mg of tar as compared to 6.98 for VLN™. The puff count was also substantially different: 10.3 vs. 5.76 for VLN™. Many other smoke constituents were substantially different from VLN™: acetaldehyde, acrolein, 4-aminobiphenyl, benzo[a]pyrene, 1,3 butadiene, and NNK. There are no bridging studies comparing de-nic tobacco to VLN™ tobacco.

Inclusion of studies in this section was limited to products that were made with VLN™ tobacco and had a nicotine content comparable to 0.4 mg/g tobacco. When different SPECTRUM® cigarettes were used in a study, only the ones with 0.4 mg nicotine (NRC102 and NRC103) are discussed. If the study evaluated gradual reduction in nicotine compared to immediate reduction, only the immediate reduction data is discussed since that will be the situation when VLN™ is introduced. (VLN™ will only be offered in one nicotine level.) If the VLN™ cigarette was used in combination with NRT and a placebo NRT, only the cigarette data with the placebo NRT was discussed (unless the NRT was relevant to the review). That is, data was parsed to reveal only the effects of VLNC cigarettes. Only studies with health risk data are included. Studies that discussed, for example, purchase intent as a function of pricing are not included. Studies that used SPECTRUM® cigarettes over a dose range testing discrimination are also not included since they did not evaluate health effects. Also, studies that reviewed original Quest labeling and consumers perception of reduced risk claims are not included since the claims for VLN™ are different.

Table VIII.D-1. Smoke chemistry (HPHC) comparison of VLN™ to Philip Morris' denicotinized research (de-nic) cigarettes under ISO smoking conditions.

| ISO Smoking Conditions | | de-nic | VLN™ King |
|------------------------|----------|-------------------|-----------------|
| Constituent | Unit | | |
| Acetaldehyde | (µg/cig) | 478 (17) | 647 (56) |
| Acrolein | (µg/cig) | 48 (1.3) | 29.6 (3.3) |
| Acrylonitrile | (µg/cig) | 13.5 (1.9) | 11.5 (0.8) |
| Aminobiphenyl, 4- | (ng/cig) | 1.71 (0.15) | 1.57 (0.11) |
| Aminonaphthalene, 1- | (ng/cig) | * | 10.1 (1) |
| Aminonaphthalene, 2- | (ng/cig) | 8.24 (0.67) | 5.63 (0.44) |
| Ammonia | (µg/cig) | * | 30.1 (5.0) |
| Benzene | (µg/cig) | 43.6 (5.6) | 37.8 (2.2) |
| Benzo[a]pyrene | (ng/cig) | 6.63 (0.15) | 2.84 (0.15) |
| Butadiene, 1,3- | (µg/cig) | 57.2 (5.1) | 34.5 (1.3) |
| Carbon Monoxide | (mg/cig) | 10.4 (0.57) | 11.8 (0.6) |
| Crotonaldehyde | (µg/cig) | * | 12.6 (1.5) |
| Formaldehyde | (µg/cig) | 8.48 (0.98) | 6.32 (0.45) |
| Isoprene | (µg/cig) | 545 (36) | 332 (15) |
| Nicotine | (mg/cig) | 0.120 (0.0022) | 0.0246 (0.0015) |
| NNK | (ng/cig) | 44.8 (4.4) | 12.5 (1.2) |
| NNN | (ng/cig) | 53.5 (1.8) | 62 (2.2) |
| NAB | (ng/cig) | * | 1.39 (0.11) |

| ISO Smoking Conditions | | de-nic | VLN™ King |
|------------------------|----------|---|---|
| NAT | (ng/cig) | * | 5.48 (0.46) |
| NO | (µg/cig) | * | 179 (7) |
| NOx | (µg/cig) | 262 (9.3) | 301 (12) |
| Toluene | (µg/cig) | 73.5 (3.4) | 60.3 (4.5) |
| Tar | (mg/cig) | 9.94 (0.15) | 6.98 (0.4) |
| Water | (mg/cig) | 0.943 (0.082) | 0.466 (0.146) |
| Puffs | (#/cig) | 10.3 (0.08) | 5.76 (0.17) |
| Laboratory | | Philip Morris Int. | Enthalpy Analytical |
| Reference | | Coffa <i>et al.</i> 2016 [pg 298] | Enthalpy Analytical 2018 ProjCode 0318-026 [pg 299] |

* Not Measured

2. Summary

A total of 68 clinical studies were identified that provided relevant safety and efficacy data on VLNC cigarettes. Of these, 38 are primary studies using VLN™/SPECTRUM®. There are supporting studies using Quest 3 (19), Xodus (5), Magic (1), and X-22 (1)¹. There are two IND's included in the submission. One on Quest 3 by Vector Tobacco (Vector Tobacco Inc. 2006, IND 69185 [\[pg 304\]](#)) and the other by 22nd Century on X-22 (22nd Century Group 2011, IND 103589 [\[pg 297\]](#)). These studies are old and the records are incomplete. 22nd Century considers these

¹ The count of the studies does not add up to the total studies reviewed. Some studies used more than one kind of cigarette and studies (4) on another NIDA provided VLNC cigarette – Ultratech were included.

studies supportive of its application and not primary. These studies on VLN/SPECTRUM demonstrate that use of VLN™ and products containing VLN™ tobacco results in a reduction in CPD without compensation. There is a concurrent reduction in nicotine and some biomarkers of exposure (NNAL, 3-HPMA, CO). As CPD decreases, generally BOE tends to decrease. Even under conditions where there was non-compliance, plasma nicotine and biomarkers were still reduced. CPD is also reduced in nondaily smokers. There is a reduction in dependence, cravings, and smoking urges. Quit attempts, smoke free days, and abstinence are increased.

There appear to be sex differences in the subjective responses to VLN™. Fast and slow nicotine metabolizers respond the same to VLN™. Studies in adolescents suggest that VLN™ is less reinforcing, implying that the VLN™ cigarettes might be less appealing to youth. There was no indication of compensation in adolescents.

VLN™ use does not appear to affect cannabis or alcohol use. Use of opioids did not appear to affect the response to VLN™. Use of VLN™ with NRT appears to increase abstinence and reduce withdrawal. Use of VLN™ by schizophrenics did not increase smoking intensity. Schizophrenics appeared to respond to VLN™ in a manner similar to normal smokers. In a preliminary study, individuals with affective disorders responded similarly to VLN™ as normal smokers. Depressed individuals also responded similarly.

There are two potential unintended consequences of using VLN™. The first is weight gain. It is well known that people who quit smoking gain weight. The same thing seems to happen when they switch to VLN™. Tobacco smoke causes the formation of aortic lesions and clots. Nicotine appears to inhibit the activation of platelets. Preliminary studies suggest that removing

nicotine from tobacco could result in more activation of platelets. There is no clinical confirmation that use of VLNC cigarettes will result in increased cardiovascular disease. The reduction in smoking and the concomitant reduction in morbidity may overshadow a small effect on platelet activation. There have been no serious adverse events attributable to VLN™.

3. Individual Study Summaries

Table VIII.D-2. *Studies conducted with VLNC cigarettes.* below summarizes the clinical studies conducted with the various products. The study end points of interest are listed. Abbreviations include BOE (Biomarkers of Exposure) and CPD (Cigarettes Per Day). The number of subjects is the number enrolled in the study. Reviews of the individual studies follows.

Table VIII.D-2. Studies conducted with VLNC cigarettes.

| Section Number | Product | Cigarette Exposure Duration | Study/ Article Title | No. of Subjects | End Points | Reference |
|----------------|---------|-----------------------------|--|-----------------|--|--|
| i | VLN™ | Single sessions | Evaluation of the abuse liability of very low nicotine cigarettes. | 55 | Abuse Liability | Altasciences 2018 Protocol CEG-P9-153 [pg 297] |
| ii | VLN™ | Single sessions | Evaluation of the abuse liability of very low nicotine mentholated cigarettes. | 60 | Abuse Liability | Altasciences 2019 Protocol CEG-p1-078 [pg297] |
| iii | VLN™ | 6-weeks | A longitudinal ambulatory study to assess changes in cigarettes consumption behavior and biomarkers of exposure during a 6-week switch to very low nicotine. | 140 | Smoking Behavior; CPD; BOE; Topography | This Application |
| iv | X-22 | 6-weeks | A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase ii clinical trial to evaluate the | 232 | Smoking Behavior; CPD | 22nd Century Group 2011, IND 103589 [pg 297] |

| | | | | | | |
|------|----------|-----------------|--|-----|---|---|
| | | | effectiveness of x-22 as a smoking cessation aid. | | | |
| v | Quest 3 | 2-weeks | A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. | 346 | Cessation | Becker <i>et al.</i> 2008 [pg297] |
| vi | Quest 3 | 6-weeks | Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. | 165 | Smoking Behavior; CPD; BOE; Subjective Questionnaire; Cessation | Hatsukami <i>et al.</i> 2010 [pg 300] |
| vii | SPECTRUM | 6-weeks | Randomized trial of reduced-nicotine standards for cigarettes. | 840 | Smoking Behavior; CPD; BOE | Donny <i>et al.</i> 2015 [pg299] |
| viii | Quest 3 | Single sessions | Transient compensatory smoking in response to placebo cigarettes. | 83 | Smoking Behavior; Topography; Subjective Questionnaire | MacQueen <i>et al.</i> 2012 [pg301] |
| ix | Quest 3 | 35-days | A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings. | 168 | CPD; Topography; BOE | Mercincavage <i>et al.</i> 2016 [pg 301] |
| x | Quest 3 | Single session | New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. | 50 | Smoking Behavior: Topography; Subjective Questionnaire | Strasser <i>et al.</i> 2007 [pg303] |
| xi | Quest 3 | Single sessions | The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers. | 27 | Smoking Behavior; Subjective Evaluations | Barrett and Darredeau 2012 [pg297] |
| xii | Quest 3 | Single session | The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on | 22 | Subjective Questionnaire | Barrett 2010 [pg 297] |

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|-------|-------------------|----------------|--|-----|--|--|
| | | | cigarette craving, withdrawal, and self-administration in male and female smokers. | | | |
| xiii | SPECTRUM | Single session | Smoking topography characteristics of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. | 50 | Smoking Behavior; Topography | Tidey <i>et al.</i> 2016 [pg304] |
| xiv | SPECTRUM | 6-weeks | The impact of smoking very low nicotine content cigarettes on alcohol use. | 839 | Smoking Behavior | Dermody <i>et al.</i> 2016 [pg299] |
| xv | SPECTRUM | 10-weeks | Nondaily smokers' changes in cigarette consumption with very low -nicotine -content cigarettes: a randomized double-blind clinical trial | 238 | Smoking Behavior; CPD; BOE; Cessation | Shiffman <i>et al.</i> 2018 [pg 303] |
| xvi | SPECTRUM | Single session | Response to varying the nicotine content of cigarettes in vulnerable populations: an initial experimental examination of acute effects. | 26 | Smoking Behavior; Topography; Subjective Questionnaire | Higgins <i>et al.</i> 2017, <i>Psychopharmacology</i> [pg300] |
| xvii | SPECTRUM | 5-days | Nicotine and anatabine exposure from very low nicotine content cigarettes. | 23 | BOE | Denlinger <i>et al.</i> 2016 [pg298] |
| xviii | Quest 3 | Single session | Alcohol-induced increases in smoking behavior for nicotine and denicotinized cigarettes in men and women. | 42 | Smoking Behavior; Topography | King <i>et al.</i> 2009 [pg301] |
| xix | Quest 3 and Xodus | 6-weeks | Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation. | 112 | BOE; Cessation | Dermody <i>et al.</i> 2015 [pg298] |
| xx | SPECTRUM | 8-weeks | Reduced nicotine content cigarettes and use of alternative | 136 | CPD; BOE | Hatsukami <i>et al.</i> 2017 [pg300] |

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|-------|-------------------|----------------|---|-----|---|--|
| | | | nicotine products: exploratory trial. | | | |
| xxi | Magic | 12-weeks | Abrupt nicotine reduction as an endgame policy: a randomized trial | 33 | CPD; BOE; Subjective Questionnaire; Cessation | Walker <i>et al.</i> 2014 [pg304] |
| xxii | SPECTRUM | 6 weeks | Evaluation of a reduced nicotine product standard: moderating effects of and impact on cannabis use. | 717 | Smoking Behavior; CPD; BOE | Pacek <i>et al.</i> 2016 [pg302] |
| xxiii | Quest 3 | 2-weeks | Treating smokers before the quit date: can nicotine patches and denicotinized cigarettes reduce cravings? | 98 | Cessation; Subjective Questionnaire | Rezaishiraz <i>et al.</i> 2007 [pg303] |
| xxiv | SPECTRUM | 6-weeks | Effects of 6-week use of reduced-nicotine content cigarettes in smokers with and without elevated depressive symptoms. | 717 | Smoking Behavior; CPD; BOE | Tidey <i>et al.</i> 2017 [pg303] |
| xxv | Quest | 6-weeks | A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase ii clinical trial to evaluate the effectiveness of quest alone and in combination with nicotine replacement therapy as a smoking cessation aid. | 234 | Cessation | Vector Tobacco Inc. 2006, IND 69185 [pg304] |
| xxvi | Quest 3 | Single session | Sex differences in acute relief of abstinence-Induced withdrawal and negative affect due to Nicotine content in cigarettes. | 44 | Topography; Subjective Questionnaire | Perkins and Karelitz, 2015 [pg302] |
| xxvii | Quest 3 and Xodus | 6-weeks | Reduced nicotine content cigarettes and nicotine patch. | 219 | CPD; BOE; Subjective Questionnaire | Hatsukami <i>et al.</i> 2013, <i>Cancer Epidemiology, Biomarkers & Prevention</i> [pg300] |

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|--------|------------------------------|----------------|---|------|---|---|
| xxviii | Quest 3 | 7-days | Reduced nicotine cigarettes: smoking behavior and biomarkers of exposure in smokers not intending to quit. | 72 | CPD; BOE; Subjective Questionnaire | Hammond and O'Connor 2014 [pg300] |
| xxix | Quest 3 | 9-days | Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. | 68 | Topography; CPD; Subjective Questionnaire | Donny and Jones 2009 [pg299] |
| xxx | Quest 3 | 6-weeks | The combined effect of very low nicotine content cigarettes, used as an adjunct to usual quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. | 1410 | Cessation | Walker <i>et al.</i> 2012 [pg304] |
| xxxi | SPECTRUM | Single session | Reduced-nicotine cigarettes in young smokers: impact of nicotine metabolism on nicotine dose effects. | 46 | BOE; Subjective Questionnaire | Faulkner <i>et al.</i> 2017 [pg299] |
| xxxii | Ultratech <0.06 mg Nicotine) | Single session | Pharmacodynamic effects of new denicotinized cigarettes. | 20 | BOE; Subjective Questionnaire | Pickworth <i>et al.</i> 1999 [pg303] |
| xxxiii | Ultratech <0.06 mg Nicotine) | Single session | Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers | 35 | Topography; Subjective Questionnaire | Kassel <i>et al.</i> 2007 [pg301] |
| xxxiv | Quest and Xodus | 6-weeks | Sex differences in response to reduced nicotine content cigarettes. | 235 | CPD; BOE; Subjective Questionnaire; Cessation | Vogel <i>et al.</i> 2014 [pg304] |
| xxxv | Xodus | 9-weeks | Complementing the standard multicomponent treatment for smokers with denicotinized cigarettes: a randomized trial. | 200 | Subjective Questionnaire; Cessation | McRobbie <i>et al.</i> 2016 [pg301] |

| | | | | | | |
|---------|------------------------------|----------------------------|--|-----|--------------------------------------|---|
| xxxvi | Quest 3 | Single session | Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. | 57 | Subjective Questionnaire | AhnAllen <i>et al.</i> 2015 [pg297] |
| xxxvii | Quest 3 | 7-days | Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes. | 72 | BOE | Ding <i>et al.</i> 2014 [pg299] |
| xxxviii | SPECTRUM | Single sessions and 1 week | Dose-response effects of spectrum research cigarettes. | 51 | BOE; Subjective Questionnaire | Hatsukami <i>et al.</i> 2013, <i>Nicotine & Tobacco Research</i> [pg300] |
| xxxix | SPECTRUM | 6-weeks | Effects of reduced nicotine content cigarettes on individual withdrawal symptoms over time and during abstinence. | 839 | Subjective Questionnaire | Dermody <i>et al.</i> 2018 [pg298] |
| xl | Quest 3 | Single sessions | Nicotine and non-nicotine smoking factors differentially modulate craving, withdrawal and cerebral blood flow as measured by arterial spin labeling. | 29 | Cerebral Blood Flow | Addicott <i>et al.</i> 2014 [pg297] |
| xli | Ultratech (0.07 mg Nicotine) | Single session | Experimental evidence for a causal relationship between smoking lapse and relapse. | 87 | BOE; Subjective Questionnaire | Juliano <i>et al.</i> 2006 [pg301] |
| xl ii | Quest 3 | Single session | Decreasing nicotine content reduces subjective and physiological effects of smoking. | 8 | Subjective Questionnaire; Physiology | Penetar <i>et al.</i> 2014 [pg302] |
| xl iii | Quest 3 | Single session | Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. | 28 | BOE; Subjective Questionnaire | Cobb <i>et al.</i> 2010 [pg298] |
| xl iv | Quest 3 | Single session | The airway sensory impact of nicotine contributes to the | 20 | Subjective Questionnaire | Naqvi and Bechara 2005 [pg302] |

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|-------|-----------|-----------------|---|-----|---|---|
| | | | conditioned reinforcing effects of individual puffs from cigarettes. | | | |
| xliv | Ultratech | Single sessions | Placebo cigarettes in a spaced smoking paradigm. | 8 | Subjective Questionnaire; BOE; Physiology | Eid <i>et al.</i> 2005 [pg299] |
| xlvi | SPECTRUM | 6-weeks | Reducing nicotine exposure results in weight gain in smokers randomized to very low nicotine content cigarettes. | 839 | Weight gain; | Rupprecht <i>et al.</i> 2017 [pg303] |
| xlvii | Quest 3 | Single sessions | Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls. | 56 | Topography; CPD, Subjective Questionnaire | Tidey <i>et al.</i> 2013 [pg304] |
| xlvi | SPECTRUM | Single sessions | Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations. | 50 | Subjective Questionnaire | Cassidy <i>et al.</i> 2018, <i>Drug and Alcohol Dependence</i> [pg298] |
| xlix | Quest 3 | 11-day | Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. | 30 | Topography; CPD; Subjective Questionnaire | Donny <i>et al.</i> 2007 [pg299] |
| i | SPECTRUM | 6-weeks | Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes. | 242 | Smoking Behavior; CPD; BOE | Nardone <i>et al.</i> 2016 [pg302] |
| li | SPECTRUM | Single sessions | Preliminary test of cigarette nicotine discrimination threshold in non-dependent versus dependent smokers. | 21 | Subjective Questionnaire | Perkins <i>et al.</i> 2017 [pg302] |
| lii | Quest 3 | Single sessions | Effects of low nicotine content cigarettes on smoke intake. | 16 | BOE; Topography; Subjective Questionnaire | Rose and Behm 2004 [pg303] |

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|-------|----------|-----------------|---|-----|---|---|
| liii | SPECTRUM | 6-weeks | Age moderates smokers' subjective response to very-low nicotine content cigarettes: evidence from a randomized controlled trial. | 839 | BOE; Topography; Subjective Questionnaire | Cassidy <i>et al.</i> 2018, <i>Nicotine and Tobacco</i> [pg298] |
| liv | SPECTRUM | Single session | Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine cigarettes in young smokers. | 46 | BOE; Topography; Subjective Questionnaire | Faulkner <i>et al.</i> 2018 [pg299] |
| lv | SPECTRUM | Single sessions | Response to reduced nicotine content cigarette among smokers differing in tobacco dependence severity. | 169 | Topography; Subjective Questionnaire | Higgins <i>et al.</i> 2018 [pg301] |
| lvi | SPECTRUM | 6-weeks | Cigarette nicotine content as a moderator of the relationship between negative effect and smoking. | 717 | CPD; Subjective Questionnaire | Robinson <i>et al.</i> 2017 [pg303] |
| lvii | Quest 3 | Single session | Effects of acute abstinence and nicotine Administration on taste perception In cigarette smokers. | 458 | Taste Tests; Subjective Questionnaire | Mullings <i>et al.</i> 2010 [pg302] |
| lviii | SPECTRUM | Single session | Threshold dose for discrimination of nicotine via cigarette smoking. | 18 | Subjective Questionnaire | Perkins <i>et al.</i> 2016 [pg302] |
| lix | SPECTRUM | 6-weeks | Estimation of compliance with exclusive smoking of very low nicotine Content cigarettes using plasma cotinine. | 100 | BOE; CPD; Subjective Questionnaire | Foulds <i>et al.</i> 2018 [pg299] |
| lx | SPECTRUM | Single sessions | Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction. | 169 | Topography; Subjective Questionnaire | Higgins, <i>et al.</i> 2017 <i>JAMA</i> [pg300] |
| lxi | Quest 3 | Single sessions | The influence of nicotine dose and nicotine dose | 148 | Topography; Subjective | Juliano <i>et al</i> 2011 [pg301] |

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|--------|----------|-----------------|--|------|-------------------------------|--|
| | | | expectancy on the cognitive and subjective effects of cigarette smoking. | | Questionnaire | |
| lxii | SPECTRUM | 20-weeks | Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. | 1250 | BOE; CPD | Hatsukami <i>et al.</i> 2018 [pg300] |
| lxiii | SPECTRUM | Single Sessions | Preliminary validity of the modified cigarette evaluation questionnaire in predicting the reinforcing effects of cigarettes that vary in nicotine content. | 26 | Subjective Questionnaire | Arger <i>et al.</i> 2017 [pg297] |
| lxiv | Quest 3 | Single Session | Reduced-nicotine cigarettes increase platelet Activation in smokers in vivo: a dilemma in harm Reduction. | 64 | Platelet Activation | Girdhar <i>et al.</i> 2008, <i>Nicotine & Tobacco Research</i> [pg300] |
| lxv | SPECTRUM | Single Sessions | Pharmacokinetic profile of Spectrum reduced nicotine cigarettes | 12 | BOE; Subjective Questionnaire | Kamens <i>et al.</i> 2019 [pg301] |
| lxvi | SPECTRUM | | Response to reduced nicotine content in vulnerable populations: Effect of menthol status | 169 | CPD; Subjective Questionnaire | Davis <i>et al.</i> 2019 [pg298] |
| lxvii | SPECTRUM | Single Sessions | Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes | 73 | Subjective Questionnaire | Perkins <i>et al.</i> 2018 [pg302] |
| lxviii | SPECTRUM | Single Sessions | The impact of nicotine dose on the reinforcing value of cigarettes in adolescents | 50 | Cigarette Purchase Task | Cassidy <i>et al.</i> 2019 [pg298] |

There are three clinical studies underway/conducted on VLN™ cigarettes by 22nd Century:

- Evaluation of the abuse liability of very low nicotine cigarettes.

- Evaluation of the abuse liability of very low nicotine mentholated cigarettes.
- A longitudinal ambulatory study to assess changes in cigarettes consumption behavior and biomarkers of exposure during a 6-week switch to very low nicotine.

i. Evaluation of the Abuse Liability of Very Low Nicotine Cigarettes (NCT0359751)

(a) Study Design

The abuse liability studies were conducted by Altasciences Clinical Research in Overland Park, KS. The two studies were performed concurrently and followed the same protocol design. The primary objective of this study was:

- To evaluate the abuse liability of VLN™ cigarettes (0.4 mg nicotine/gram of tobacco) relative to own-brand cigarettes and 4 mg nicotine polacrilex gum under controlled use and uncontrolled (*ad libitum*) use conditions.

The secondary objectives of the study were:

- To compare the nicotine pharmacokinetic (PK) profiles of VLN™ cigarettes relative to own-brand cigarettes and nicotine polacrilex gum under controlled use and uncontrolled use conditions.
- To characterize product use behavior of VLN™ cigarettes, own-brand cigarettes, and nicotine polacrilex gum.

This study was a randomized, two-part, 3-way crossover, designed to evaluate the abuse liability, PK, and product use behavior associated with study products, including VLN™ cigarettes, subjects' own-brand regular cigarettes, and nicotine polacrilex gum in healthy adult male and female exclusive smokers. Subjects participated in a standard Screening visit and one 7-day Confined Assessment Phase, which included a product trial session (Day -1), and two study parts

(Part A and Part B). Following the Screening visit, eligible subjects checked in to the study site on Day -1. Following the polacrilex gum training session, subjects were required to abstain from nicotine- and tobacco-containing products for approximately 20 hours until the first product use session on Days 1 to 3; use of other nicotine-containing products was prohibited throughout the study. No additional tobacco or nicotine products was provided after the second product use on Days 4 to 6.

On Day 1, subjects were randomized to one of three product sequence groups in Part A, which consisted of an *ad libitum* product use session for each of the following study products for 4 hours in a randomized crossover manner (Days 1 to 3; one product per day):

Product A: VLN™ regular cigarette

Product B: Own-brand regular filtered standard king size cigarette

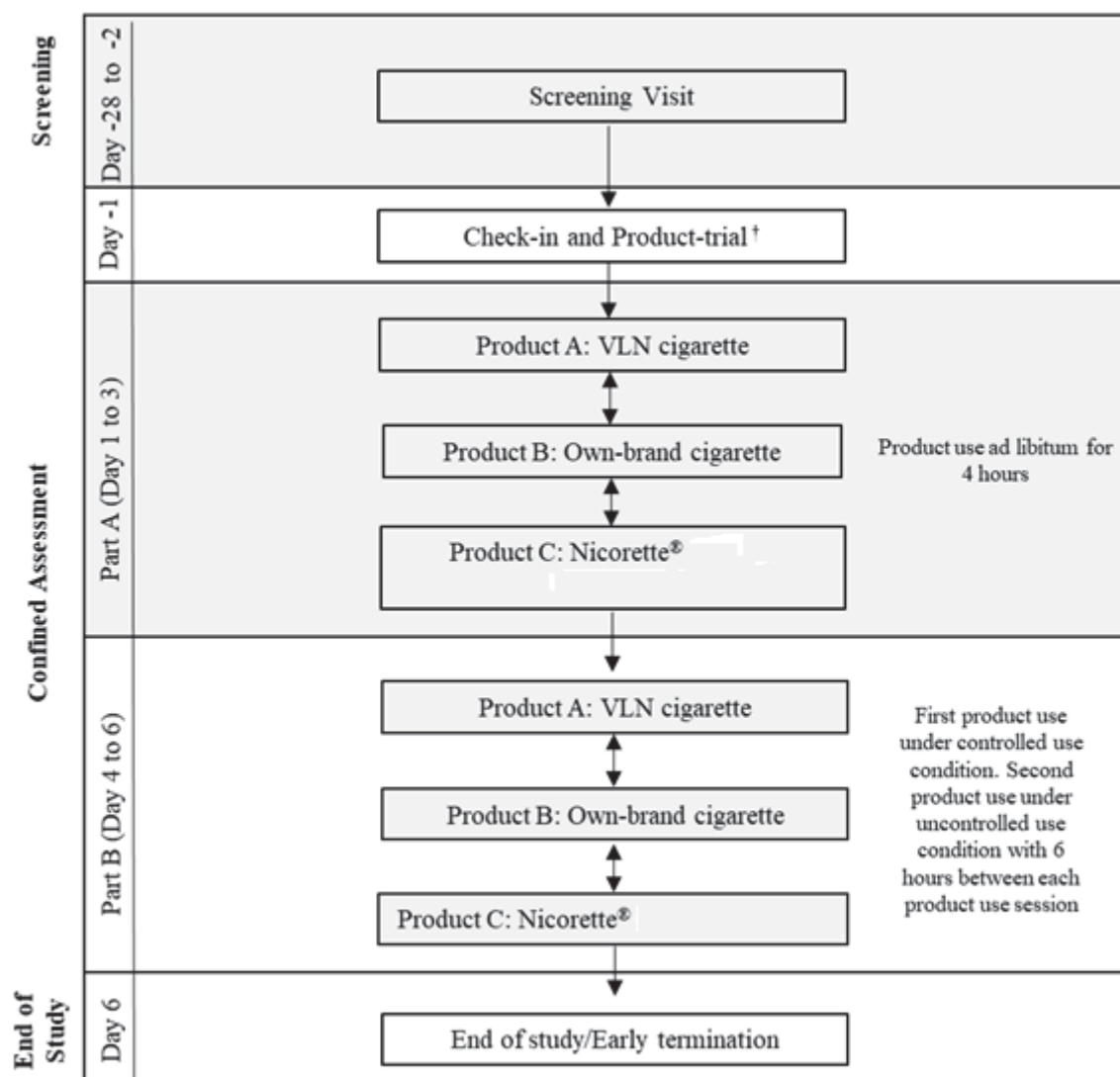
Product C: 4 mg Nicotine polacrilex gum (Nicorette®)

A pharmacodynamic measure (“use product again” visual analog scale [VAS]) was administered at the end of each *ad libitum* product use period. Product use behaviors (i.e., number of units consumed, duration of gum in mouth) were collected throughout each *ad libitum* product use period.

Upon completion of Part A, subjects were randomized to one of three product sequence groups in Part B, which consisted of 3 study days (Days 4 to 6), with one product per day. Each study day consisted of: 1) Controlled Product Use Session (10 puffs from their own-brand cigarette or VLN™ cigarette [maximum 3 ± 2 seconds per puff] at approximately 30 ± 5 -second interpuff intervals, or chew the nicotine polacrilex gum using the “chew and park” method for 10

minutes); and 2) Uncontrolled Product Use Session (*ad libitum* use for 10 minutes). The Controlled Product Use Session and Uncontrolled Product Use Session were separated by approximately 6 hours. During Part B, pharmacodynamic measures, PK, and product use behavior (Uncontrolled only) were collected at various time points each day. Figure VIII.D-1. *Abuse Liability Study Design*, below shows the outline of the study design.

Figure VIII.D-1. Abuse Liability Study Design



[†] *Ad libitum* use of the nicotine gum for 10 minutes. Subjects will be instructed on how to correctly use the nicotine gum using the “chew and park” method.

The Table VIII.D-3 below shows the schedule of assessments.

Table VIII.D-3. Schedule of assessments.

| | Screening | Check-in | Part A | Part B | | | | | | | | | | | | | | | | End of Study/ET |
|--|----------------|-----------------|------------------|---|-----------------|---|---|---|---|---|--|--|--|--|--|--|--|--|--|-----------------|
| Day: | -28 to -2 | -1 | 1 to 3 | 4 to 6 (Daily controlled use and uncontrolled use sessions) | | | | | | | | | | | | | | | | 6 |
| Assessment | | | | Assessment timepoints (minutes ²) | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | |
| Review of eligibility | X | X | | | | | | | | | | | | | | | | | | |
| Physical examination | X | X ³ | | | | | | | | | | | | | | | | | | X ²² |
| Height, weight, BMI | X | | | | | | | | | | | | | | | | | | | |
| HIV, Hepatitis B/C | X | | | | | | | | | | | | | | | | | | | |
| Pregnancy test | X ⁴ | X ⁵ | | | | | | | | | | | | | | | | | | |
| FSH (post-menopausal women) | X | | | | | | | | | | | | | | | | | | | |
| Vital signs ⁶ | X | X | | | | | | | | | | | | | | | | | | X |
| Oral temperature | X | X | | | | | | | | | | | | | | | | | | X |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | | | X |
| Urine cotinine screen | X | | | | | | | | | | | | | | | | | | | |
| Urine drug and alcohol test | X | X | | | | | | | | | | | | | | | | | | |
| Clinical laboratory tests ⁷ | X | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications | X | X | X | <----- Recorded throughout -----> | | | | | | | | | | | | | | | | X |
| AE Monitoring ⁸ | X | X | X | <----- Recorded throughout -----> | | | | | | | | | | | | | | | | X |
| Randomization | | | pre ⁹ | pre ¹⁰ | | | | | | | | | | | | | | | | |
| Product use | | X ¹¹ | X ¹² | | < ¹³ | 0 | - | - | - | > | | | | | | | | | | |

² All listed timepoints were minutes after the start of product use³ Abbreviated (symptom-directed) physical examination performed at the investigator's discretion⁴ Serum pregnancy test⁵ Urine pregnancy test⁶ Vital signs included respiratory rate, pulse rate and blood pressure⁷ Clinical laboratory assessments included hematology, biochemistry, and urinalysis⁸ Spontaneous AE reporting was continuous throughout the study, beginning with the time the subject gave informed consent; however, at regular intervals, AE checks were performed using a non-leading question.⁹ Day 1 only¹⁰ Day 4 only¹¹ Trial of 4 mg nicotine polacrilex gum for 10 minutes¹² Product use under *ad libitum* condition for 4 hours on each day¹³ First product under controlled use condition manner (10 puffs [maximum 3 ± 2 seconds per puff] with approximately 30-second inter-puff-intervals for cigarettes and 10 minutes "chew and park" for nicotine polacrilex gum) and second product under uncontrolled use condition for approximately 10 minutes (*ad libitum*) with approximately 6 hours in between 1st and 2nd use sessions

| | Screening | Check-in | Part A | Part B | | | | | | | | | | | | | | End of Study/ET | | |
|---|-----------|----------|-----------------|---|---|---|---|---|----|----|----|----|----|----|----|----|-----|-----------------|-----|---|
| Day: | -28 to –2 | -1 | 1 to 3 | 4 to 6 (Daily controlled use and uncontrolled use sessions) | | | | | | | | | | | | | | 6 | | |
| Assessment | | | | Assessment timepoints (minutes ²) | | | | | | | | | | | | | | | | |
| PK sampling ¹⁴ | | | | pre | | 2 | 5 | 7 | 10 | 12 | 15 | 20 | 30 | 45 | 60 | 90 | 120 | 150 | 180 | |
| Pharmacodynamic Training/practice ¹⁵ | | X | | | | | | | | | | | | | | | | | | |
| Tobacco/Nicotine Withdrawal Questionnaire ¹⁶ | | | | pre | | | 5 | | | | 15 | | 30 | | 60 | 90 | | | | |
| Direct Effects of Product Questionnaire | | | | pre | | | 5 | | | | 15 | | 30 | | 60 | 90 | | | | |
| Use the product again VAS | | | X ¹⁷ | | | | | | | | | | | | 90 | | | | | |
| Amount of product used | | | X ¹⁸ | < 19 | - | - | - | > | | | | | | | | | | | | |
| Tobacco cessation information | | | | | | | | | | | | | | | | | | | | X |
| Admission | | X | | | | | | | | | | | | | | | | | | |
| Discharge | | | | | | | | | | | | | | | | | | | | X |

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; pre=pre-use

Safety assessments including adverse events (AEs), physical examinations, vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature), electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), and urine drug and alcohol screens were collected at designated time points throughout the study. Subjects were discharged from the clinic on Day 6, once all procedures were completed (or at Early Termination).

¹⁴ Blood samples collected at same time points following the start of the 1st and 2nd product use sessions. Pre-product use samples should be collected within approximately 5 minutes prior to the start of product use, all other time points should be taken within ± 1 minute for the first 30 minutes and ± 5 minutes from the nominal time for all other time points (except when coinciding with PD testing). Actual time of blood draw will be recorded.

¹⁵ Additional PD training sessions may be performed throughout the study, as necessary.

¹⁶ Administered at same time points following the start of the 1st and 2nd product use sessions

¹⁷ Questionnaire administered at end of each product use session, within 10 minutes of completing the product use session (i.e., 4 hours \pm 10 minutes)

¹⁸ Number of units consumed and duration of gum in mouth

¹⁹ Uncontrolled Product Use Sessions only; number of inhalations per cigarette, duration of inhalations [per puff], duration of gum in mouth

(b) *Results*

A total of 66 subjects enrolled in the study and 55 completed the study. Table VIII.D-4 shows the demographics of the study participants. The overall mean age was 41 with 60% males. A total of 3.6% were Hispanic, while the remaining identified as non-Hispanic. Whites made up 56% and African Americans 8%. On average the subjects reported smoking 17.6 cigarettes per day prior to enrollment (Table VIII.D-5). Fifty-five subjects completed the study (Table VIII.D-6). Part A of the study was *ad libitum* use of product over 4 hours. The subjects consumed slightly more VLN™ cigarettes (8.2 vs. 7.8) than their usual brand but smoked the cigarettes for less time (4.7 mins vs. 6.0). During the Part B, subjects were allowed to only smoke one cigarette in an uncontrolled manner in the morning followed by controlled session in the afternoon. Smoking topography was measured during the uncontrolled session. VLN™ smokers took less puffs than usual brand (9.5 vs. 12.6) resulting in less time smoking.

Table VIII.D-4. Demographics of the randomized population.

| Demographic variable | Part A^{a20} N=66 | Part B N=63 |
|-----------------------------|--------------------------------------|------------------------|
| Age (years), mean (SD) | 41.4 (10.94) | 41.5 (11.15) |
| Sex, n (%) | | |
| Male | 40 (60.6) | 38 (60.3) |
| Female | 26 (39.4) | 25 (39.7) |
| Race, n (%) | | |
| White | 57 (86.4) | 55 (87.3) |
| Black | 9 (13.6) | 8 (12.7) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (3.0) | 2 (3.2) |

²⁰ Randomized Population for Part A includes the same subjects as the overall Safety Population.

| | | |
|-------------------------------------|--------------|--------------|
| Not Hispanic or Latino | 64 (97.0) | 61 (96.8) |
| BMI (kg/m ²), mean (SD) | 26.09 (3.95) | 26.13 (4.00) |

Table VIII.D-5. Reported tobacco consumption rates prior to start of study.

| Tobacco Product | | Overall (N=66) |
|----------------------------------|-----------|-------------------|
| Chewing Tobacco | n | 1 |
| | Mean (SD) | 0.0 (--) |
| | Median | 0.0 |
| | Min, Max | 0, 0 |
| Cigar(s) | n | 3 |
| | Mean (SD) | 0.2 (0.16) |
| | Median | 0.3 |
| | Min, Max | 0, 0 |
| Cigarette(s) | n | 66 |
| | Mean (SD) | 17.6 (7.36) |
| | Median | 15.0 |
| | Min, Max | 10, 40 |
| Cigarillo(s) | n | 2 |
| | Mean (SD) | 2.6 (3.42) |
| | Median | 2.6 |
| | Min, Max | 0, 5 |
| Electronic Cigarette(s)/E-Vapors | n | 1 |
| | Mean (SD) | 1.0 (--) |
| | Median | 1.0 |
| | Min, Max | 1, 1 |

Table VIII.D-6. Disposition of subjects (Completers) (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

| | | | Part A | | | Part B | | | Overall |
|--|-------|-----|------------|------------|------------|------------|------------|------------|------------|
| | | | ABC | BCA | CAB | ABC | BCA | CAB | |
| Subjects Enrolled [N] | | | | | | | | | 55 |
| Subjects Randomized [N] | | | 16 | 18 | 21 | 19 | 18 | 18 | 55 |
| Subjects Who Received Study Product [n(%)] | Day 1 | Yes | 16 (100.0) | 18 (100.0) | 21 (100.0) | | | | 55 (100.0) |
| | | No | 0 (0.0) | 0 (0.0) | 0 (0.0) | | | | 0 (0.0) |
| | Day 2 | Yes | 16 (100.0) | 18 (100.0) | 21 (100.0) | | | | 55 (100.0) |
| | | No | 0 (0.0) | 0 (0.0) | 0 (0.0) | | | | 0 (0.0) |
| | Day 3 | Yes | 16 (100.0) | 18 (100.0) | 21 (100.0) | | | | 55 (100.0) |
| | | No | 0 (0.0) | 0 (0.0) | 0 (0.0) | | | | 0 (0.0) |
| | Day 4 | Yes | | | | 19 (100.0) | 18 (100.0) | 18 (100.0) | 55 (100.0) |
| | | No | | | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Day 5 | Yes | | | | 19 (100.0) | 18 (100.0) | 18 (100.0) | 55 (100.0) |
| | | No | | | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Day 6 | Yes | | | | 19 (100.0) | 18 (100.0) | 18 (100.0) | 55 (100.0) |
| | | No | | | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subjects Who Completed the Study [n(%)] | | Yes | | | | | | | 55 (100.0) |
| | | No | | | | | | | 0 (0.0) |
| Subjects Included in Randomized Population (Part A) [n(%)] | | | 16 (100.0) | 18 (100.0) | 21 (100.0) | | | | 55 (100.0) |
| Subjects Included in Randomized Population (Part B) [n(%)] | | | | | | 19 (100.0) | 18 (100.0) | 18 (100.0) | 55 (100.0) |

Table VIII.D-7. Summary of product use Part A.

| | VLN™ Cigarette N=66 | Own-Brand Cigarette N=65 | Nicotine Gum N=65 |
|--------------------------------------|------------------------|-----------------------------|----------------------|
| Number of Units Consumed | | | |
| Mean (SD) | 8.2 (4.34) | 7.8 (2.61) | 3.5 (1.36) |
| Median | 7.0 | 8.0 | 4.0 |
| Min, Max | 2, 18 | 3, 13 | 1, 6 |
| Time Spent per Unit (minutes) | | | |
| Mean (SD) | 4.7 (1.71) | 6.0 (2.07) | 16.3 (11.45) |
| Median | 4.0 | 6.0 | 12.0 |
| Min, Max | 1, 14 | 0, 12 | 0, 56 |

Table VIII.D-8. Summary of product use Part B.

| | VLN Cigarette N=57 | Own-Brand Cigarette N=56 | Nicotine Gum N=58 |
|---|-------------------------------|-------------------------------------|------------------------------|
| Number of Inhalations per Subject | | | |
| Mean (SD) | 9.5 (3.42) | 12.6 (4.29) | |
| Median | 9.5 | 12.0 | |
| Min, Max | 2, 17 | 3, 22 | |
| Average Duration of Inhalations per Puff (sec)/ Duration of Gum in Mouth (min) | | | |
| Mean (SD) | 2.0 (1.04) | 1.9 (0.93) | 7.1 (3.52) |
| Median | 2.0 | 2.0 | 9.0 |
| Min, Max | 1, 8 | 1, 5 | 0, 11 |

Subjects used the products under controlled conditions in Part B of the study (Controlled Product Use Session: 10 puffs from one of their own-brand cigarettes or VLN™ cigarette [maximum 3 ± 2 seconds per puff] at approximately 30 ± 5 -second interpuff intervals or chew the nicotine polacrilex gum using the “chew and park” method for 10 minutes). Table VIII.D-9 lists the baseline-adjusted PK values. Figure VIII.D-2. *Plasma nicotine levels after controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum)*., shows the plasma nicotine levels after controlled use. The plasma level after using the usual brand was typical of cigarette smoking. There was a quick rise, peaking at 13.7 ng/ml at 8.29 minutes, followed by a long decay. The gum results were also typical of nicotine gum. There was a slow rise peaking at 3.5 ng/ml at 33.6 minutes with a slow decay. VLN™ peaked at 0.47 ng/ml at 9.75 minutes with a slow decline. Figure VIII.D-3. *Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum)*., shows the plasma nicotine levels after un-controlled smoking. Subjects were allowed to smoke one cigarette or chew one piece of gum *ad libitum* for up to 10

minutes. The plasma level after using the usual brand produced a quick rise, peaking at 16.97 ng/ml at 7.85 minutes, followed by a long decay. The gum results showed a slow rise peaking at 3.2 ng/ml at 28.7 minutes with a slow decay. VLN™ peaked at 0.57 ng/ml at 9.38 minutes with a slow decline. As might be expected the peak times and max levels were slightly different between the controlled and un-controlled smoking. Under both conditions the VLN™ nicotine levels were markedly less than usual brand and even less than nicotine gum. The plasma nicotine area under the curve for VLN™ under controlled use conditions was 26.2 ng*min/ml. Usual brand was 770.8 and gum was 342.77. VLN™ cigarettes contain on average at least 95% less nicotine than conventional cigarettes on the market. The amount of nicotine absorbed (AUC) was 97% less than usual brand. The nicotine gum contained 4 mg of nicotine and VLN™ had 0.33 mg of nicotine/cigarette. On a content basis, VLN™ contained 92% less nicotine than the gum. The AUC for gum under controlled use was 342.77 and for VLN™ 26.2, a 92% reduction. The plasma nicotine profile was not different for VLN™ under controlled or un-controlled use. In Figure VIII.D-2 and Figure VIII.D-3 it is difficult to really see the plasma levels of VLN™ because they were so close to the zero axis. Figure VIII.D-4. *Baseline adjusted plasma nicotine levels after controlled use (Log Scale) (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).*., shows the plasma levels under controlled usage (compare to Figure VIII.D-2) where the data has been adjusted for the baseline at pre-exposure and the data graphed on a log scale. VLN™ was substantially less than both gum and usual brand.

Figure VIII.D-2. Plasma nicotine levels after controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

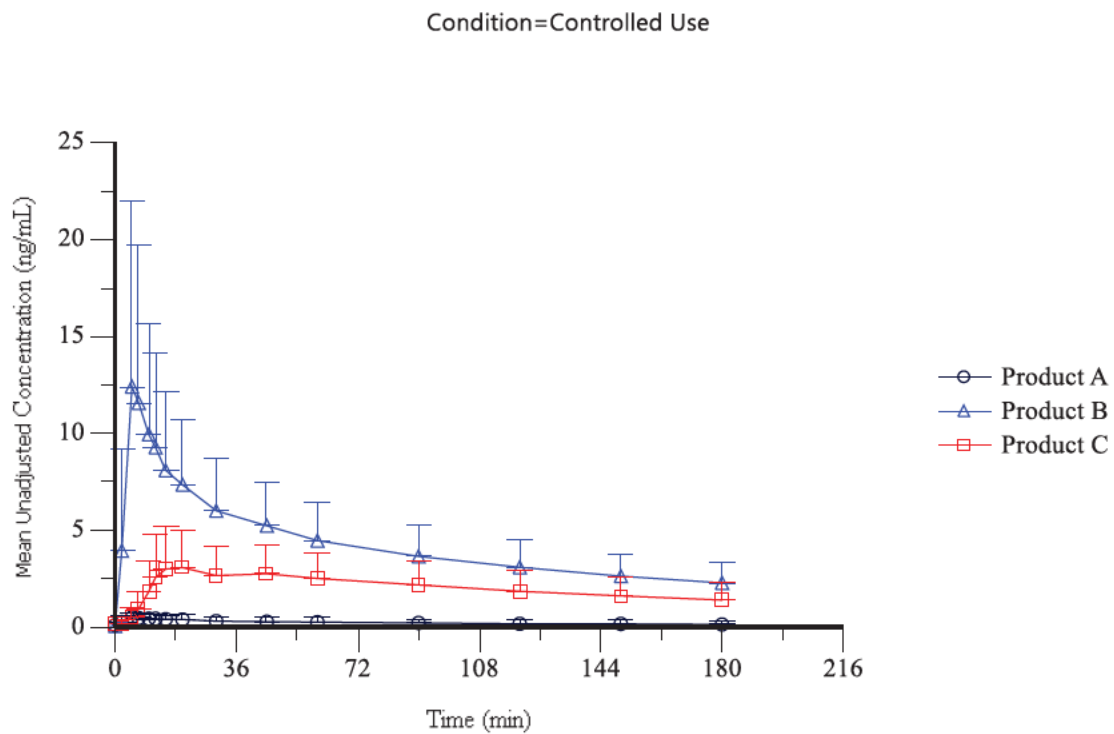


Figure VIII.D-3. Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

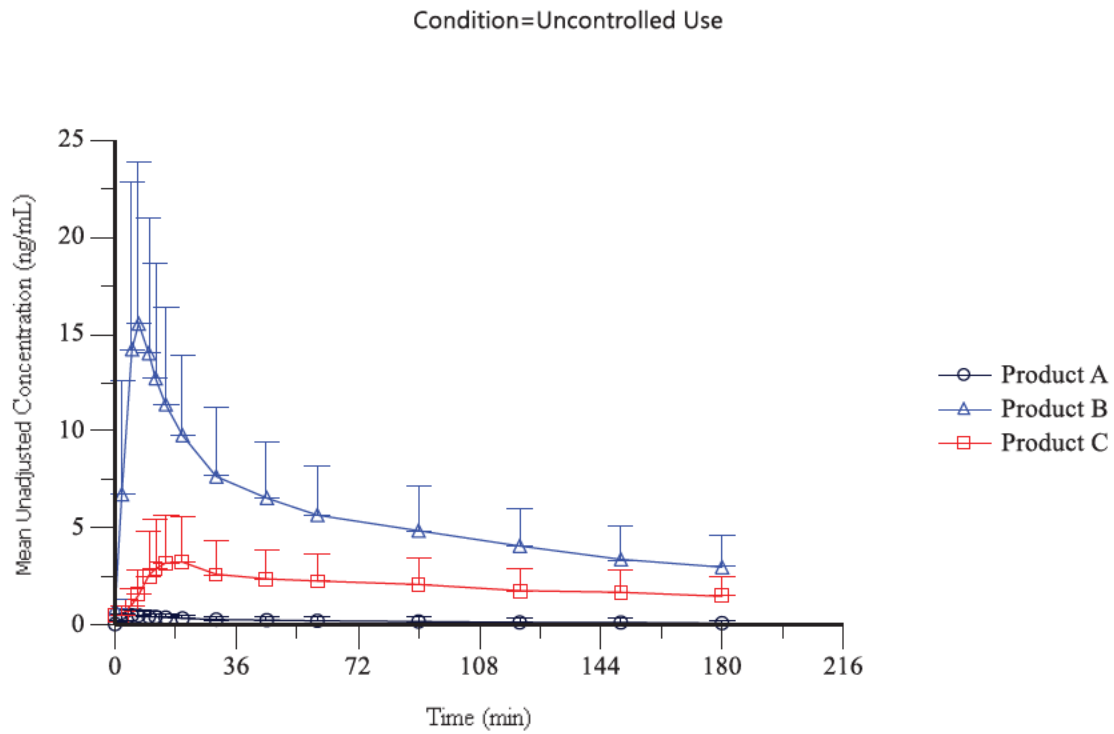


Figure VIII.D-4. Baseline adjusted plasma nicotine levels after controlled use (Log Scale) (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

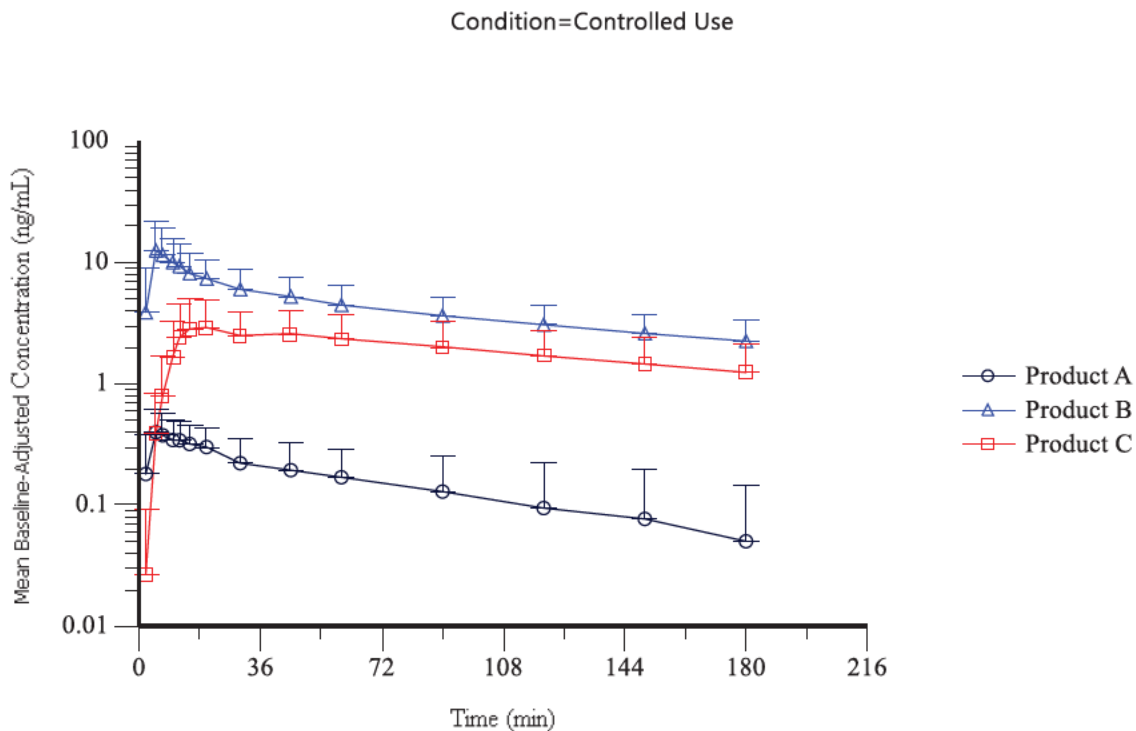


Table VIII.D-9. Summary of baseline-adjusted plasma nicotine PK values.

| Product | Condition | AUC (ng*min/ml) | C _{max} (ng/ml) | t _{max} (min) | T _½ (min) | K _{el} (1/min) |
|--------------|------------------|---------------------|-----------------------------|---------------------------|-------------------------|----------------------------|
| Usual Brand | Controlled Use | 770.80 [#] | 13.7 [#] | 8.29 | 123.49 | 0.0063 |
| VLN™ | Controlled Use | 26.2 ^{**} | 0.47 ^{**} | 9.75 | 213.38 | 0.0098 |
| Nicotine Gum | Controlled Use | 342.77 [*] | 3.5 [*] | 33.6 | 125.36 | 0.0062 |
| Usual Brand | Uncontrolled Use | 879.75 [#] | 16.97 [#] | 7.85 | 101.89 | 0.0078 |
| VLN™ | Uncontrolled Use | 28.3 ^{**} | 0.57 ^{**} | 9.38 | 110.77 | 0.0123 |
| Nicotine Gum | Uncontrolled Use | 277.3 [*] | 3.2 [*] | 28.7 | 166.42 | 0.0078 |

* p<0.05 to Usual Brand

p<0.05 to Nicotine Gum

Three different questionnaires were administered to assess subjective endpoints: Intent to Use Product Again, Product Effects, and Tobacco/ Nicotine Withdrawal. The intent to use was administer at 90 minutes after use. The other questionnaires were administered at 5, 15, 30, 60,

and 90 minutes after use. These assessments were performed after controlled and uncontrolled use of the products.

The Tobacco/Nicotine Withdrawal items were administered as 100-point VAS and were intended to measure withdrawal symptoms and craving. The VAS is anchored with “Not at All” on the left and “Extremely” on the right. The questionnaire items are as follows:

1. Urges to Smoke
2. Anxious
3. Difficulty Concentrating
4. Impatient
5. Craving a Cigarette

Craving and urges were statistically different between usual brand and VLN™ (Table VIII.D-10. *Product Use Again Comparisons.*). There was no difference between VLN™ and gum for these parameters. Usual brand appeared initially suppress the urge to smoke and craving more than VLN™ or nicotine gum (Figure VIII.D-5) There were no differences between the controlled and uncontrolled smoking. These results suggest that VLN™ reduces the urge and craving, but not quite to the level of usual brand.

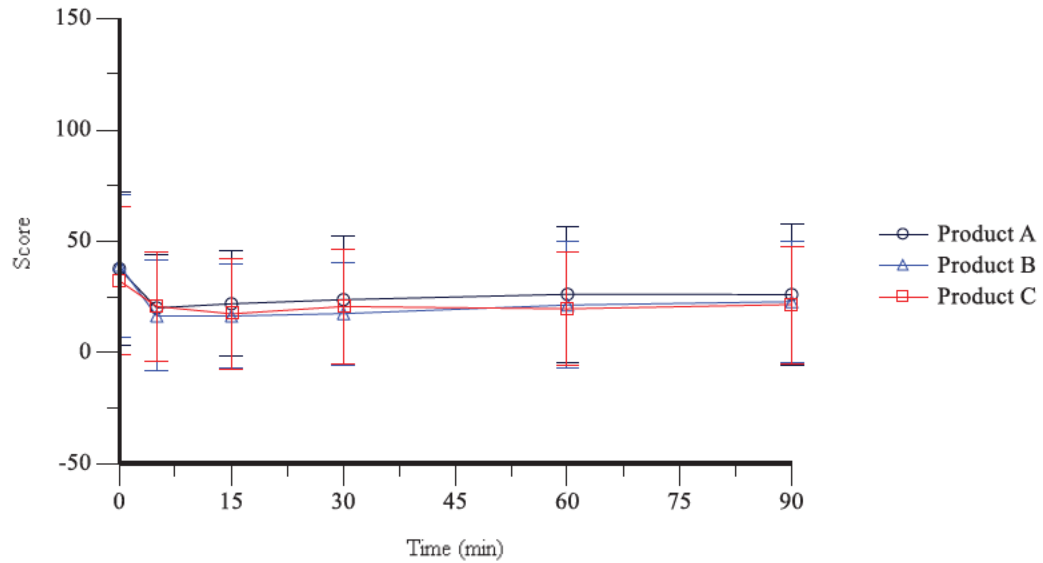
Table VIII.D-10. Product Use Again Comparisons.

| Question | Comparison | LSM | | LSM Difference (SD) | 95% CI | P value |
|--|---------------------------------------|-------|-------|---------------------|----------------|---------|
| | | Test | Ref | | | |
| Is the product “Satisfying” right now? | VLN Cigarette vs. Own-Brand Cigarette | 42.98 | 80.53 | -37.55 (5.16) | -47.66, -27.44 | <0.0001 |
| | VLN Cigarette vs. Nicotine Gum | 42.98 | 50.90 | -7.92 (5.11) | -17.95, -2.10 | 0.1202 |
| | Own-Brand Cigarette vs. Nicotine Gum | 80.53 | 50.90 | 29.63 (5.13) | 19.58, 39.68 | <0.0001 |
| Is the product making you feel “Calm” right now? | VLN Cigarette vs. Own-Brand Cigarette | 44.32 | 76.60 | -32.28 (4.59) | -41.27, -23.29 | <0.0001 |
| | VLN Cigarette vs. Nicotine Gum | 44.32 | 50.76 | -6.44 (4.57) | -15.40, 2.52 | 0.1569 |
| | Own-Brand Cigarette vs. Nicotine Gum | 76.60 | 50.76 | 25.84 (4.54) | 16.94, 34.73 | <0.0001 |
| | VLN Cigarette vs. Own-Brand Cigarette | 34.21 | 63.16 | -28.95 (4.80) | -38.36, -19.55 | <0.0001 |

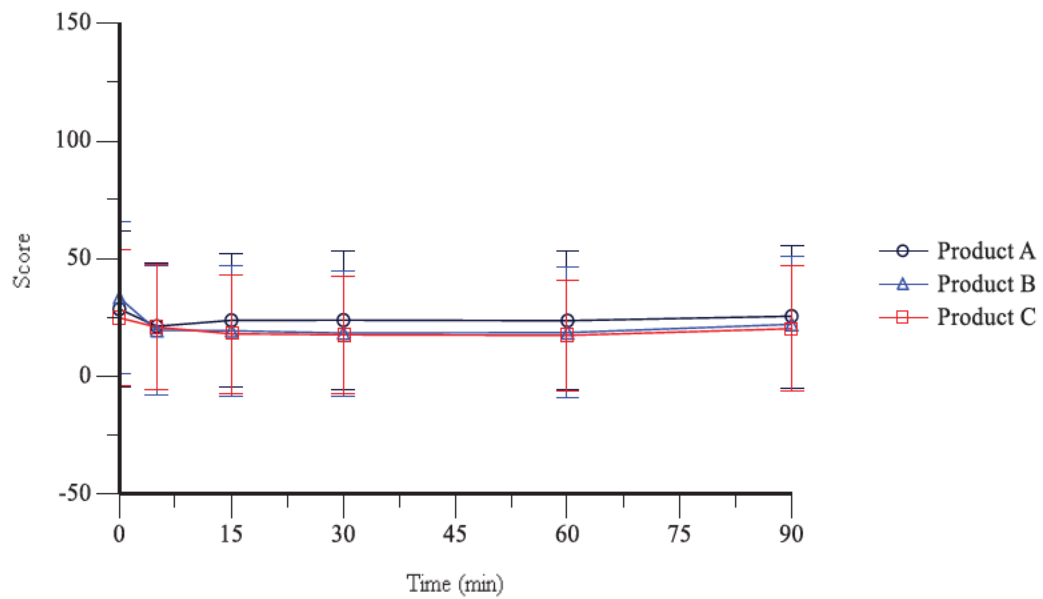
| Question | Comparison | LSM | | LSM Difference (SD) | 95% CI | P value |
|--|---------------------------------------|---------|-------|------------------------|----------------|---------|
| | | Test | Ref | | | |
| Is the product helping you "Concentrate" | VLN Cigarette vs. Nicotine Gum | 34.21 | 41.44 | -7.24 (4.80) | -16.60, 2.13 | 0.1286 |
| | Own-Brand Cigarette vs. Nicotine Gum | 63.16 | 41.44 | 21.72 (4.74) | 12.43, 31.01 | <0.0001 |
| Is the product making you feel more "Awake" right now? | VLN Cigarette vs. Own-Brand Cigarette | 33.63 | 61.52 | -27.90 (4.48) | -36.68, -19.11 | <0.0001 |
| | VLN Cigarette vs. Nicotine Gum | 33.63 | 37.38 | -3.76 (4.49) | -12.55, 5.04 | 0.3996 |
| | Own-Brand Cigarette vs. Nicotine Gum | 61.5185 | 37.38 | 24.14 (4.43) | 15.45, 32.82 | <0.0001 |
| Is the product making you feel "Sick" right now? | VLN Cigarette vs. Own-Brand Cigarette | 12.76 | 19.11 | -6.34 (3.16) | -12.53, -0.15 | 0.0447 |
| | VLN Cigarette vs. Nicotine Gum | 12.76 | 20.89 | -8.13 (3.13) | -14.25, -2.00 | 0.009 |
| | Own-Brand Cigarette vs. Nicotine Gum | 19.11 | 20.89 | -1.78 (3.14) | -7.94, 4.38 | 0.5671 |
| Is the product reducing your "Hunger" for food right now? | VLN Cigarette vs. Own-Brand Cigarette | 19.77 | 32.35 | -12.58 (3.42) | -19.27, -5.88 | 0.0003 |
| | VLN Cigarette vs. Nicotine Gum | 19.77 | 24.51 | -4.73 (3.39) | -11.38, 1.92 | 0.1612 |
| | Own-Brand Cigarette vs. Nicotine Gum | 32.35 | 24.51 | 7.85 (3.41) | 1.17, 14.52 | 0.0216 |
| Would you like "More" of the product right now? | VLN Cigarette vs. Own-Brand Cigarette | 46.36 | 75.61 | -29.25 (5.33) | -39.70, -18.80 | <0.0001 |
| | VLN Cigarette vs. Nicotine Gum | 46.36 | 43.58 | 2.78 (5.31) | -7.63, -13.19 | 0.5977 |
| | Own-Brand Cigarette vs. Nicotine Gum | 75.61 | 43.58 | 32.03 (5.30) | 21.65, 42.41 | <0.0001 |

Figure VIII.D-5. Mean tobacco/nicotine withdrawal questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

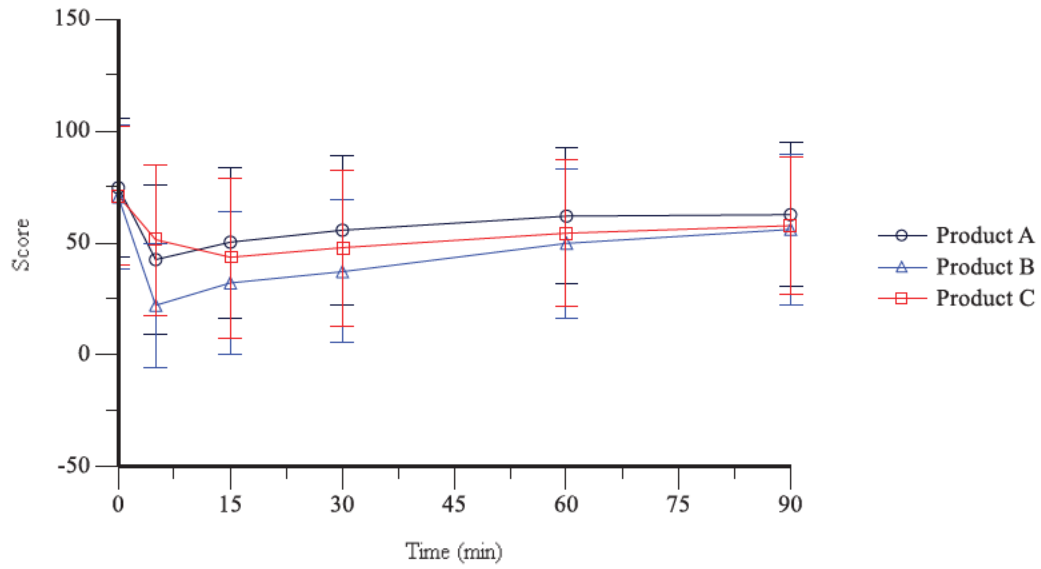
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Anxious



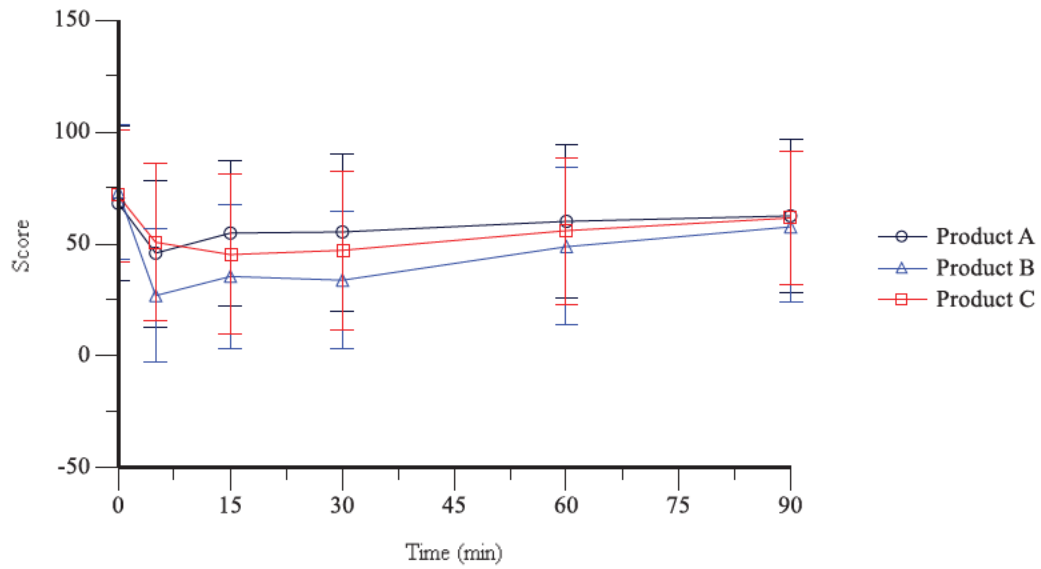
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Anxious



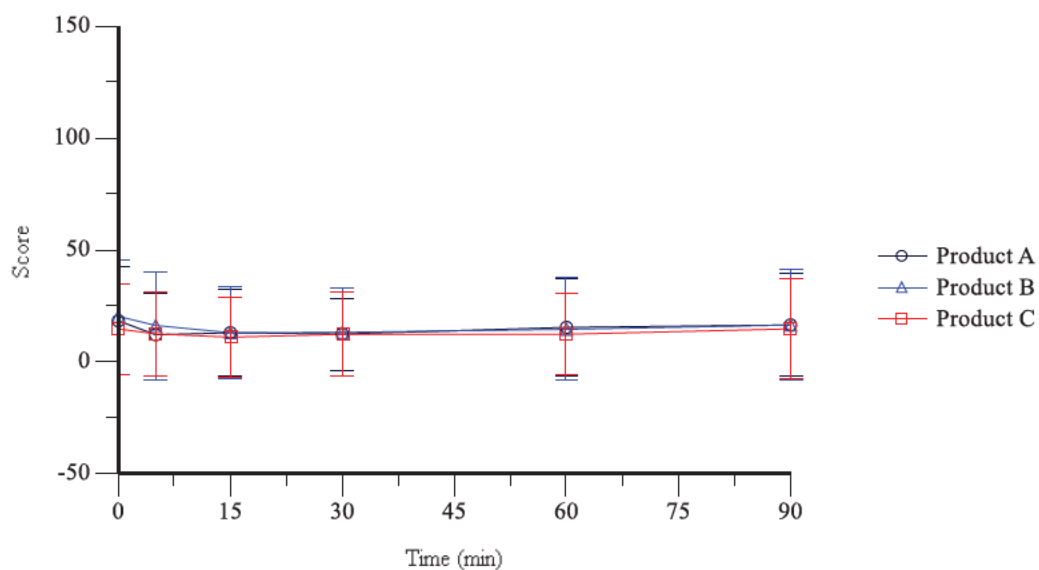
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



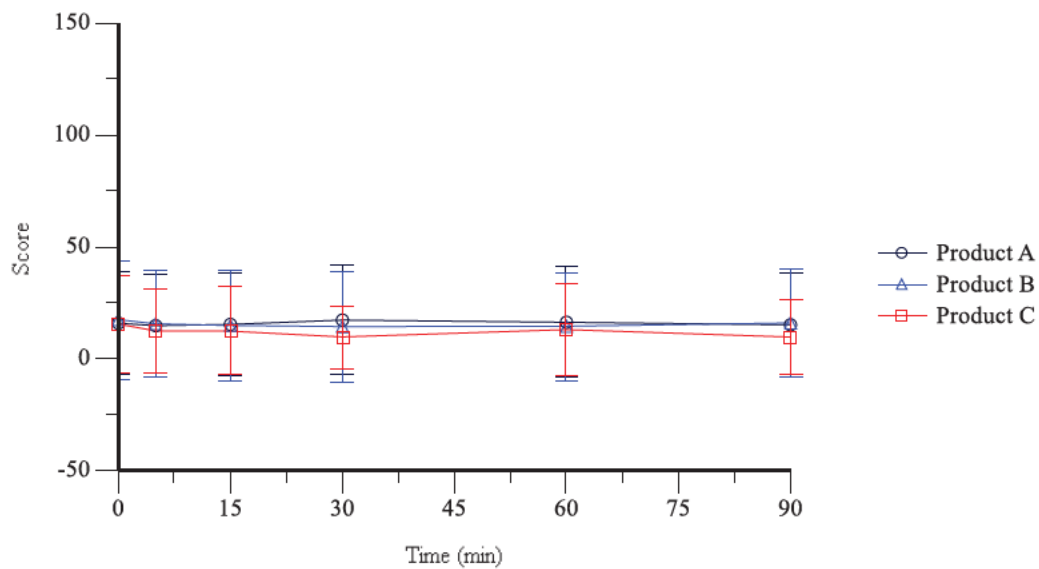
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



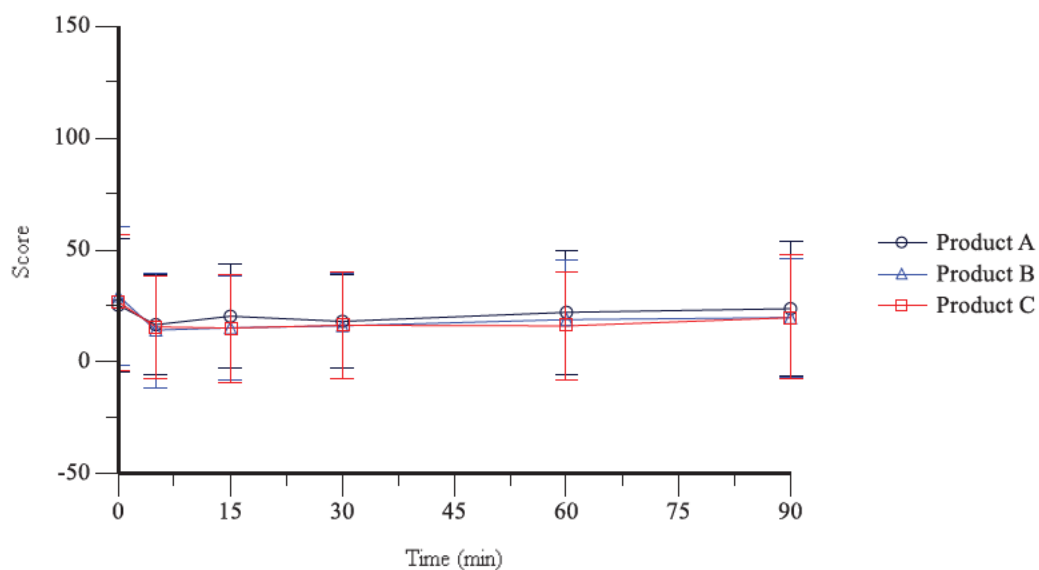
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Difficulty Concentrating



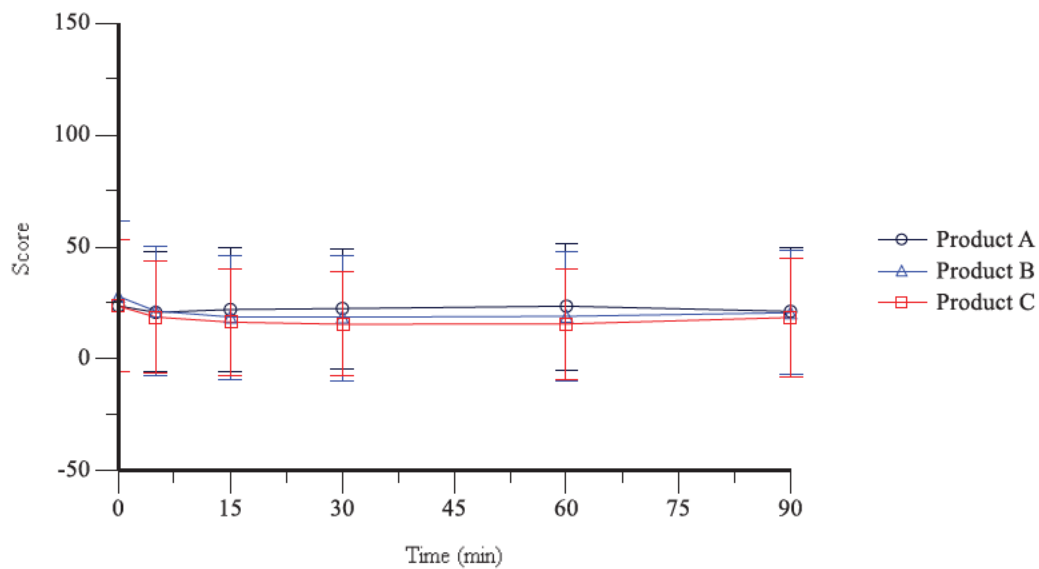
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Difficulty Concentrating



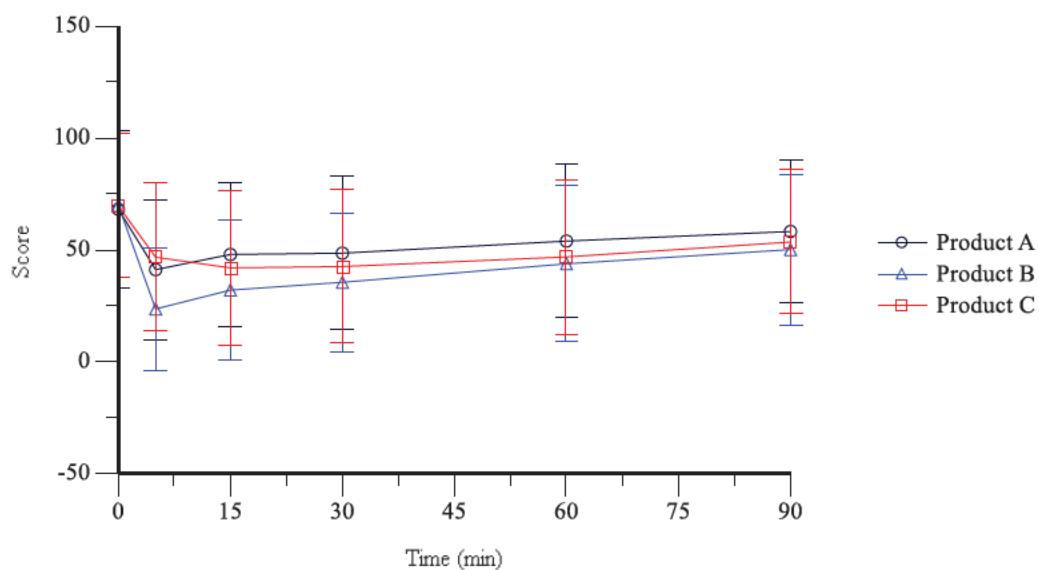
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Impatient



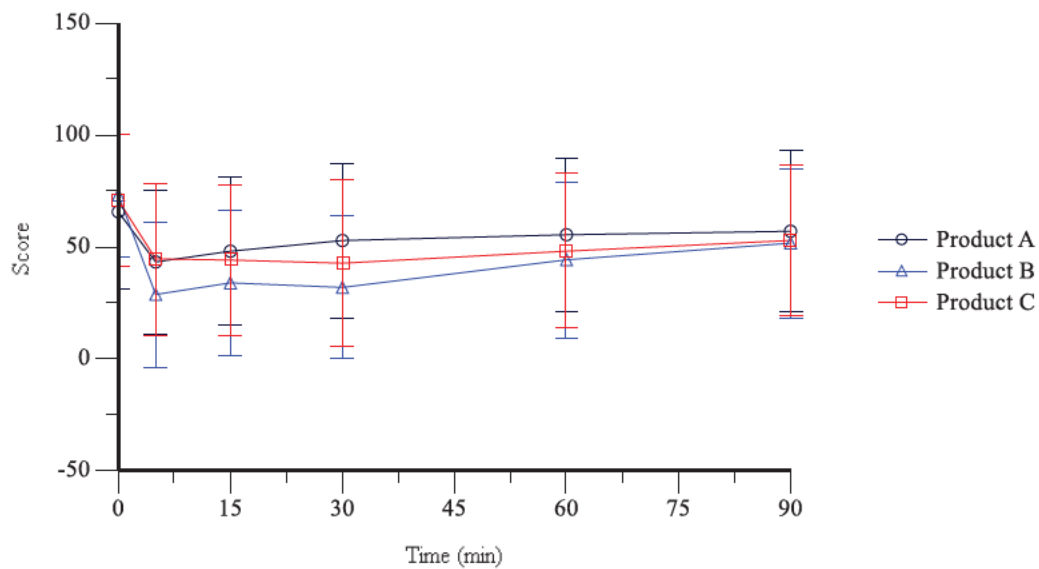
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Impatient



Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges



Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges



The Direct Effects of Product items were administered as 100-point VAS and were intended to measure the effects of the product being sampled at the moment. The VAS is

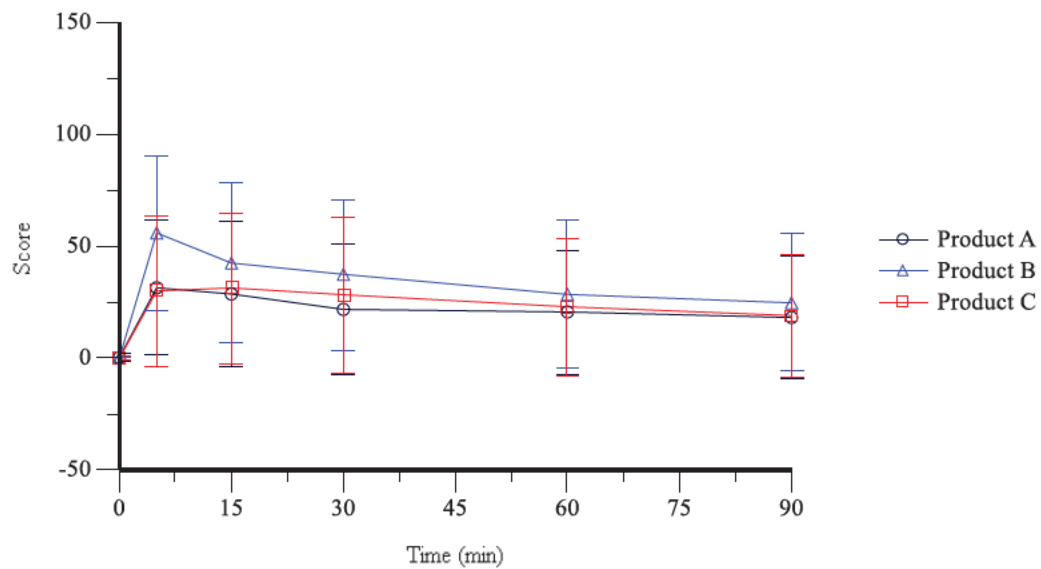
anchored with “Not at All” on the left and “Extremely” on the right. The questionnaire items were as follows:

1. Is the product “Pleasant” right now?
2. Is the product “Satisfying” right now?
3. Is the product making you feel “Calm” right now?
4. Is the product helping you “Concentrate” right now?
5. Is the product making you feel more “Awake” right now?
6. Is the product making you feel “Sick” right now?
7. Is the product reducing your “Hunger” for food right now?
8. Would you like “More” of the product right now?

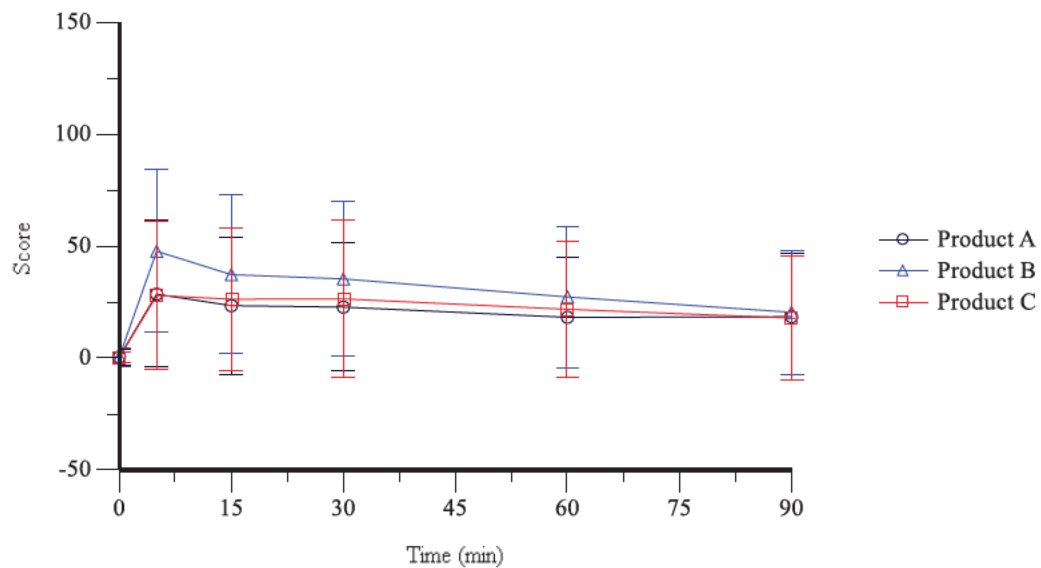
The effects (E_{max}) of VLN™ were statistically less than usual brand for all measures on the direct product effects questionnaire under both controlled and uncontrolled usage. VLN™ was not different from nicotine gum (Figure VIII.D-6). There was a tendency that usual brand made the subjects more awake, feeling calmer, helped them concentrate, and wanting more product. The usual brand also tended to be more satisfying and pleasant. The usual brand was statistically different from VLN™ for the question Is the product “Pleasant” right now? VLN™ was not different from nicotine gum.

Figure VIII.D-6. Mean direct effect of product questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

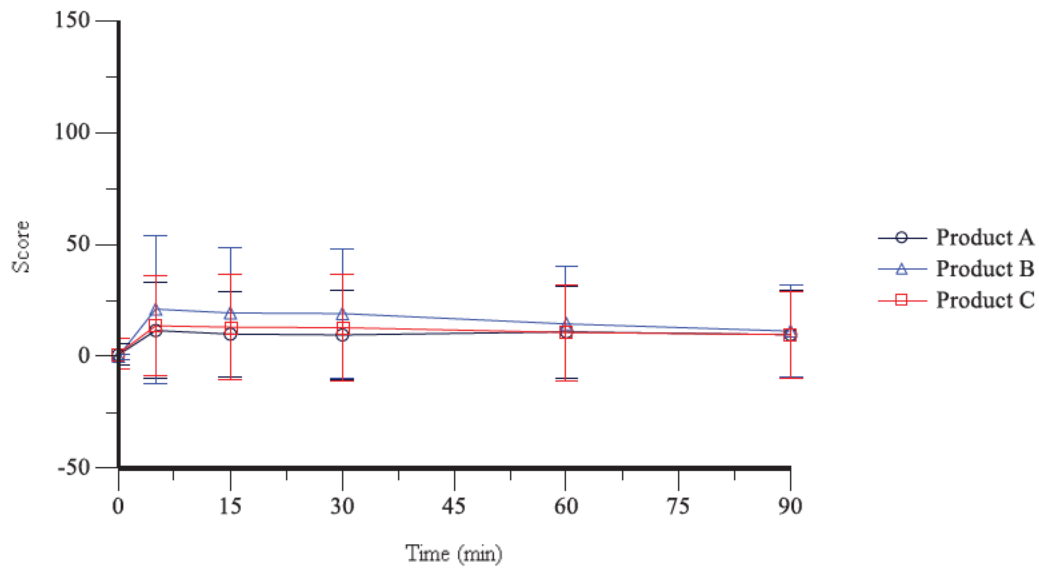
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Awake



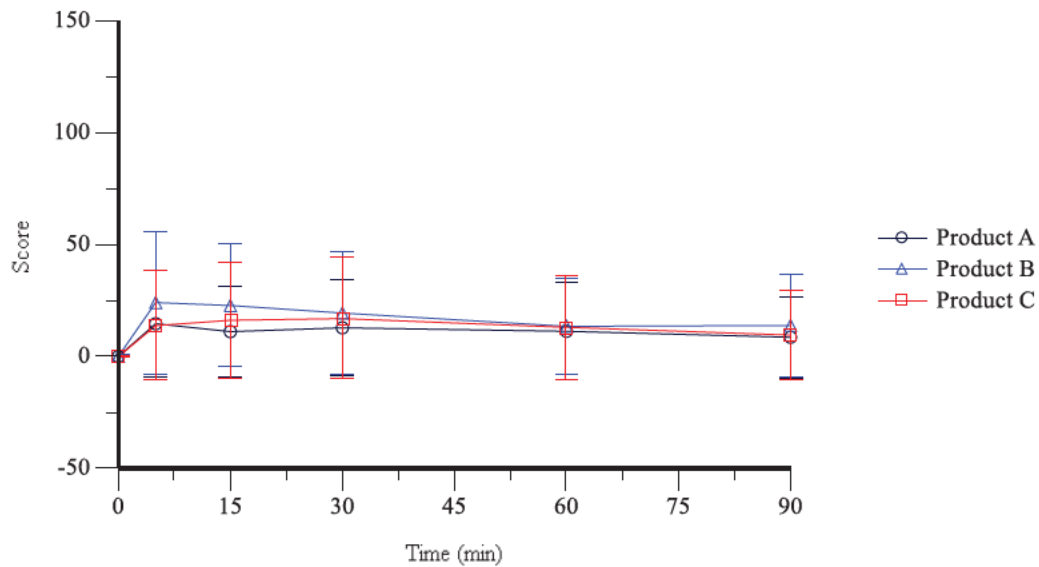
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Awake



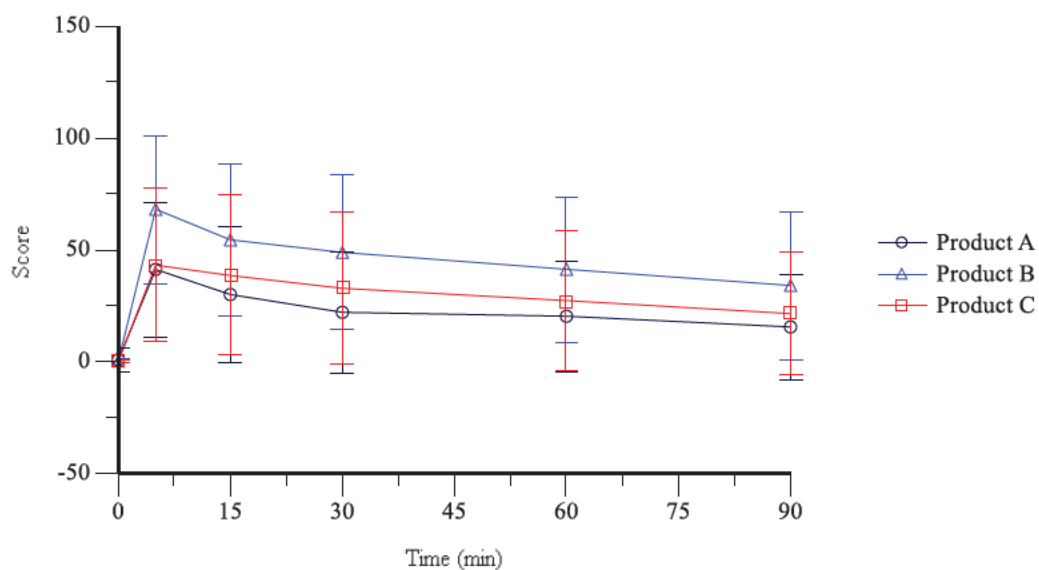
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Hunger



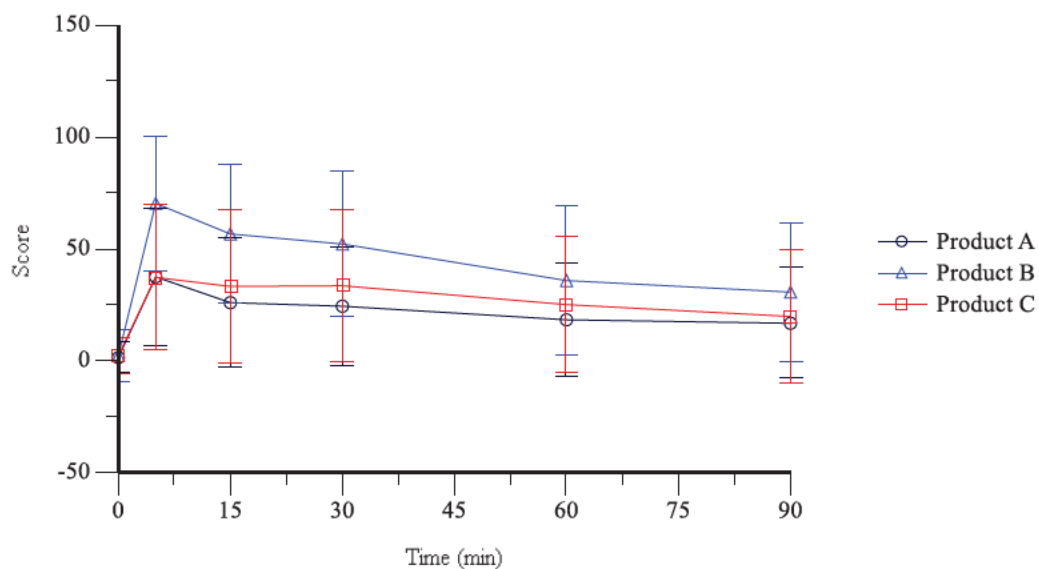
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Hunger



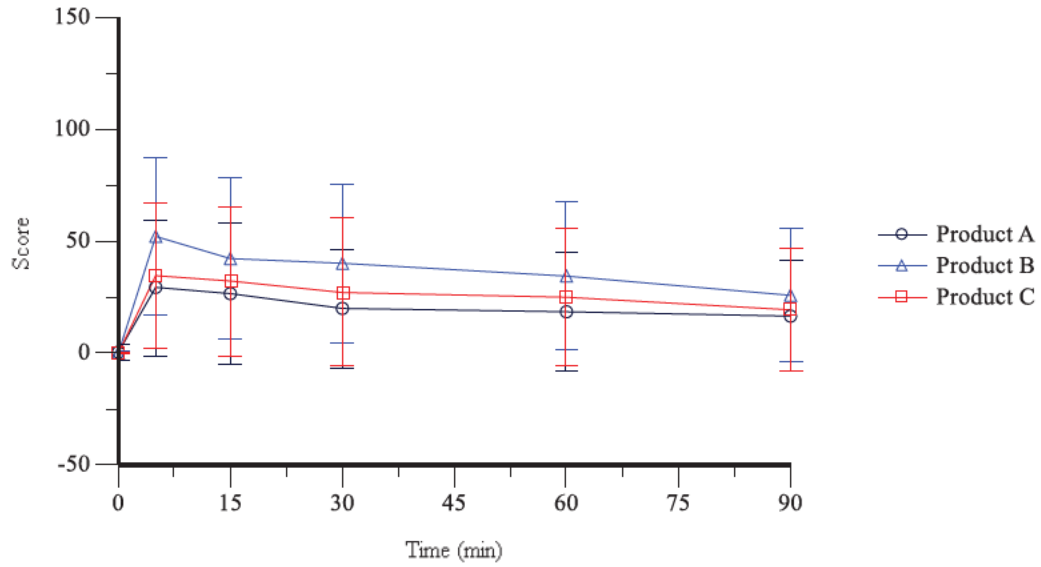
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Calm



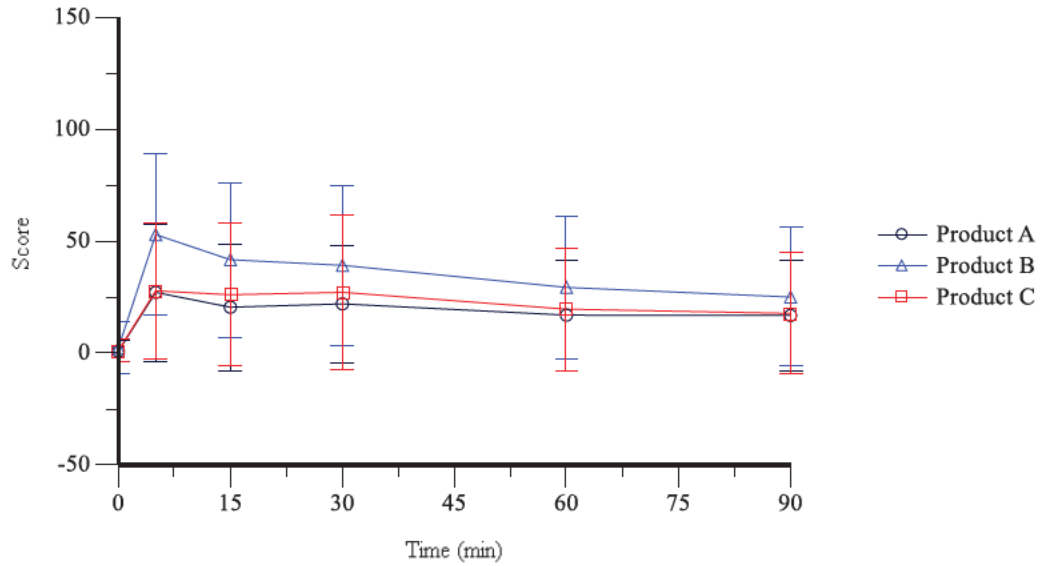
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Calm



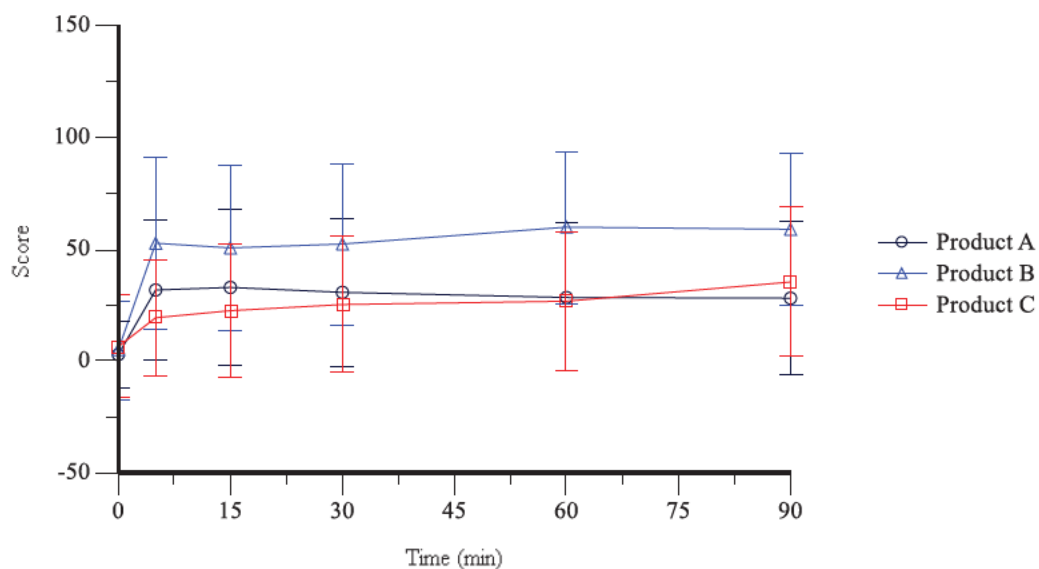
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Concentrate



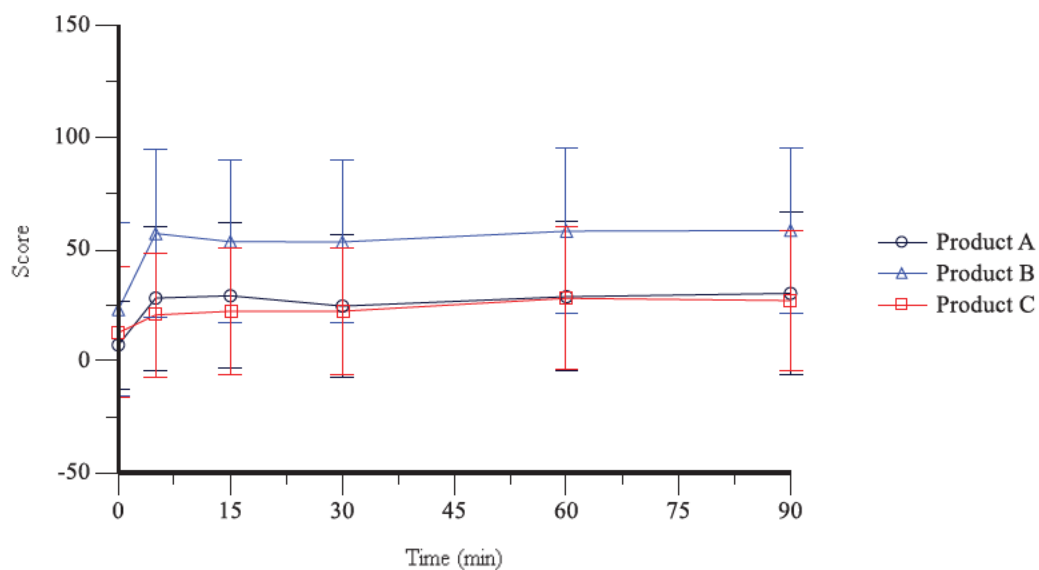
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Concentrate



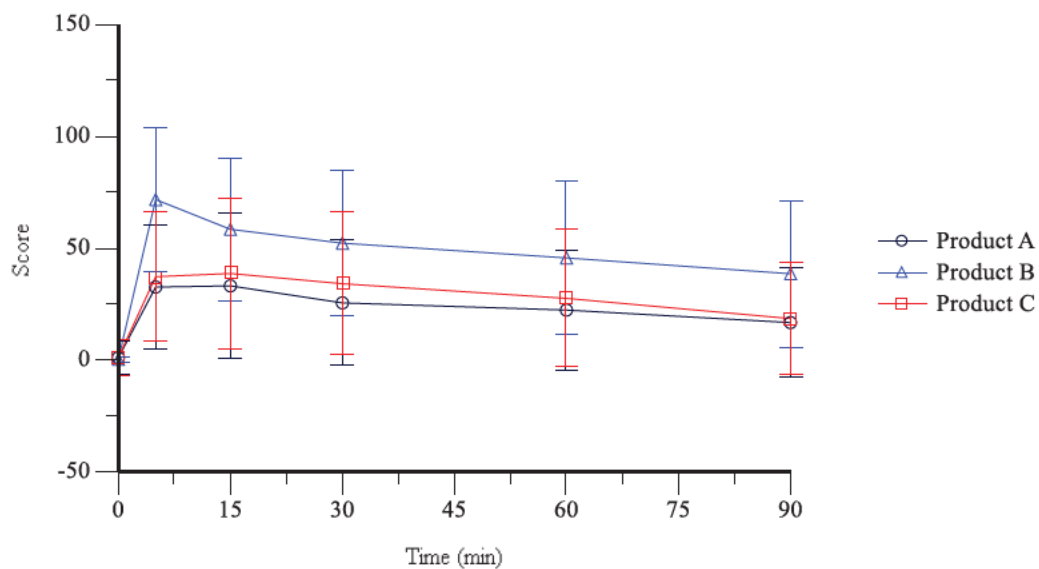
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=More



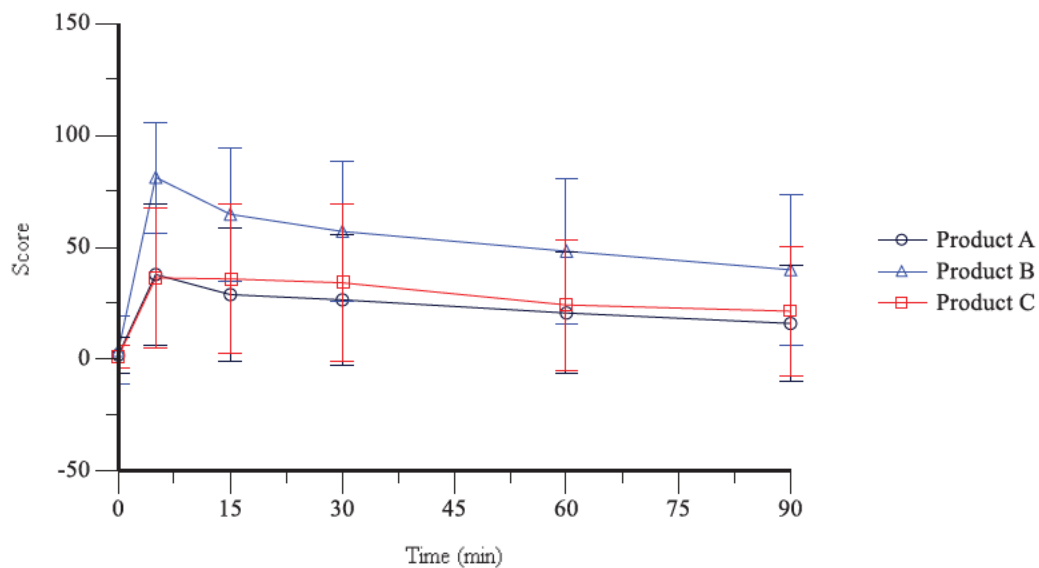
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=More



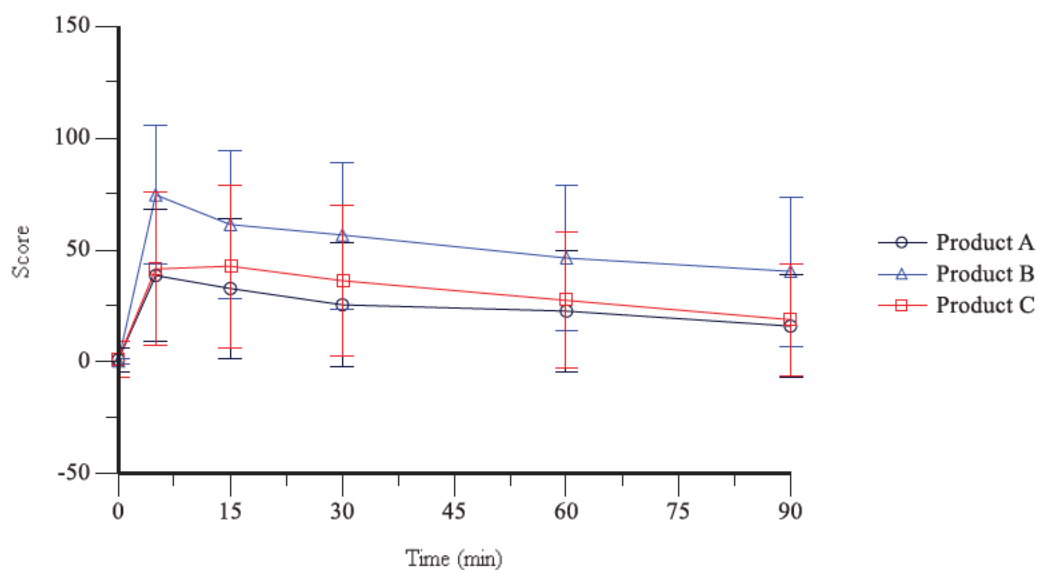
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Pleasant



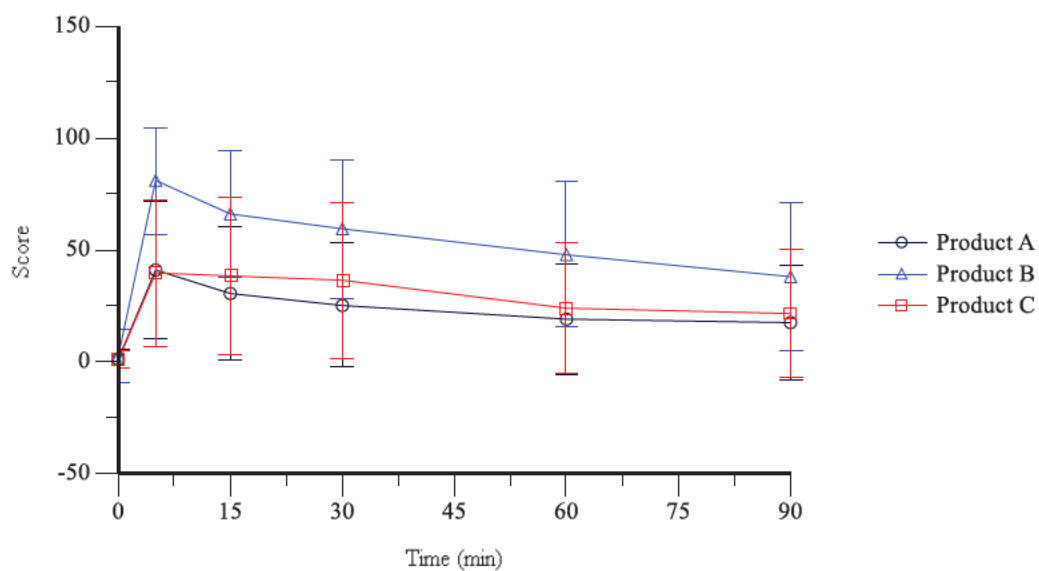
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Pleasant



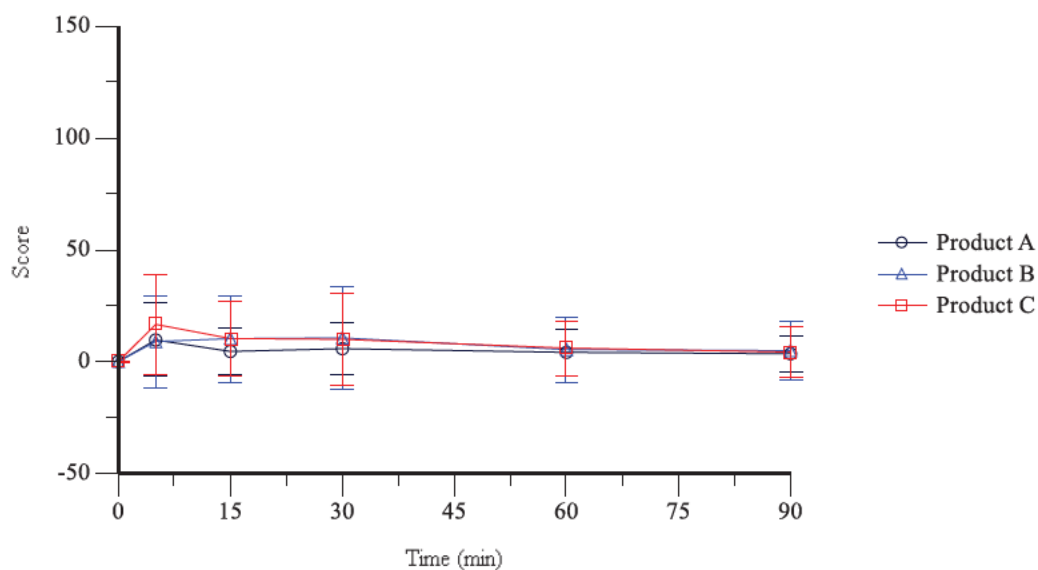
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Satisfy



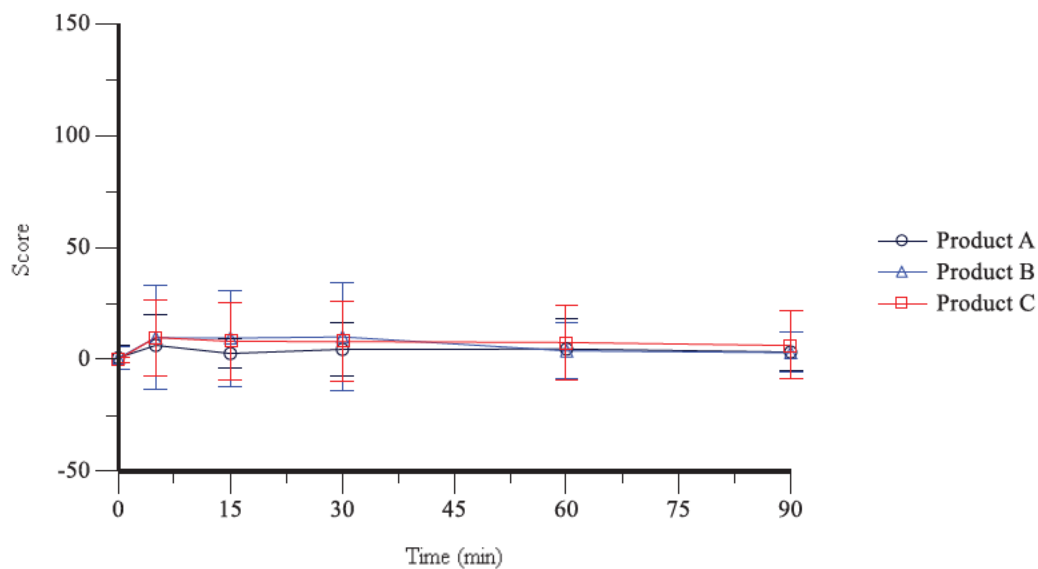
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Satisfy



Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Sick



Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Sick



The Use the Product Again questionnaire is a bipolar 100-point VAS used to assess how much a subject would be willing to use the sampled product again. The VAS is anchored by

“Definitely Would Not” on the left and “Definitely Would” on the right; the neutral point is also labeled with an anchor (“Don’t Care”). Table VIII.D-11 shows the results of the Use the Product Again Questionnaire administered after Part A with *ad libitum* smoking. VLN™ had the lowest mean score of 34 with usual brand rating 95. Nicotine gum was in the middle with 59. The results with VLN™ suggest that the subjects were “unwilling to use the product again”

Table VIII.D-11. Use the product again results after ad libitum use.

| Parameter | Statistic | VLN™ Cigarette N= 63 | Own-Brand Cigarette N=63 | Nicotine Gum N=63 |
|--------------------------|-----------|----------------------------|--------------------------------|----------------------|
| Use the Product Again | Mean (SD) | 34.0 (26.08) | 95.0 (9.86) | 58.8 (35.60) |
| | Median | 32.0 | 100.0 | 50.0 |
| | Min, Max | 0, 90 | 45, 100 | 0, 100 |

In Part B where the subjects only consumed a single product under control and uncontrolled conditions, a similar pattern was observed. The median response from VLN™ was similar to the nicotine gum.

Table VIII.D-12. Use the product again results from Part B.

| Parameter | Statistic | VLN™ Cigarette N= 63 | Own-Brand Cigarette N=63 | Nicotine Gum N=63 |
|--|-----------|----------------------------|--------------------------------|----------------------|
| Use the Product Again- Controlled Use | Mean (SD) | 38.1 (32.52) | 91.4 (14.92) | 47.9 (33.12) |
| | Median | 47.0 | 99.0 | 50.0 |
| | Min, Max | 0, 100 | 31, 100 | 0, 100 |
| Use the Product Again- Uncontrolled Use | Mean (SD) | 38.5 (33.41) | 88.9 (17.75) | 47.7 (35.79) |
| | Median | 50.0 | 100.0 | 50.0 |
| | Min, Max | 0, 100 | 20, 100 | 0, 100 |

(c) *Conclusions*

The primary objective of this study was to evaluate the abuse liability of VLN™ cigarettes compared with own-brand cigarettes and nicotine polacrilex gum, by assessing subjective effects such as urge to smoke and pleasantness under controlled and uncontrolled use conditions.

Overall, analysis of the primary endpoints of Urges to Smoke VAS $E_{\max_urge(\text{controlled})}$ and Pleasant VAS $E_{\max_plst(\text{controlled})}$ showed that use of own-brand cigarette under Controlled Use conditions in Part B was associated with statistically significant greater reductions in subject-reported urge to smoke and greater ratings of pleasantness compared with VLN™ cigarettes and nicotine gum. VLN™ cigarettes did not differ statistically from nicotine gum on either of the primary endpoints. Analysis of PK data showed that under both controlled and Uncontrolled Use conditions, peak and overall exposure to nicotine was statistically significantly lower for VLN™ cigarette compared with own-brand cigarette and nicotine gum. Therefore, despite lower nicotine exposure, VLN™ cigarettes were considered as pleasant and were able to reduce urges to smoke similarly to nicotine gum, a currently marketed nicotine replacement therapy.

Consistent with the findings on the primary endpoints, reduction in craving a cigarette ($E_{\max_crav[\text{controlled}]}$), a subscale of the Tobacco/Nicotine Withdrawal Scale, was statistically significantly lower for VLN™ cigarette and nicotine gum compared with own-brand cigarette. However, VLN™ cigarette did not statistically differ from nicotine gum indicating similar craving suppression despite lower nicotine concentrations. These findings are generally consistent with the literature that have demonstrated acute craving suppression following smoking, regardless of nicotine content (Donny *et al.* 2007 [pg299]) The other items in the scale, i.e., Anxious VAS, Difficulty Concentrating VAS, and Impatient VAS, did not differ between products. Results for the

Tobacco/Nicotine Withdrawal VAS when subjects were permitted to use the products under uncontrolled conditions in Part B were consistent with those observed during controlled use.

In terms of overall product effects, during controlled use, VLN™ cigarette and nicotine gum were rated as being less satisfying than own-brand cigarettes. In addition, both products were associated with a lower magnitude of effects related to feeling calm or feeling more awake, feeling less hungry, helping with concentration, and wanting more of the product compared with own-brand cigarette. These results were consistent when subjects used the products under uncontrolled conditions suggesting that regardless of use condition, VLN™ cigarettes were associated with weaker “positive” or reinforcing product effects compared with own-brand cigarettes and associated with similar reinforcing effects when compared with nicotine gum. With respect to negative effects (i.e., Sick VAS), under Controlled Use conditions, VLN™ cigarettes showed lower ratings of feeling sick compared with own-brand cigarettes and nicotine gum; however, scores on this scale were low overall compared with scores on other subscales and the same results were not observed for the Uncontrolled Use condition; therefore, these findings may not be clinically meaningful.

In Part A, when subjects were permitted to use each product *ad libitum* over a period of 4 hours and in Part B during controlled and Uncontrolled Use conditions subjects were asked to rate their preference for using each of the products again at the end of the product use session. In both Part A and Part B, mean scores on Use Product Again VAS were markedly higher for own-brand cigarette compared with VLN™ cigarettes. Furthermore, the mean score for VLN™ cigarette during Part A was consistent with subjects being “unwilling to use the product again” (i.e., < 50

points on the bipolar scale); however, scores were neutral ("do not care") following VLN™ product use in Part B and consistent with the neutral scores observed for nicotine gum.

Patterns of product use were also recorded during Part A and results show that subjects smoked a similar number of VLN™ and own-brand cigarettes (approximately 8 cigarettes over 4 hours) but spent approximately 2 minutes longer smoking each own-brand cigarette. Patterns of use were also assessed during the Uncontrolled Use condition in Part B, and subjects were found to inhale a slightly lower number of puffs when using VLN™ cigarettes as compared with own-brand cigarettes. However, there was no difference in the duration of inhalation between VLN™ and own-brand cigarettes. These findings suggest that despite the lower nicotine content in VLN™ cigarettes, subjects were not taking longer puffs or smoking more VLN™ cigarettes to compensate.

The primary endpoints in the study showed that use of the VLN™ cigarette under single controlled product use conditions was associated with lower peak ratings of pleasantness, lower reductions in urges to smoke compared with own-brand cigarettes, and markedly lower peak nicotine exposure in a sample of adult smokers. Furthermore, despite statistically significant lower nicotine exposure compared with nicotine polacrilex gum, VLN™ cigarettes were associated with similar reductions in urges to smoke and were rated to be as pleasant as nicotine polacrilex gum. These results suggest that VLN™ cigarettes have lower abuse liability compared with own-brand cigarettes and similar abuse liability as nicotine polacrilex gum. In addition, VLN™ cigarettes showed comparable effectiveness in reducing the urge to smoke and similar reductions in craving as nicotine polacrilex gum, a currently marketed nicotine replacement therapy.

ii. *Evaluation of the Abuse Liability of Very Low Nicotine Mentholated Cigarettes (NCT03559725)*

(a) *Study Design*

This abuse liability study was conducted by Altasciences Clinical Research in Overland Park, KS.

The primary objective of the study was:

- To evaluate the abuse liability of VLN™ menthol cigarettes (0.4 mg nicotine/gram of tobacco) relative to own-brand mentholated cigarettes and 4 mg nicotine polacrilex White Ice Mint gum under controlled use and uncontrolled (*ad libitum*) use conditions.

The secondary objectives of the study were:

- To compare the nicotine pharmacokinetic (PK) profiles of VLN™ menthol cigarettes relative to own-brand mentholated cigarettes and nicotine polacrilex gum under controlled use and uncontrolled use conditions.
- To characterize product use behavior of VLN™ menthol cigarettes, own-brand mentholated cigarettes, and nicotine polacrilex gum.

This study was randomized, two-part, 3-way crossover, designed to evaluate the abuse liability, PK, and product use behavior associated with study products, including VLN™ menthol cigarettes, subjects' own-brand mentholated cigarettes, and nicotine White Ice Mint polacrilex gum in healthy adult male and female exclusive smokers. Subjects participated in a standard Screening visit and one 7-day Confined Assessment Phase, which included a product trial session (Day -1), and two study parts (Part A and Part B). Following the Screening visit, eligible subjects checked in to the study site on Day -1. Following the polacrilex gum training session, subjects were required to abstain from nicotine- and tobacco-containing products for approximately 20 hours until the first product use session on Days 1 to 3; use of other nicotine-containing products

was prohibited throughout the study. No additional tobacco or nicotine products was provided after the second product use on Days 4 to 6.

On Day 1, subjects were randomized to one of three product sequence groups in Part A, which consisted of an *ad libitum* product use session for each of the following study products for 4 hours in a randomized crossover manner (Days 1 to 3; one product per day):

Product A: VLN™ Menthol King cigarette

Product B: Own-brand menthol filtered standard king size cigarette

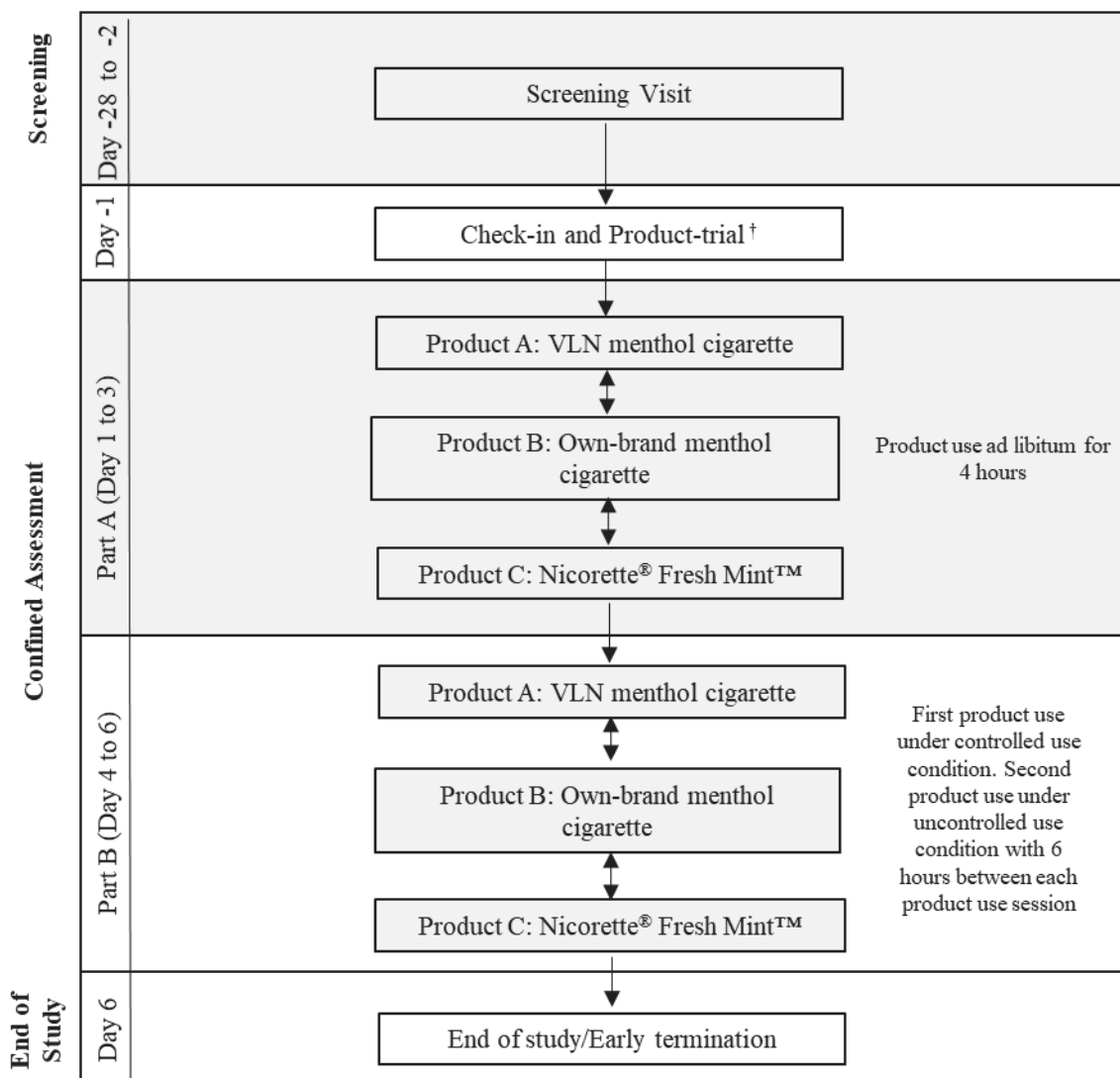
Product C: 4 mg Nicotine polacrilex gum (Nicorette® White Ice Mint™)

A pharmacodynamic measure (“use product again” visual analog scale [VAS]) was administered at the end of each *ad libitum* product use period. Product use behaviors (i.e., number of units consumed, duration of gum in mouth) were collected throughout each *ad libitum* product use period.

Upon completion of Part A, subjects were randomized to one of three product sequence groups in Part B, which consisted of 3 study days (Days 4 to 6), with one product per day. Each study day consisted of: 1) Controlled Product Use Session (10 puffs from their own-brand cigarette or VLN™ cigarette [maximum 3 ± 2 seconds per puff] at approximately 30 ± 5 -second interpuff intervals or chew the nicotine polacrilex gum using the “chew and park” method for 10 minutes); and 2) Uncontrolled Product Use Session (*ad libitum* use for 10 minutes). The Controlled Product Use Session and Uncontrolled Product Use Session were separated by approximately 6 hours. During Part B, pharmacodynamic measures, PK, and product use behavior

(Uncontrolled only) were collected at various time points each day. Figure VIII.D-7 below shows the outline of the study design.

Figure VIII.D-7. Abuse liability study design.



[†] Ad libitum use of the nicotine gum for 10 minutes. Subjects will be instructed on how to correctly use the nicotine gum using the “chew and park” method.

Table VIII.D-13 below shows the schedule of assessments.

Table VIII.D-13. Schedule of assessments.

| | Screening | Check-in | Part A | Part B | | | | | | | | | | | | | | | | End of Study/ET |
|---|-----------------|-----------------|-------------------|---|----------|---|---|---|---|--|--|--|--|--|--|--|--|--|--|-----------------|
| Day: | -28 to -2 | -1 | 1 to 3 | 4 to 6 (Daily controlled use and uncontrolled use sessions) | | | | | | | | | | | | | | | | 6 |
| Assessment | | | | Assessment timepoints (minutes ²¹) | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | |
| Review of eligibility | X | X | | | | | | | | | | | | | | | | | | |
| Physical examination | X | X ²² | | | | | | | | | | | | | | | | | | X ²² |
| Height, weight, BMI | X | | | | | | | | | | | | | | | | | | | |
| HIV, Hepatitis B/C | X | | | | | | | | | | | | | | | | | | | |
| Pregnancy test | X ²³ | X ²⁴ | | | | | | | | | | | | | | | | | | |
| FSH (post-menopausal women) | X | | | | | | | | | | | | | | | | | | | |
| Vital signs ²⁵ | X | X | | | | | | | | | | | | | | | | | | X |
| Oral temperature | X | X | | | | | | | | | | | | | | | | | | X |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | | | X |
| Urine cotinine screen | X | | | | | | | | | | | | | | | | | | | |
| Urine drug and alcohol test | X | X | | | | | | | | | | | | | | | | | | |
| Clinical laboratory tests ²⁶ | X | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications | X | X | X | <----- Recorded throughout -----> | | | | | | | | | | | | | | | | X |
| AE Monitoring ²⁷ | X | X | X | <----- Recorded throughout -----> | | | | | | | | | | | | | | | | X |
| Randomization | | | pre ²⁸ | pre ²⁹ | | | | | | | | | | | | | | | | |
| Product use | | X ³⁰ | X ³¹ | | <0 32 | - | - | - | > | | | | | | | | | | | |

²¹ All listed timepoints were minutes after the start of product use²² Abbreviated (symptom-directed) physical examination performed at the investigator's discretion²³ Serum pregnancy test²⁴ Urine pregnancy test²⁵ Vital signs included respiratory rate, pulse rate and blood pressure²⁶ Clinical laboratory assessments included hematology, biochemistry, and urinalysis²⁷ Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gave informed consent; however, at regular intervals, AE checks were performed using a non-leading question.²⁸ Day 1 only²⁹ Day 4 only³⁰ Trial of 4 mg nicotine polacrilex gum for 10 minutes³¹ Product use under *ad libitum* condition for 4 hours on each day³² First product under controlled use condition manner (10 puffs [maximum 3 ± 2 seconds per puff] with approximately 30-second inter-puff-intervals for cigarettes and 10 minutes "chew and park" for nicotine polacrilex gum) and second product under uncontrolled use condition for approximately 10 minutes (*ad libitum*) with approximately 6 hours in between 1st and 2nd use sessions

| | Screening | Check-in | Part A | Part B | | | | | | | | | | | | | | End of Study/ET | | |
|---|-----------|----------|-----------------|---|------|---|---|---|----|----|----|----|----|----|------------------|----|-----|-----------------|-----|---|
| Day: | -28 to -2 | -1 | 1 to 3 | 4 to 6 (Daily controlled use and uncontrolled use sessions) | | | | | | | | | | | | | | 6 | | |
| Assessment | | | | Assessment timepoints (minutes ²¹) | | | | | | | | | | | | | | | | |
| PK sampling ³³ | | | | pre | | 2 | 5 | 7 | 10 | 12 | 15 | 20 | 30 | 45 | 60 | 90 | 120 | 150 | 180 | |
| Pharmacodynamic Training/practice ³⁴ | | X | | | | | | | | | | | | | | | | | | |
| Tobacco/Nicotine Withdrawal Questionnaire ³⁵ | | | | pre | | | 5 | | | | 15 | | 30 | | 60 | 90 | | | | |
| Direct Effects of Product Questionnaire ³⁵ | | | | pre | | | 5 | | | | 15 | | 30 | | 60 | 90 | | | | |
| Use the product again VAS | | | X ³⁶ | | | | | | | | | | | | 90 ³⁵ | | | | | |
| Amount of product used | | | X ³⁷ | | < 38 | - | - | - | > | | | | | | | | | | | |
| Tobacco cessation information | | | | | | | | | | | | | | | | | | | | X |
| Admission | | X | | | | | | | | | | | | | | | | | | |
| Discharge | | | | | | | | | | | | | | | | | | | | X |

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; pre=pre-use

Safety assessments including adverse events (AEs), physical examinations, vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature), electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), and urine drug and alcohol screens were collected at designated time points throughout the study. Subjects were discharged from the clinic on Day 6, once all procedures were completed (or at Early Termination).

³³ Blood samples collected at same time points following the start of the 1st and 2nd product use sessions. Pre-product use samples should be collected within approximately 5 minutes prior to the start of product use, all other time points should be taken within ± 1 minute for the first 30 minutes and ± 5 minutes from the nominal time for all other time points (except when coinciding with PD testing). Actual time of blood draw will be recorded.

³⁴ Additional PD training sessions may be performed throughout the study, as necessary.

³⁵ Administered at same time points following the start of the 1st and 2nd product use sessions

³⁶ Questionnaire administered at end of each product use session, within 10 minutes of completing the product use session (i.e., 4 hours \pm 10 minutes)

³⁷ Number of units consumed and duration of gum in mouth

³⁸ Uncontrolled Product Use Sessions only; number of inhalations per cigarette, duration of inhalations [per puff], duration of gum in mouth

(b) *Results*

A total of 61 subjects enrolled in the study and 55 completed the study. Table VIII.D-14 shows the demographics of the study participants. The overall mean age was 36 with 57% males. A total of 3.3% were Hispanic, while the remaining identified as non-Hispanic. Whites made up 34% and African Americans 62%. On average the subjects reported smoking 15.1 cigarettes per day prior to enrollment (Table VIII.D-15). Fifty-five subjects completed the study (Table VIII.D-16). Part A of the study was *ad libitum* use of product over 4 hours. The subjects consumed slightly more VLN™ cigarettes (6.8 vs. 6.2) than their usual brand but smoked the cigarettes for less time (5.1 mins vs. 6.3). During the Part B, subjects were allowed to only smoke one cigarette in an uncontrolled manner in the morning followed by controlled session in the afternoon. Smoking topography was measured during the uncontrolled session. VLN™ smokers took less puffs than usual brand (9.9 vs. 12.3) resulting in less time smoking.

Table VIII.D-14. Demographics of the randomized population.

| Demographic variable | Part A N=61 | Part B N=60 |
|---|------------------------|------------------------|
| Age (years), mean (SD) | 36.3 (10.45) | 36.3 (10.52) |
| Sex, n (%) | | |
| Male | 35 (57.4) | 34 (56.7) |
| Female | 26 (42.6) | 26 (43.3) |
| Race, n (%) | | |
| White | 21 (34.4) | 21 (35) |
| Black | 38 (62.3) | 37 (61.7) |
| American Indian or Alaska Native | 1 (1.6) | 1 (1.7) |
| Native Hawaiian or other Pacific Islander | 1 (1.6) | 1 (1.7) |

| | | |
|-------------------------------------|--------------|-------------|
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (3.3) | 2 (3.3) |
| Not Hispanic or Latino | 59 (96.7) | 58 (96.7) |
| BMI (kg/m ²), mean (SD) | 25.74 (4.04) | 25.8 (4.05) |

Table VIII.D-15. Reported tobacco consumption rates prior to start of study.

| | Tobacco Product | | Overall (N=61) |
|--|-----------------------------------|-----------|----------------|
| Number of Tobacco Product Used Per Day | Cigar(s) | n | 4 |
| | | Mean (SD) | 1.0 (1.54) |
| | | Median | 0.4 |
| | | Min, Max | 0, 3 |
| | Cigarette(s) | n | 61 |
| | | Mean (SD) | 15.1 (5.83) |
| | | Median | 15.0 |
| | | Min, Max | 10, 40 |
| | Cigarillo(s) | n | 1 |
| | | Mean (SD) | 3.0 (--) |
| | | Median | 3.0 |
| | | Min, Max | 3, 3 |
| | Electronic Cigarette(s) /E-Vapors | n | 3 |
| | | Mean (SD) | 0.7 (1.09) |
| | | Median | 0.1 |
| | | Min, Max | 0, 2 |

Table VIII.D-16. Disposition of subjects (All Subjects)

| | N (%) |
|-------------------------------|------------|
| Part A | |
| Number of Randomized Subjects | 61 |
| Subjects who Completed Part A | 60 (98.4%) |
| Subjects who Withdrew Early | 1 (1.6%) |
| Reasons for Discontinuation | |
| Other | 1 (1.6%) |
| Part B | |

| | |
|-------------------------------|------------|
| Number of Randomized Subjects | 60 |
| Subjects who Completed Part B | 55 (90.2%) |

Table VIII.D-17. Summary of Product Use Part A

| | VLN™ Menthol Cigarette N=60 | Own-brand Cigarette N=60 | Nicotine Gum N=60 |
|---|--|-------------------------------------|------------------------------|
| Number of Units Consumed^a | | | |
| Mean (SD) | 6.8 (3.38) | 6.2 (1.85) | 3.1 (1.42) |
| Median | 6.0 | 6.0 | 3.0 |
| Min, Max | 1, 17 | 2, 10 | 1, 7 |
| Time Spent per Unit (Minutes) | | | |
| Mean (SD) | 5.1 (2.41) | 6.3 (2.33) | 12.8 (14.17) |
| Median | 5.0 | 6.0 | 10.0 |
| Min, Max | 0, 36 | 1, 29 | 0, 87 |

Max=maximum; Min=minimum; SD=standard deviation

^a Units=cigarettes or pieces of gum

Table VIII.D-18. Summary of Product Use Part B

| | VLN™ Menthol Cigarette N=56 | Own-brand Cigarette N=57 | Nicotine Gum N=55 |
|--|--|-------------------------------------|------------------------------|
| Number of Inhalations per Subject | | | |
| Mean (SD) | 9.9 (3.24) | 12.3 (3.27) | |
| Median | 10.0 | 12.0 | |
| Min, Max | 1, 18 | 7, 22 | |
| Average Duration of Inhalations per Puff (Sec) / Duration of Gum in Mouth (Min) | | | |
| Mean (SD) | 2.1 (1.09) | 1.9 (0.93) | 5.9 (3.88) |
| Median | 2.0 | 2.0 | 6.0 |
| Min, Max | 0, 11 | 1, 7 | 0, 12 |

Subjects used the products under controlled conditions in Part B of the study (Controlled Product Use Session: 10 puffs from one of their own-brand cigarettes or VLN™ Menthol cigarette [maximum 3 ± 2 seconds per puff] at approximately 30 ± 5 -second interpuff intervals or chew the nicotine polacrilex gum using the “chew and park” method for 10 minutes). Table VIII.D-19 lists the baseline-adjusted PK values. Figure VIII.D-8. *Plasma nicotine levels after controlled use (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum)*, shows the plasma nicotine levels after controlled use. The plasma level after using the usual brand was typical of cigarette smoking. There was a quick rise, peaking at 13.684 ng/ml at 7 minutes, followed by a long decay. The gum results were also typical of nicotine gum. There was a slow rise peaking at 3.074 ng/ml at 45 minutes with a slow decay. VLN™ Menthol peaked at 0.404 ng/ml at 7 minutes with a slow decline. Figure VIII.D-9. *Plasma nicotine levels after uncontrolled use (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum)*, shows the plasma nicotine levels after uncontrolled smoking. Subjects were allowed to smoke one cigarette or chew one piece of gum *ad libitum* for up to 10 minutes. The plasma level after using the usual brand produced a quick rise, peaking at 19.236 ng/ml at 7 minutes, followed by a long decay. The gum results showed a slow rise peaking at 1.987 ng/ml at 20 minutes with a slow decay. VLN™ Menthol peaked at 0.534 ng/ml at 7 minutes with a slow decline. As might be expected the peak times and max levels were slightly different between the controlled and un-controlled smoking. Under both conditions the VLN™ nicotine levels were markedly less than usual brand and even less than nicotine gum. The plasma nicotine area under the curve for VLN™ Menthol under controlled use conditions was 30.449 ng*min/ml. Usual brand was 931.994 and gum was 359.257. VLN™ Menthol cigarettes contain

on average at least 95% less nicotine than conventional cigarettes on the market. The amount of nicotine absorbed (AUC) was 97% less than usual brand. The nicotine gum contained 4 mg of nicotine and VLN™ had 0.33 mg of nicotine/cigarette. On a content basis, VLN™ contained 92% less nicotine than the gum. The AUC for gum under controlled use was 359.257 and for VLN™ Menthol 30.449, a 92% reduction. The plasma nicotine profile was not different for VLN™ under controlled or un-controlled use.

Figure VIII.D-8. Plasma nicotine levels after controlled use (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum)

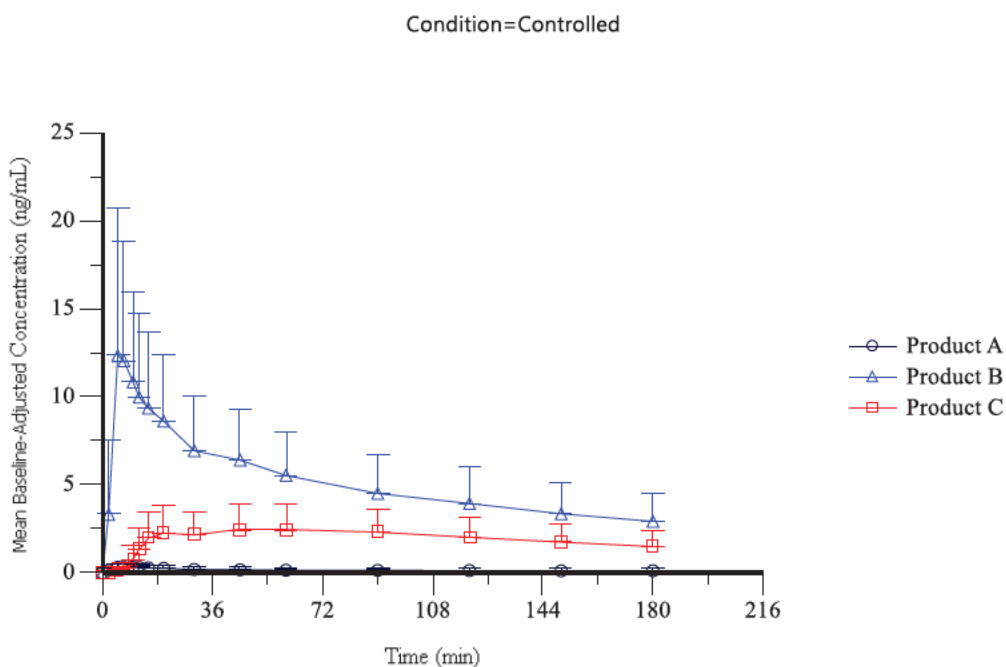


Figure VIII.D-9. Plasma nicotine levels after uncontrolled use (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum)

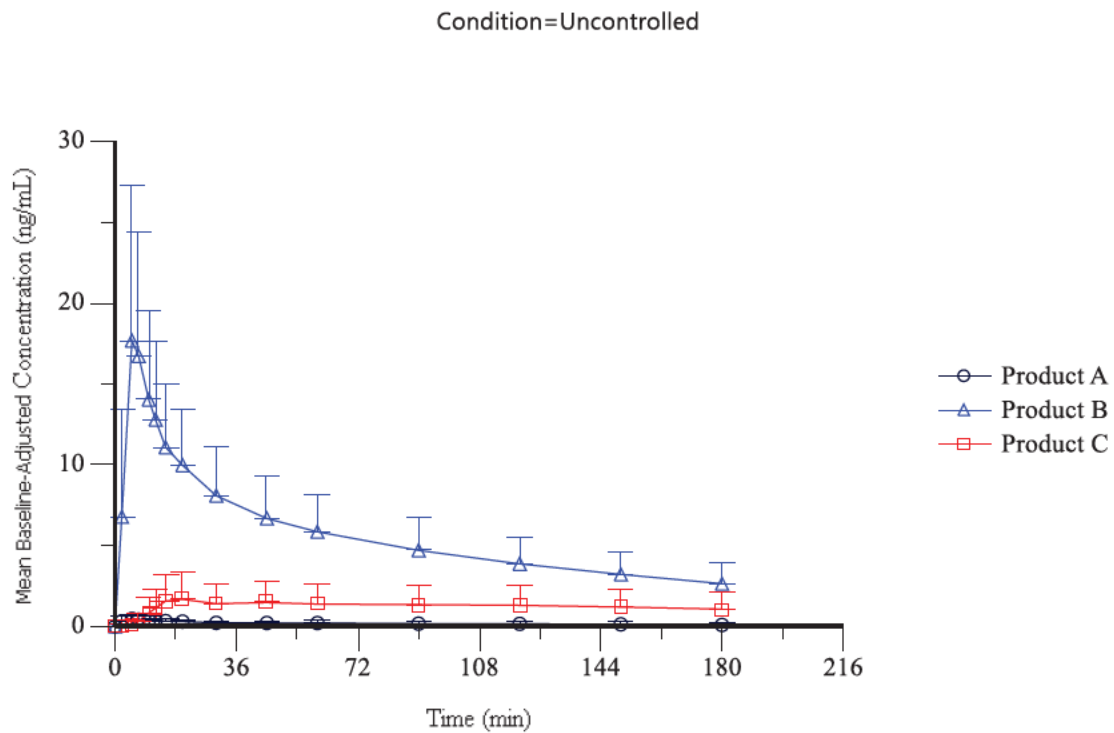


Table VIII.D-19. Summary of baseline-adjusted plasma nicotine PK values

| Product | Condition | AUC (ng*min/ml) | C _{max} (ng/ml) | t _{max} (min) | T _½ (min) |
|--------------|------------------|-----------------------|-----------------------------|---------------------------|-------------------------|
| Usual Brand | Controlled Use | 931.994 [#] | 13.684 [#] | 7 | 132.80 |
| VLN™ Menthol | Controlled Use | 30.449 ^{**} | 0.404 ^{**} | 7 | 97.14 |
| Nicotine Gum | Controlled Use | 359.257 [*] | 3.074 [*] | 45 | 135.35 |
| Usual Brand | Uncontrolled Use | 1035.256 [#] | 19.236 [#] | 7 | 105.73 |
| VLN™ Menthol | Uncontrolled Use | 33.503 ^{**} | 0.534 ^{**} | 7 | 120.12 |
| Nicotine Gum | Uncontrolled Use | 231.736 [*] | 1.987 [*] | 20 | 137.46 |

* p<0.0001 to Usual Brand

p<0.0001 to Nicotine Gum

Three different questionnaires were administered to assess subjective endpoints: Intent to Use Product Again, Product Effects, and Tobacco/ Nicotine Withdrawal. The intent to use was administer at 90 minutes after use. The other questionnaires were administered at 5, 15, 30, 60,

and 90 minutes after use. These assessments were performed after controlled and uncontrolled use of the products.

The Tobacco/Nicotine Withdrawal items were administered as 100-point VAS and were intended to measure withdrawal symptoms and craving. The VAS is anchored with “Not at All” on the left and “Extremely” on the right. The questionnaire items are as follows:

1. Urges to Smoke
2. Anxious
3. Difficulty Concentrating
4. Impatient
5. Craving a Cigarette

Craving and urges were statistically different between usual brand and VLN™ (Table VIII.D-20). There was no difference between VLN™ and gum for these parameters. Usual brand appeared initially suppress the urge to smoke and craving more than VLN™ or nicotine gum (Figure VIII.D-10). There were no differences between the controlled and uncontrolled smoking. These results suggest that VLN™ reduces the urge and craving, but not quite to the level of usual brand.

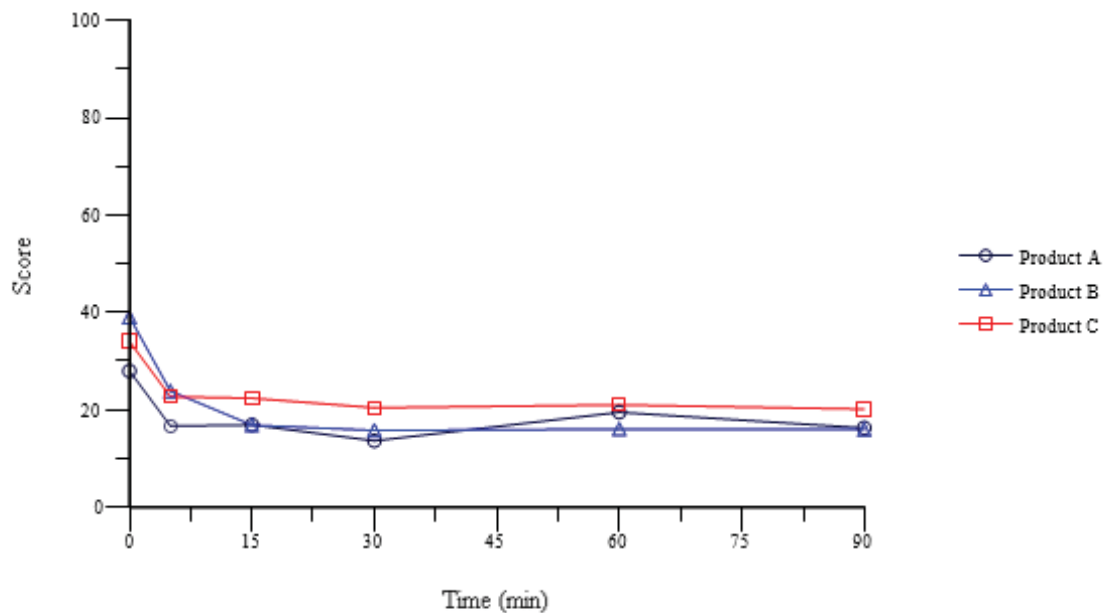
Table VIII.D-20. Inferential Analysis of Direct Effects Questionnaire.

| Question | Comparison | LSM | | LSM Difference (SE) | 95% CI | P-value |
|--|---|-------|-------|---------------------|----------------|---------|
| | | Test | Ref | | | |
| Is the product “Satisfying” right now? | VLN™ Menthol Cigarette vs. Menthol Own- brand Cigarette | 47.34 | 85.95 | -38.61 (4.68) | -47.78, -29.44 | <0.0001 |
| | VLN™ Menthol Cigarette vs. Nicotine Gum | 47.34 | 50.15 | -2.81 (4.68) | -11.98, 6.35 | 0.5443 |
| | Mentholated Own-brand Cigarette vs. Nicotine Gum | 85.95 | 50.15 | 35.80 (4.66) | 26.67, 44.93 | <0.0001 |

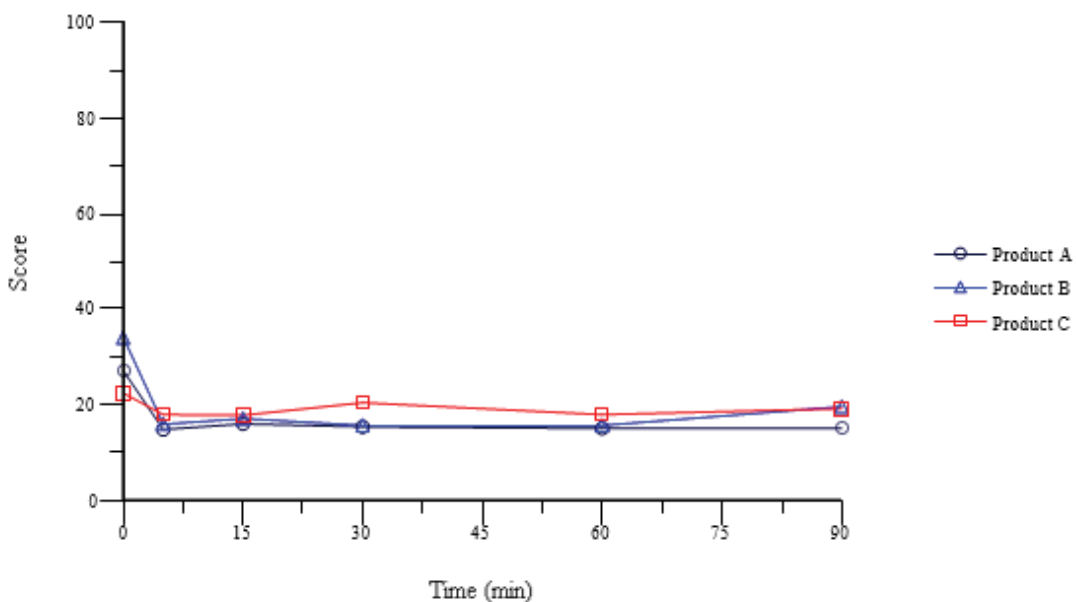
| Question | Comparison | LSM | | LSM Difference (SE) | 95% CI | P-value |
|--|--|-------|-------|---------------------|----------------|---------|
| | | Test | Ref | | | |
| Is the product making you feel “Calm” right now? | VLN™ Menthol Cigarette vs. Mentholated Own-brand Cigarette | 53.41 | 76.58 | -23.17 (4.30) | -31.59, -14.74 | <0.0001 |
| | VLN™ Menthol Cigarette vs. Nicotine Gum | 53.41 | 58.59 | -5.18 (4.30) | -13.61, 3.25 | 0.2262 |
| | Mentholated Own-brand Cigarette vs. Nicotine Gum | 76.58 | 58.59 | 17.99 (4.27) | 9.63, 26.35 | <0.0001 |
| Is the product helping you “Concentrate” right now? | VLN™ Menthol Cigarette vs. Mentholated Own-brand Cigarette | 46.90 | 67.81 | -20.91 (4.81) | -30.34, -11.48 | <0.0001 |
| | VLN™ Menthol Cigarette vs. Nicotine Gum | 46.90 | 47.65 | -0.75 (4.80) | -10.16, 8.67 | 0.8750 |
| | Mentholated Own-brand Cigarette vs. Nicotine Gum | 67.81 | 47.65 | 20.16 (4.79) | 10.77, 29.55 | <0.0001 |
| Is the product making you feel more “Awake” right now? | VLN™ Menthol Cigarette vs. Mentholated Own-brand Cigarette | 41.83 | 65.84 | -24.01 (4.87) | -33.55, -14.48 | <0.0001 |
| | VLN™ Menthol Cigarette vs. Nicotine Gum | 41.83 | 43.70 | -1.87 (4.88) | -11.44, 7.70 | 0.6991 |
| | Mentholated Own-brand Cigarette vs. Nicotine Gum | 65.84 | 43.70 | 22.14 (4.86) | 12.63, 31.66 | <0.0001 |
| Would you like “More” of the product right now? | VLN™ Menthol Cigarette vs. Mentholated Own-brand Cigarette | 42.50 | 74.72 | -32.22 (5.04) | -42.10, -22.35 | <0.0001 |
| | VLN™ Menthol Cigarette vs. Nicotine Gum | 42.50 | 39.42 | 3.08 (5.03) | -6.77, 12.94 | 0.5366 |
| | Mentholated Own-brand Cigarette vs. Nicotine Gum | 74.72 | 39.42 | 35.30 (4.99) | 25.52, 45.09 | <0.0001 |

Figure VIII.D-10. Mean tobacco/nicotine withdrawal questionnaire responses following product administration (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

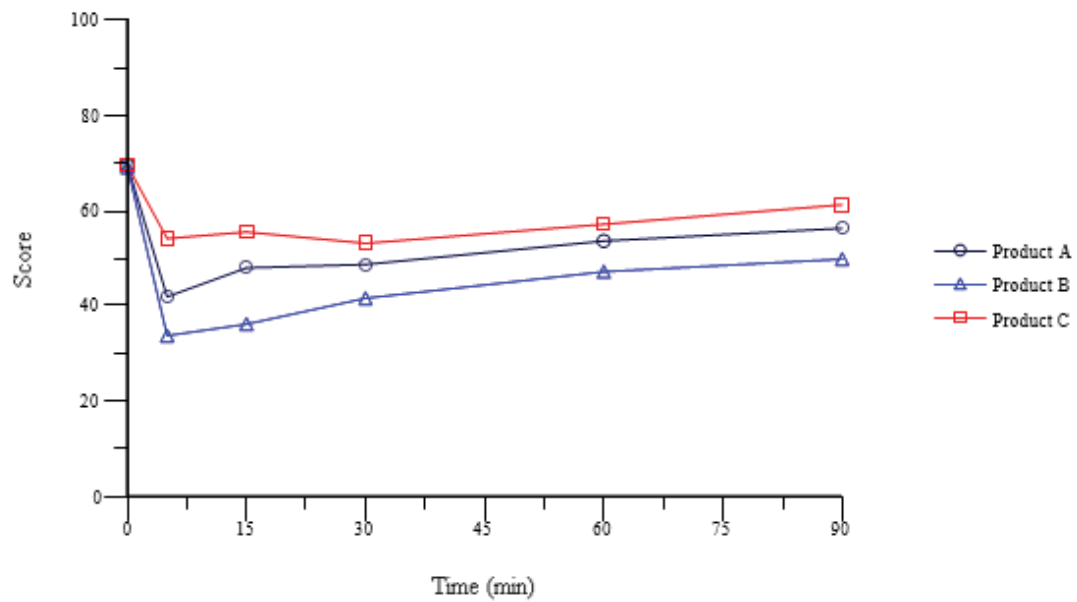
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Anxious



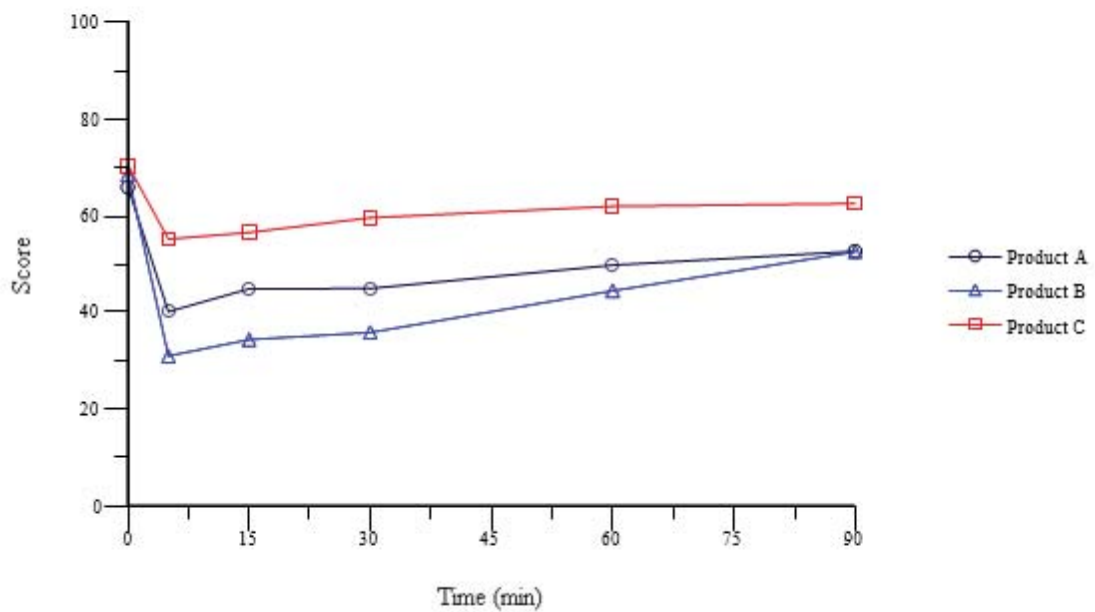
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Anxious



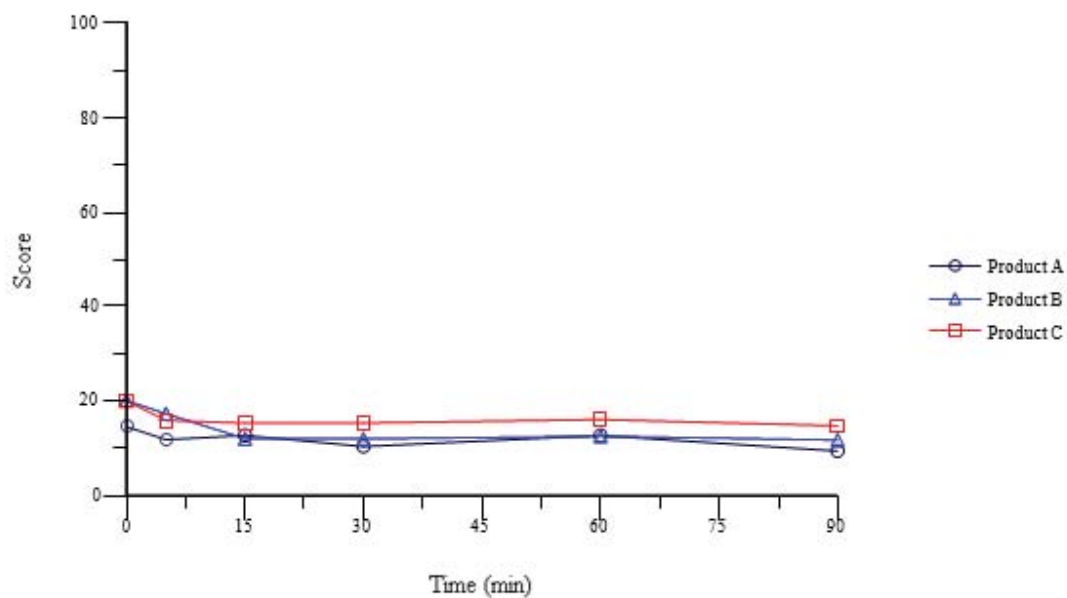
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



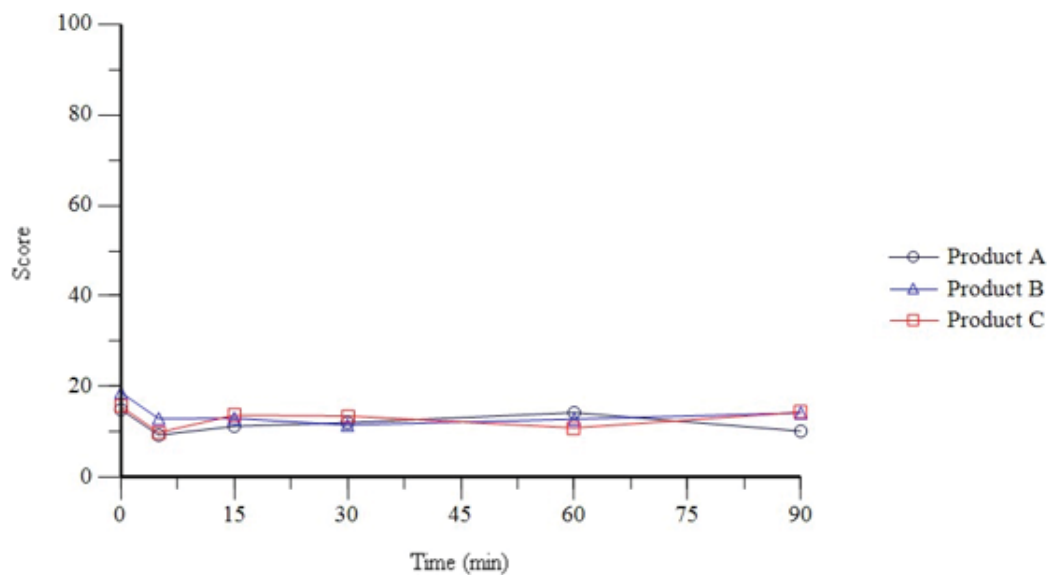
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



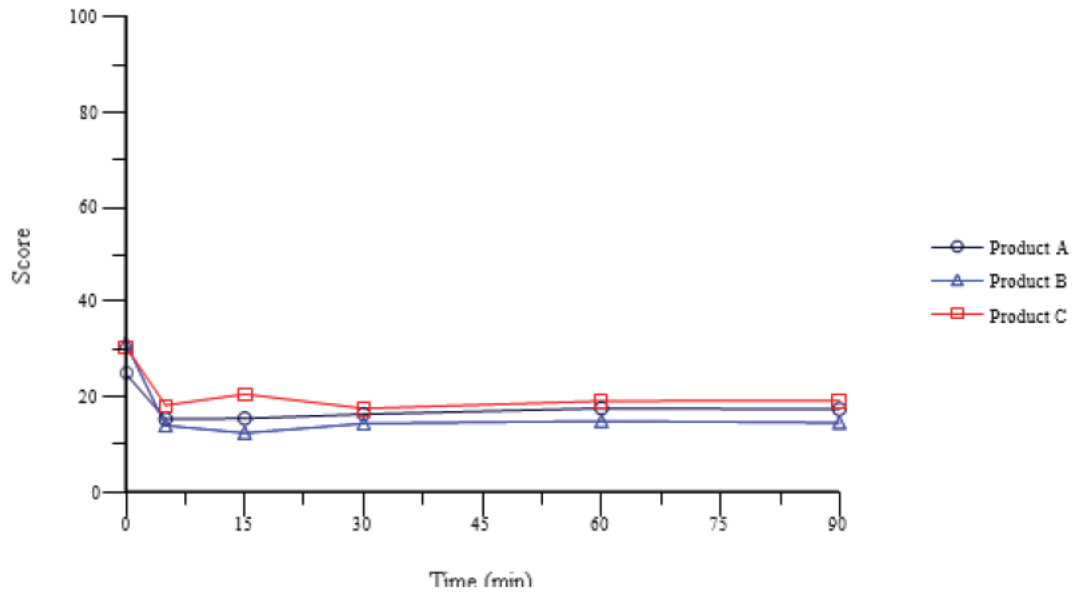
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Difficulty Concentrating



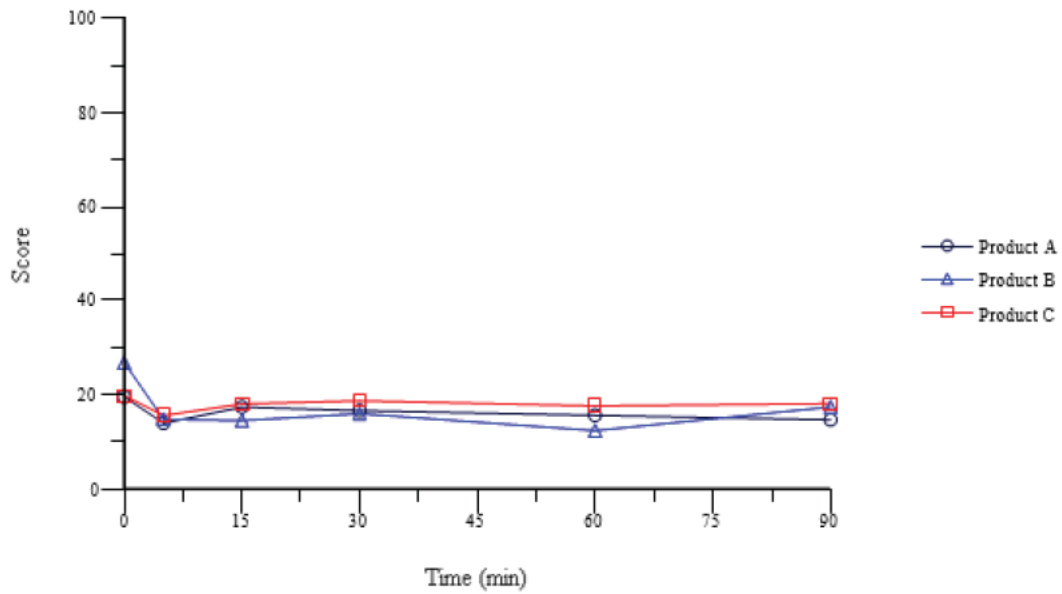
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Difficulty Concentrating



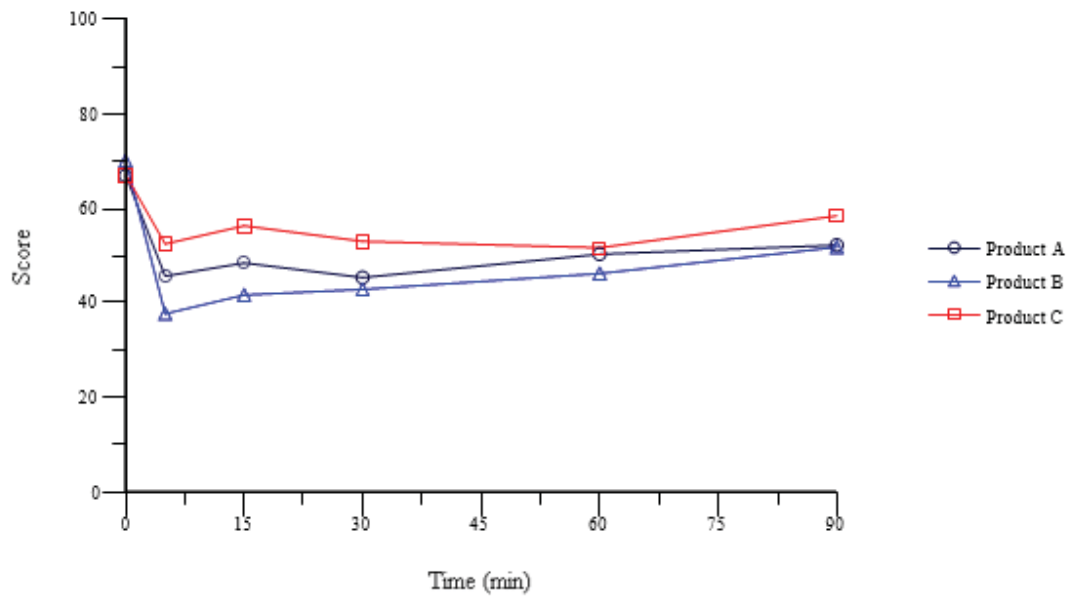
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Impatient



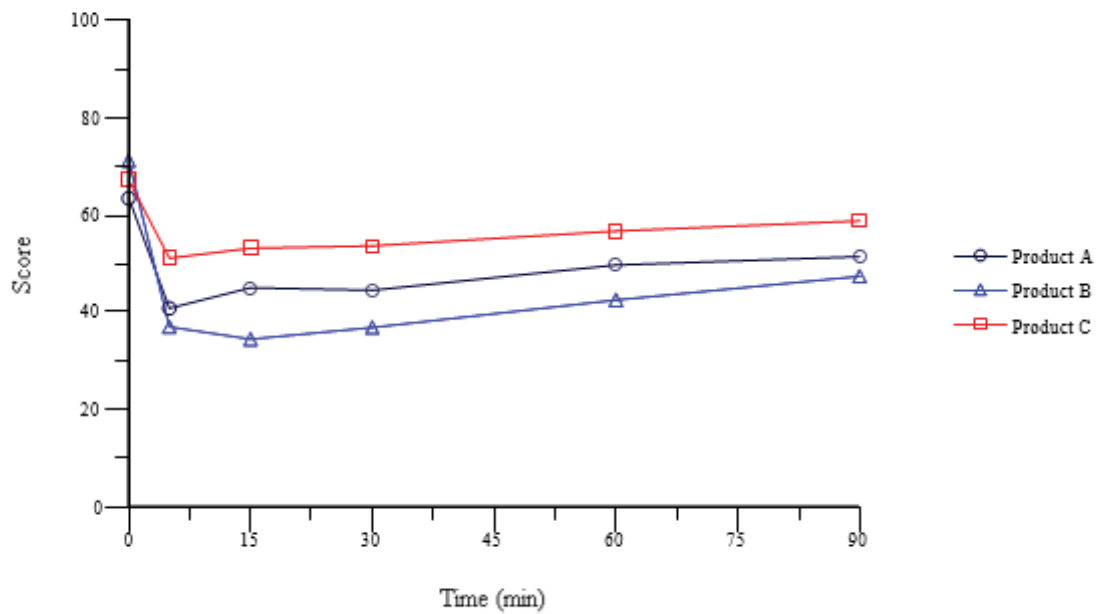
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Impatient



Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges



Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges

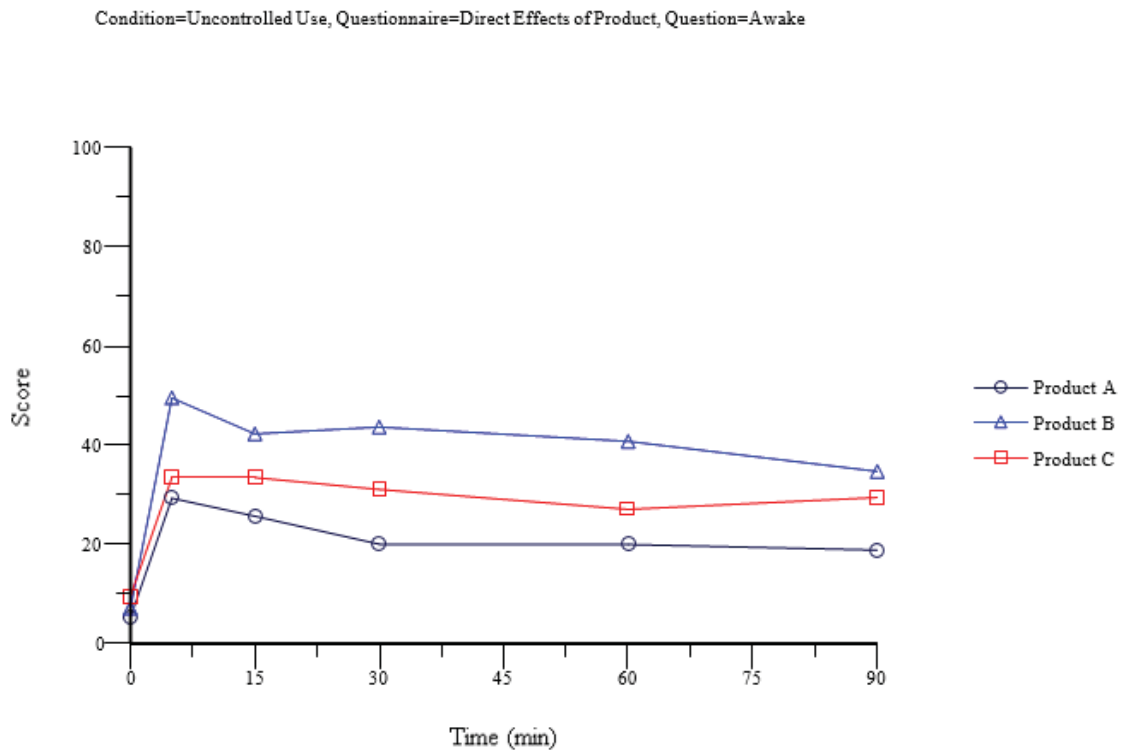
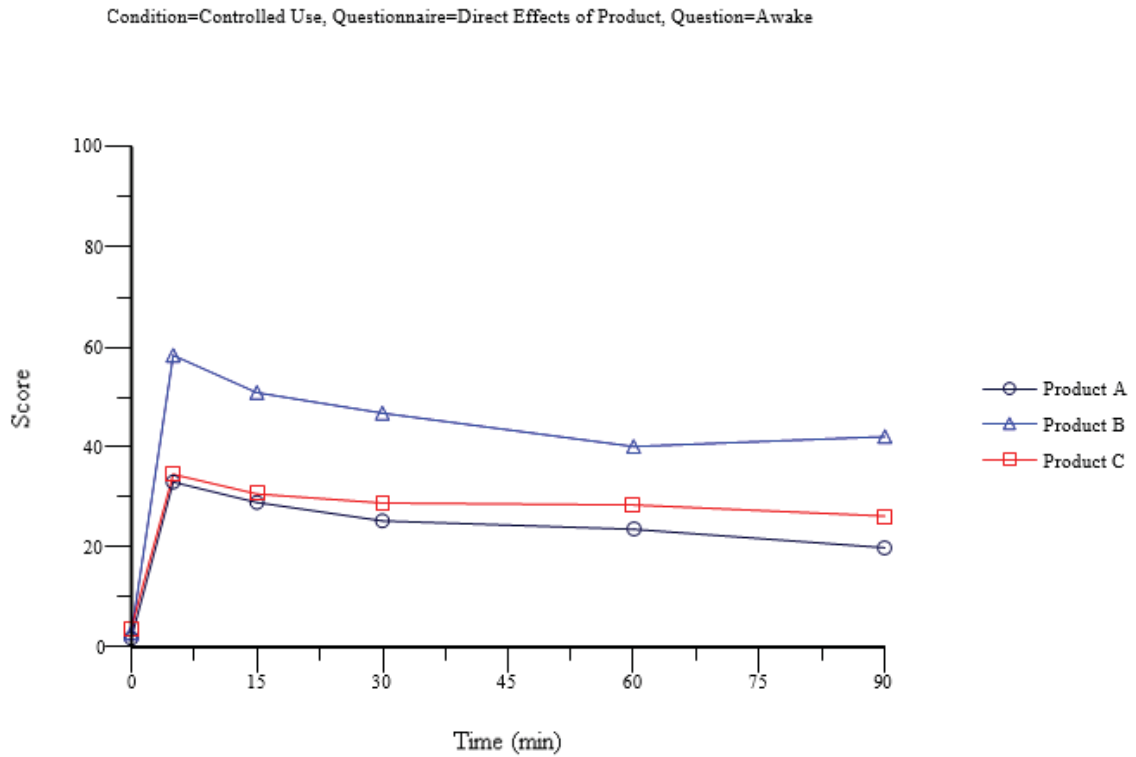


The Direct Effects of Product items were administered as 100-point VAS and were intended to measure the effects of the product being sampled at the moment. The VAS is anchored with “Not at All” on the left and “Extremely” on the right. The questionnaire items were as follows:

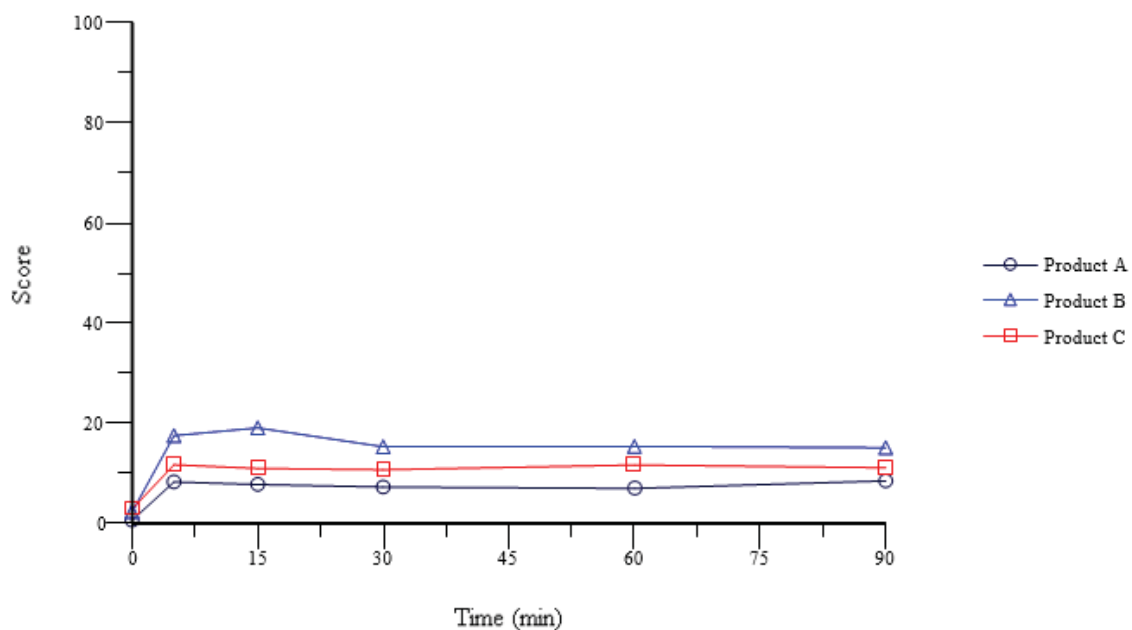
1. Is the product “Pleasant” right now?
2. Is the product “Satisfying” right now?
3. Is the product making you feel “Calm” right now?
4. Is the product helping you “Concentrate” right now?
5. Is the product making you feel more “Awake” right now?
6. Is the product making you feel “Sick” right now?
7. Is the product reducing your “Hunger” for food right now?
8. Would you like “More” of the product right now?

The effects (E_{max}) of VLN™ were statistically less than usual brand for all measures on the direct product effects questionnaire under both controlled and uncontrolled usage. VLN™ was not different from nicotine gum (Figure VIII.D-11). There was a tendency that usual brand made the subjects more awake, feeling calmer, helped them concentrate, and wanting more product. The usual brand also tended to be more satisfying and pleasant. The usual brand was statistically different from VLN™ for the question Is the product “Pleasant” right now? VLN™ was not different from nicotine gum.

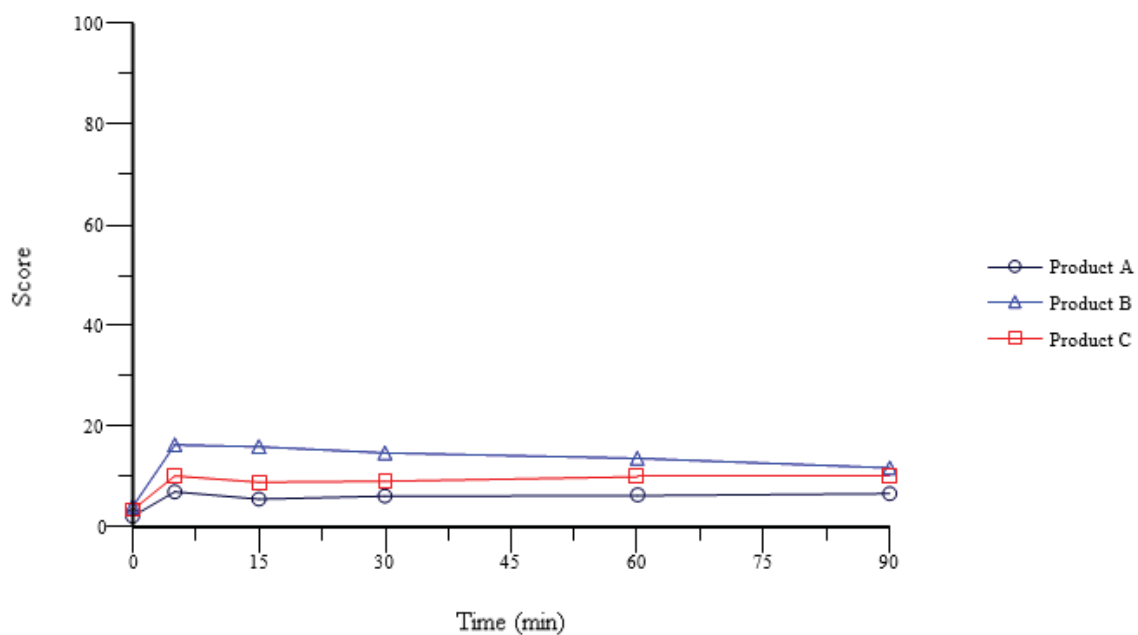
Figure VIII.D-11. Mean direct effect of product questionnaire responses following product administration (Product A = VLN™ Menthol, Product B = Usual Brand, Product C = 4 mg Nicotine gum).



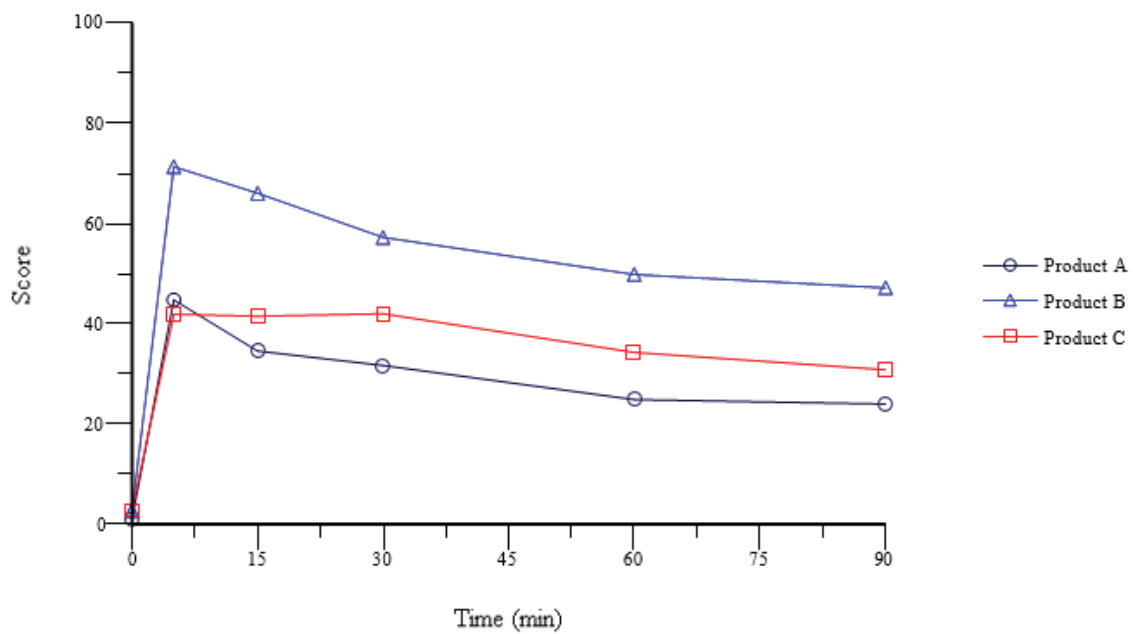
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Hunger



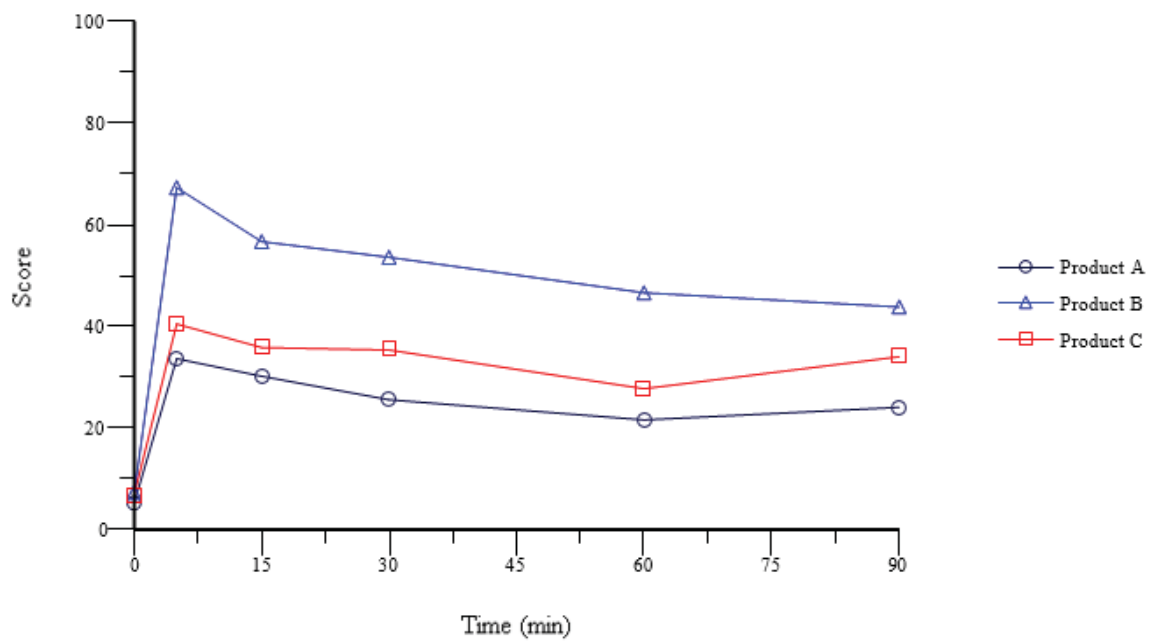
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Hunger



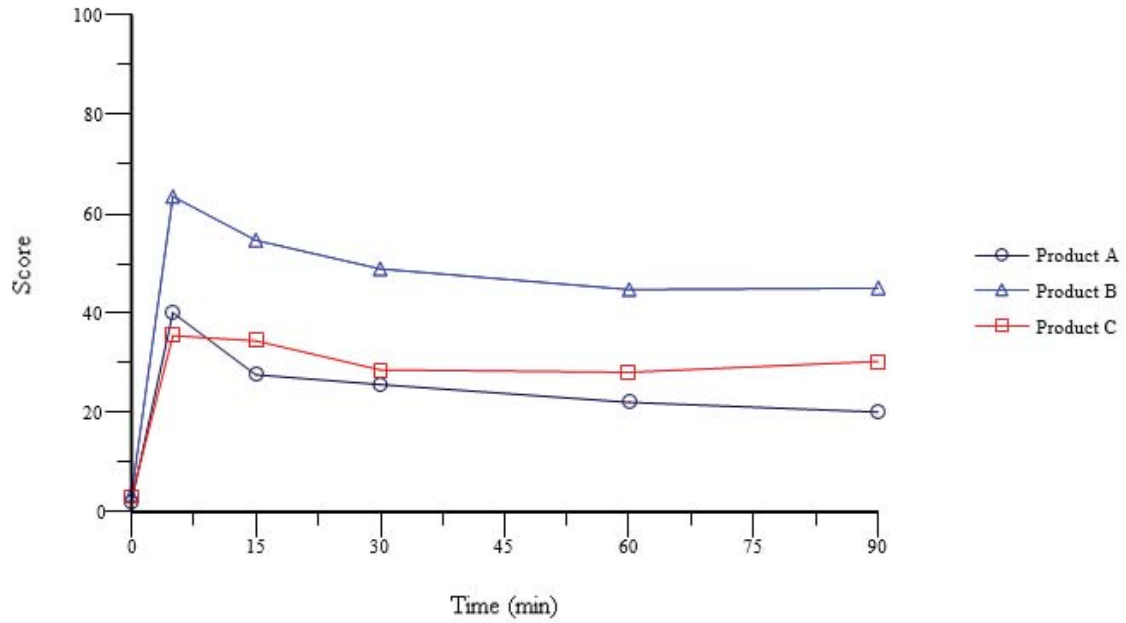
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Calm



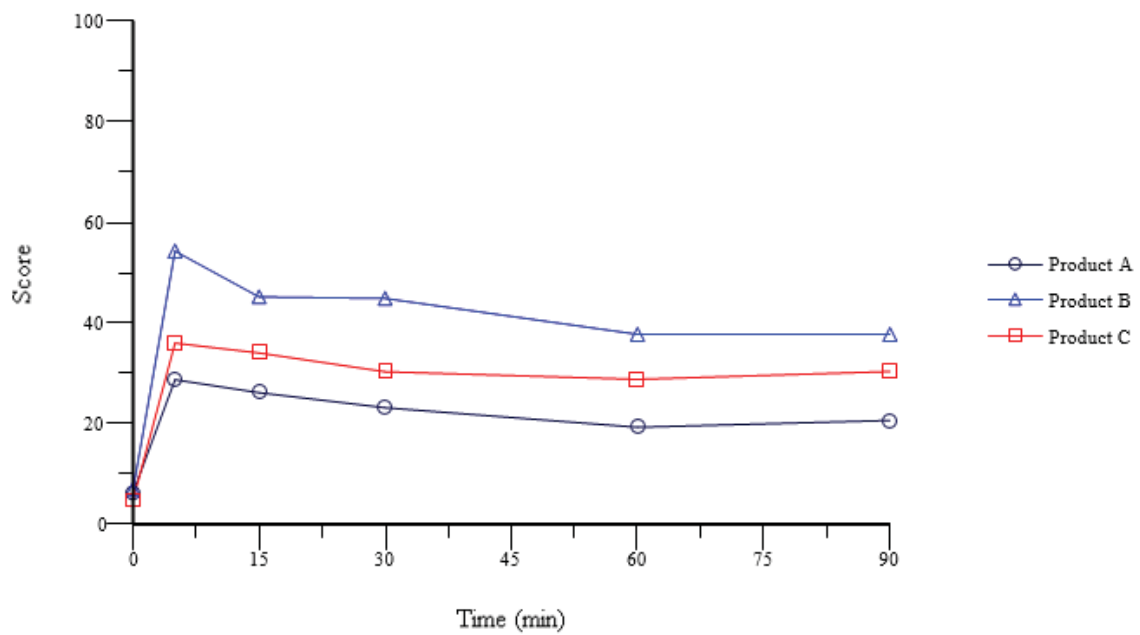
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Calm



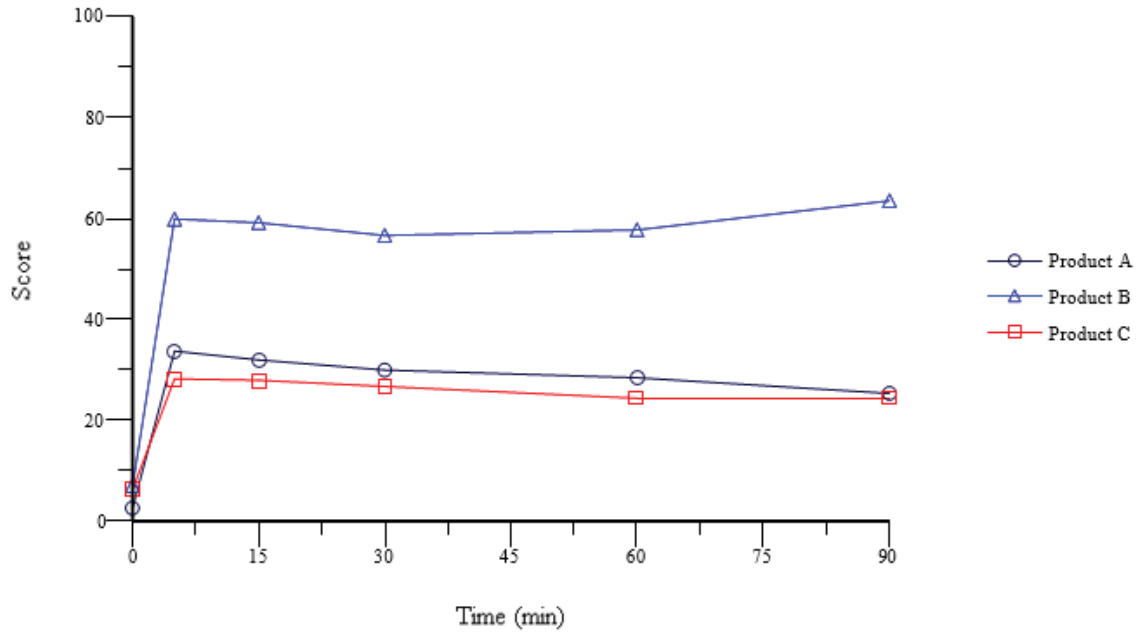
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Concentrate



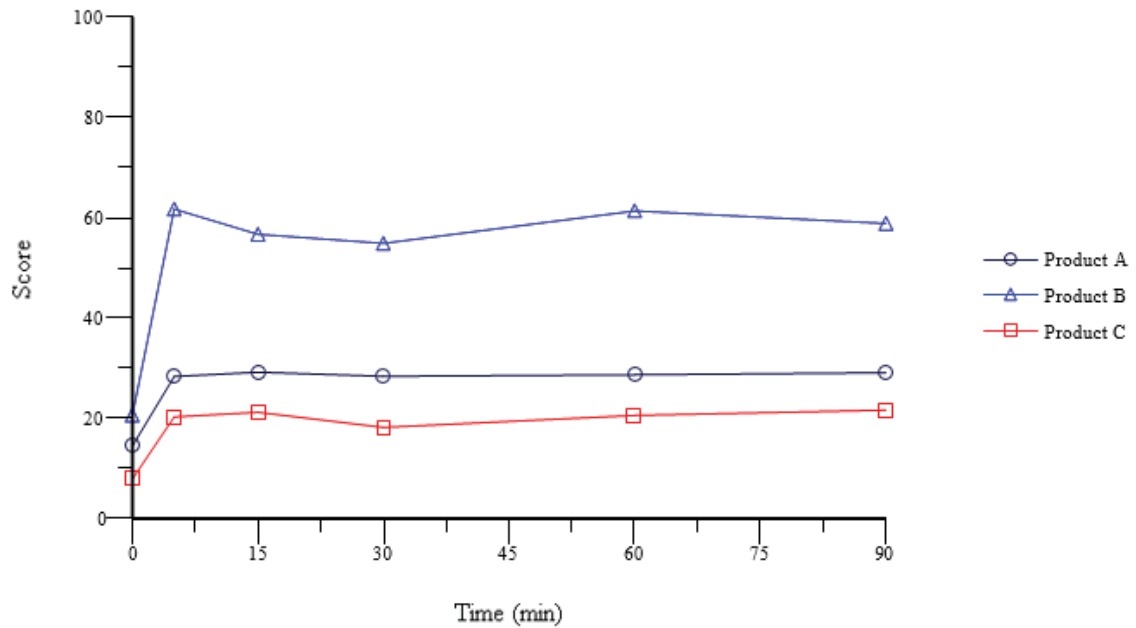
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Concentrate



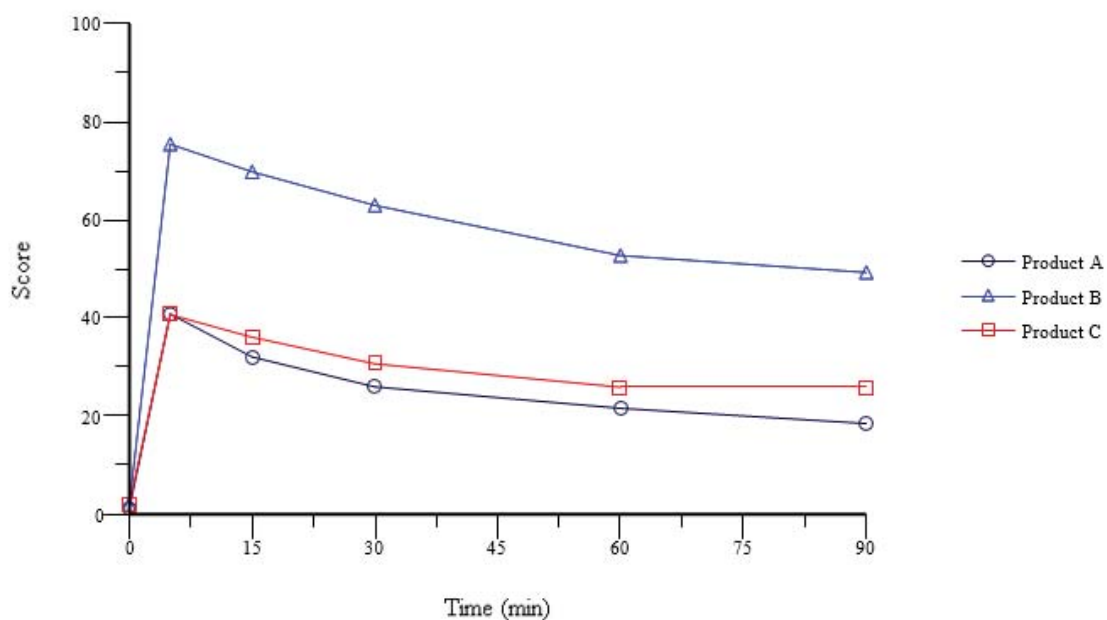
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=More



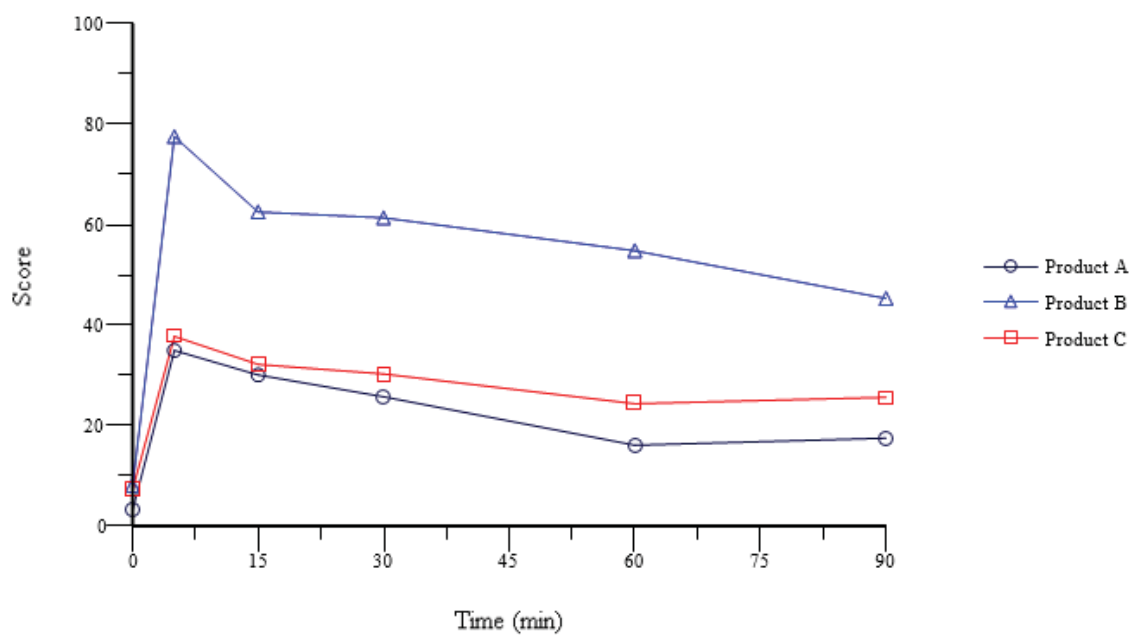
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=More



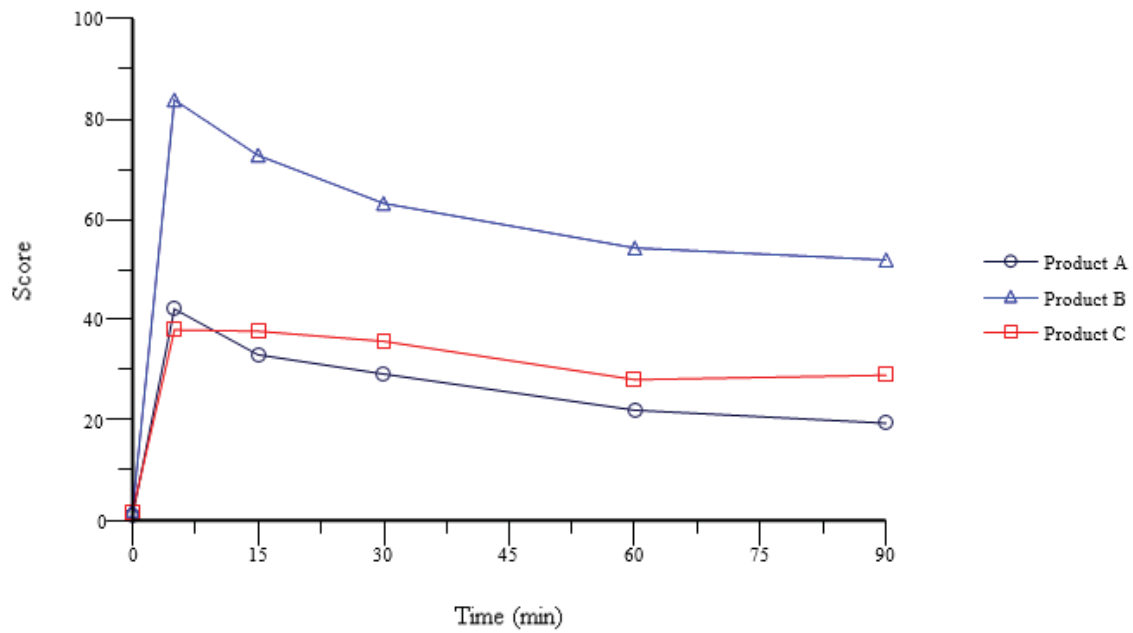
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Pleasant



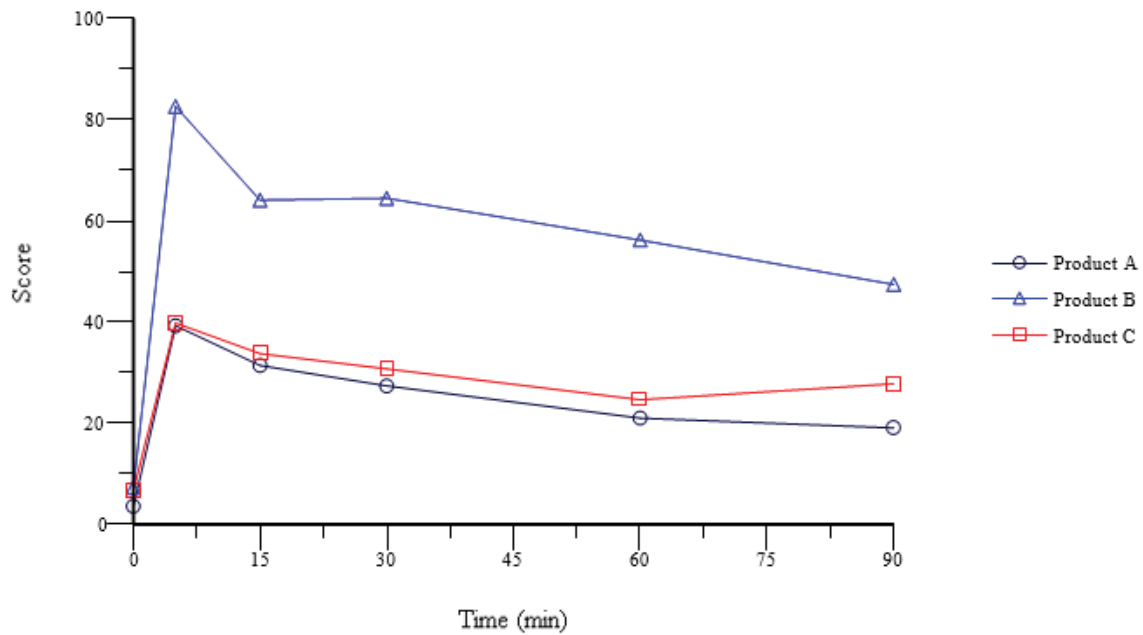
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Pleasant



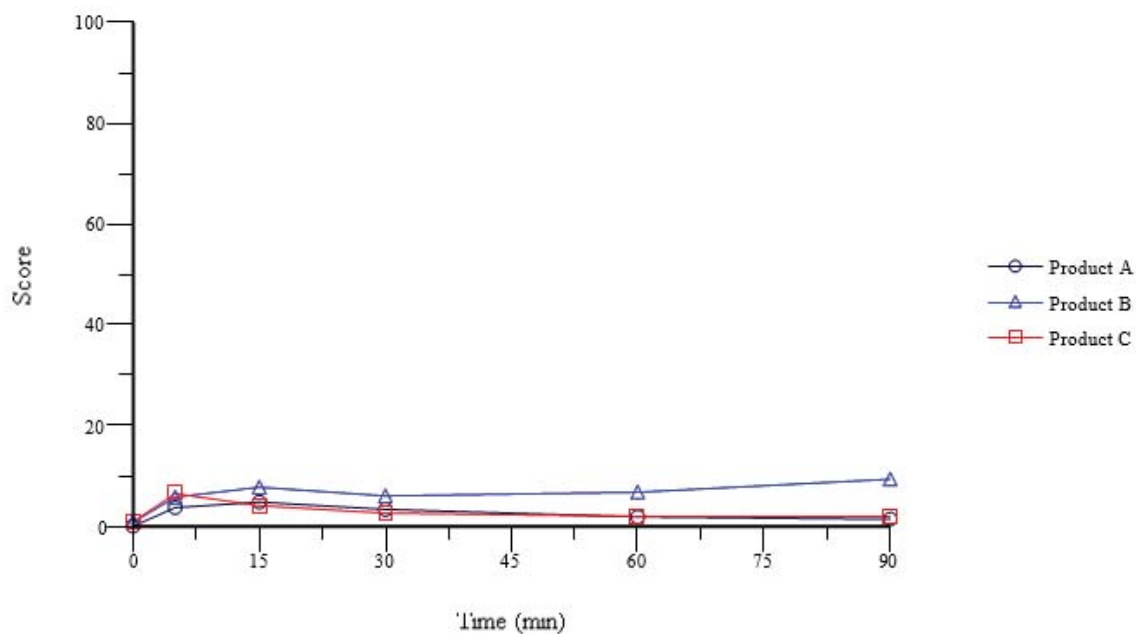
Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Satisfy



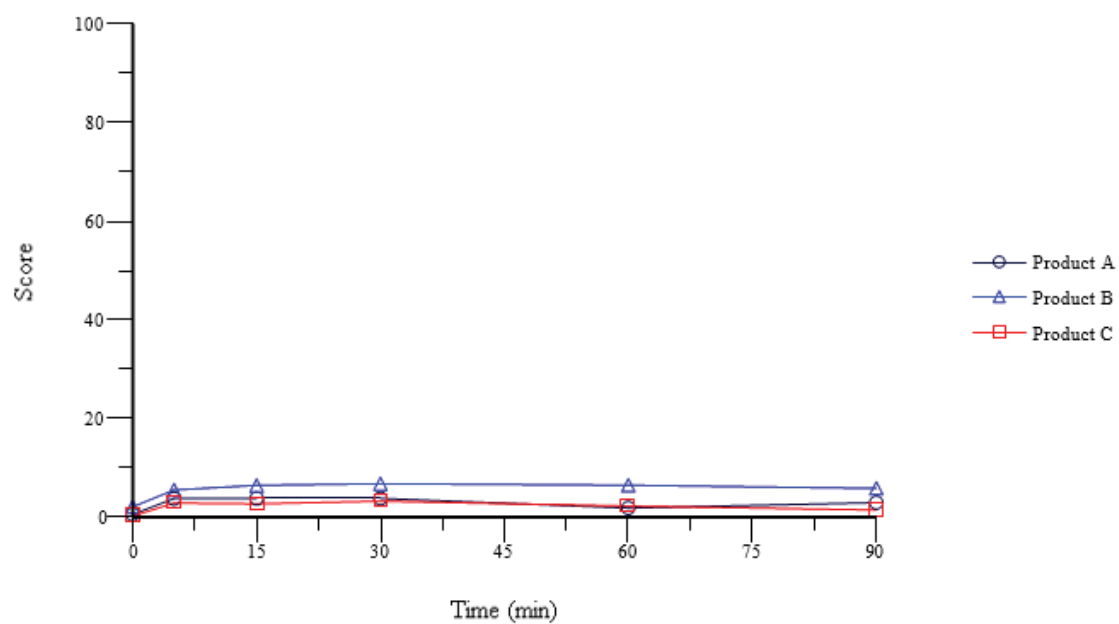
Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Satisfy



Condition=Controlled Use, Questionnaire=Direct Effects of Product, Question=Sick



Condition=Uncontrolled Use, Questionnaire=Direct Effects of Product, Question=Sick



The Use the Product Again questionnaire is a bipolar 100-point VAS used to assess how much a subject would be willing to use the sampled product again. The VAS is anchored by “Definitely Would Not” on the left and “Definitely Would” on the right; the neutral point is also labeled with an anchor (“Don’t Care”). Table VIII.D-21 shows the results of the Use the Product Again Questionnaire administered after Part A with *ad libitum* smoking. VLN™ had the lowest mean score of 42 with usual brand rating 96. Nicotine gum was similar to VLN™ with 46. The results with VLN™ Menthol suggest that the subjects were indifferent about whether they would use the products again.

Table VIII.D-21. Use the product again results after *ad libitum* use.

| Parameter | Statistic | VLN™ Menthol Cigarette N= 58 | Own-brand Cigarette N=58 | Nicotine Gum N=58 |
|--------------------------|-----------|---------------------------------------|--------------------------------|----------------------|
| Use the Product Again | Mean (SD) | 42.0 (31.50) | 95.6 (11.29) | 46.2 (31.57) |
| | Median | 41.5 | 100.0 | 47.5 |
| | Min, Max | 0, 100 | 44, 100 | 0, 100 |

Conclusions:

The primary objective of this study was to evaluate the abuse liability of VLN™ Menthol cigarettes compared with own-brand menthol cigarettes and nicotine polacrilex gum, by assessing subjective effects such as urge to smoke and pleasantness under controlled and uncontrolled use conditions. An additional objective was to compare the plasma nicotine PK profile between VLN™ Menthol cigarettes, mentholated own-brand cigarettes, and nicotine polacrilex gum. Product use behaviors under controlled and uncontrolled use conditions were

also evaluated to determine whether smokers' product use patterns were altered when using lower nicotine products.

Overall, analysis of the primary endpoints of Urges to Smoke (VAS Emax_urge(controlled)) and Pleasant VAS Emax_plst(controlled) showed that use of mentholated own-brand cigarette under Controlled Use conditions in Part B was associated with statistically significant greater reductions in subject-reported urges to smoke and greater ratings of pleasantness compared with nicotine gum, thereby confirming study validity. Although the VLN™ Menthol cigarette was associated with lower ratings of pleasantness compared with mentholated own-brand cigarette, the two products did not statistically differ on the primary endpoint of reductions in subject-reported urges to smoke. In addition, comparisons between VLN™ Menthol cigarette and nicotine gum revealed statistically significant greater reductions in the urges to smoke following use of VLN™ Menthol cigarette, and the two products had comparable ratings of pleasantness. Analysis of PK data showed that under Controlled conditions, peak and overall exposure to nicotine was statistically significantly lower for the VLN™ Menthol cigarette compared with mentholated own-brand cigarette and nicotine gum. Therefore, despite lower nicotine exposure and lower or similar ratings of pleasantness, VLN™ cigarettes were considered as effective in reducing the urges to smoke as mentholated own-brand cigarettes and more effective in reducing the urges to smoke compared with nicotine gum, a currently marketed nicotine replacement therapy.

Consistent with the findings on the Pleasant VAS primary endpoint, under Controlled Use conditions, reductions in craving a cigarette and difficulty concentrating, two subscales of the Tobacco/Nicotine Withdrawal Scale, were statistically significantly lower for VLN™ Menthol cigarette and nicotine gum compared with own brand cigarette. In contrast, scores on the Anxious

VAS were comparable following use of VLN™ Menthol cigarette and mentholated own-brand cigarette, suggesting that subjects experienced similar reductions in anxiety following use of both combustible products notwithstanding marked differences in nicotine exposure. Use of a VLN™ Menthol cigarette was also associated with greater reductions in craving a cigarette and less anxiety compared with use of nicotine gum. The other item in the scale (i.e., Impatient VAS) did not differ between products under Controlled Use conditions.

When subjects were permitted to use the products under Uncontrolled conditions in Part B, mentholated own-brand cigarette was associated with greater reductions in subject-reported urges to smoke and cigarette craving compared with the other two products. Although no differences in urges to smoke were observed between VLN™ Menthol cigarettes and nicotine gum, use of the VLN™ Menthol cigarettes was associated with a greater reduction in craving a cigarette compared with nicotine gum. In addition, VLN™ Menthol cigarettes were as effective in reducing anxiety as the other two products. The other items in the scale (i.e., Difficulty Concentrating VAS and Impatient VAS) did not differ between products under Uncontrolled Use conditions. PK data were consistent under the Uncontrolled Use conditions, with lower peak and overall exposure to nicotine for VLN™ cigarette compared with mentholated own-brand cigarette and nicotine gum.

In terms of overall product effects, during controlled use, VLN™ Menthol cigarette and nicotine gum were rated as being less satisfying than mentholated own-brand cigarette. In addition, both products were associated with a lower magnitude of effects related to feeling calm and more awake, feeling less hungry, helping with concentration, and wanting more of the

product compared with mentholated own-brand cigarette. In general, these results were consistent when subjects used the products under uncontrolled conditions, suggesting that regardless of use condition, VLN™ Menthol cigarettes were associated with weaker “positive,” or reinforcing product effects, compared with mentholated own-brand cigarettes, and were associated with similar reinforcing effects when compared with nicotine gum. For both Controlled and Uncontrolled Use conditions, minimal negative effects (i.e., Sick VAS) were observed across products.

In Part A, when subjects were permitted to use each product ad libitum over a period of 4 hours, and in Part B during Controlled and Uncontrolled Use conditions, subjects were asked to rate their preference for using each of the products again at the end of the product use session. In both Part A and Part B, mean scores on Use Product Again VAS were markedly higher for mentholated own-brand cigarette compared with VLN™ Menthol cigarette. The mean score for VLN™ Menthol cigarette was within the neutral range and did not notably differ with those for nicotine gum, suggesting that subjects were relatively indifferent about using these products again.

Patterns of product use were also recorded during Part A, and results show that subjects smoked a similar number of VLN™ Menthol cigarettes compared with mentholated own-brand cigarettes over 4 hours (7 or 6 cigarettes, respectively), and spent a similar amount of time smoking each product. Patterns of use were also assessed during the Uncontrolled Use condition of Part B; subjects were found to inhale a slightly lower number of puffs when using VLN™ Menthol cigarettes as compared with mentholated own-brand cigarettes, however, there was no difference in the duration of inhalation between the two products. These findings suggest that

despite the lower nicotine content in VLN™ Menthol cigarettes, subjects were not taking longer puffs or smoking substantially more VLN™ mentholated cigarettes to compensate.

The primary endpoints in the study showed that use of the VLN™ Menthol cigarette under single controlled product use conditions was associated with similar reductions in urges to smoke as own-brand mentholated cigarettes despite lower peak ratings of pleasantness and markedly lower peak nicotine exposure in a sample of adult smokers. VLN™ Menthol cigarettes also had statistically significantly lower nicotine exposure compared with nicotine polacrilex gum but were rated to be as pleasant and were associated with greater reductions in urges to smoke. These results suggest that VLN™ cigarettes have lower abuse liability compared with own-brand mentholated cigarettes and similar abuse liability to nicotine polacrilex gum. In addition, VLN™ cigarettes show comparable effectiveness in reducing the urge to smoke and reducing withdrawal related anxiety as own-brand mentholated cigarettes and show greater reductions in the urge to smoke and cigarette craving compared with nicotine polacrilex gum, a currently marketed nicotine replacement therapy.

iii. 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)

(a) Study Design

This was an open-label, randomized, forced-switching study conducted at multiple study sites. Seventy (70) 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 cannot 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 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.

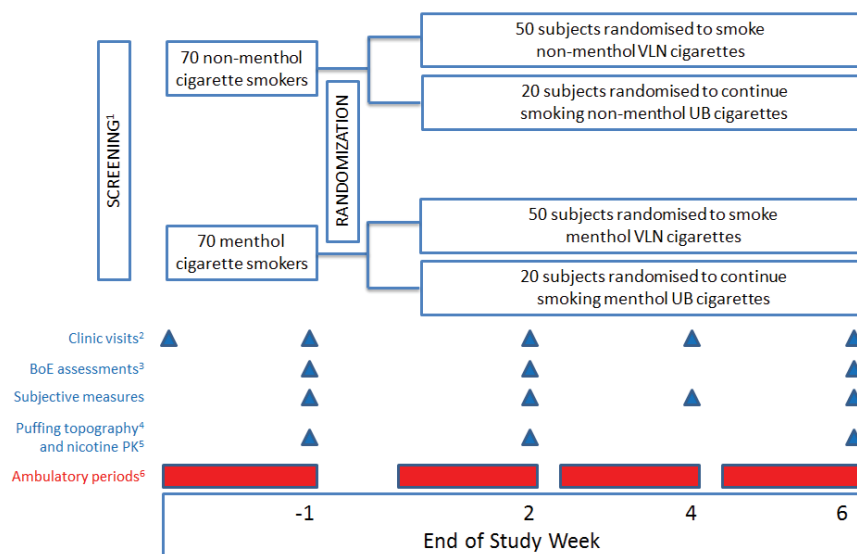
On Day -1 of Week 1, subjects were randomly selected to either remain smoking their non-menthol (20 subjects) or menthol (20 subjects) UB cigarettes, or to switch to smoking non-menthol (50 subjects) or menthol (50 subjects) VLN™ cigarettes as per their UB cigarette flavor.

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-12 below shows the study design. The study protocol is included with this application.

Figure VIII.D-12. 6-Week study design.



¹Including trial of VLN cigarettes.

²E-diary training at start of Week -1.

³24h urine BoE, blood COHb and plasma cotinine

⁴Subset of 18 subjects assigned to smoke non-menthol VLN cigarettes and 18 subjects assigned to smoke menthol VLN cigarettes

⁵Subset of 12 subjects assigned to smoke non-menthol VLN cigarettes and 12 subjects assigned to smoke menthol VLN cigarettes

⁶E-diary completion for cigarette consumption, and used cigarette butt collection

(b) Results

This study is still underway. The report will be submitted when it is completed.

iv. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of X-22 as a smoking cessation aid (NCT01400815).

The objective of this study (22nd Century Group 2011, IND 103,589 [pg297]) was to evaluate the efficacy of X-22 cigarettes as a cessation aid. X-22 was evaluated under IND 103,589. This was a prospective, randomized, multicenter, double-blinded, parallel, active controlled, phase II clinical trial in which 234 healthy smokers with an intent to quit were enrolled and followed over 19 weeks. The Company concluded that the study failed to demonstrate the efficacy X-22 under conditions of the test. The results of the study were reported to the FDA under IND annual updates. A final report was never written for the study. The IND is currently inactive. All available records from the Company related to the IND are included under IND

103,589. Additional information may possibly be found in the original IND submission and updates.

At the beginning of the treatment phase, subjects were randomized in a 1:1 ratio to receive either X-22 very low nicotine menthol cigarettes or active control menthol cigarettes and switched from smoking their usual brand to the test cigarettes. Subjects smoked their study cigarettes *ad libitum* for 6-weeks prior to the defined quit date. After the quit date, subjects were instructed to abstain from smoking or using any tobacco product and were evaluated for safety and efficacy during a 4-week abstinence phase and a 4-week follow-up phase. Exhaled CO and salivary cotinine were monitored. Nicotine intake was not a primary endpoint in this study. Semiquantitative monitoring of salivary cotinine was carried out using NicAlert test strips.

The hypothesis of this study was that greatly reducing the amount of nicotine compared with conventional, commercially-available cigarettes, including low-yield (“light” or “ultra light”) cigarettes, to very low levels may disrupt the behavioral and pharmacodynamic cues associated with smoking. Therefore, the active control cigarettes in this study were chosen to be similar to commercially-available low-yield cigarettes which have nicotine contents and machine smoking yields much greater than those of VLNC cigarettes (nicotine content of ca. 13 mg per cigarette vs. <1 mg per cigarette, and nicotine yield of 0.7 mg of nicotine per cigarette vs. ≤0.05 mg of nicotine per cigarette).

Healthy smokers who had planned to quit smoking were screened for eligibility at Visit 1 (Screening Phase), and all subjects received behavioral support through approximately 15-

minute individual counseling sessions at Visits 4, 5, 6, and 9, including distribution of printed materials. Subjects continued to smoke their usual brand *ad libitum* during Week 1.

One week following Screening, at Visit 2 (beginning of the Treatment Phase), eligible subjects were randomized (stratified by gender) in a 1:1 ratio to 1 of the 2 treatment arms:

- Group 1: X-22 Smoking Cessation Product
- Group 2: Active Control Cigarettes

At Visit 2, subjects switched from their usual brand (UB) cigarettes to X-22 cigarettes (Group 1) or blinded active control cigarettes (Group 2) and smoked the assigned study cigarettes *ad libitum* for 6 weeks prior to the target quit date. Visit 5/Week 6 was considered the “quit date” for all study subjects. Subjects were instructed to quit all smoking at midnight on the night before the Visit 5 appointment.

After randomization, during the Treatment and Abstinence Phases, subjects returned to the study center at 2-week intervals for 10 weeks (Visits 2 to 7) and received a telephone call from the site between visits at Weeks 1, 3, 5, 7, and 9.

During the Follow-up Phase, subjects received a follow-up telephone call at Week 14. At the Week 14 follow-up telephone call, subjects who reported that they had not smoked in the past 7 days were asked to return to the study site within 1 week for Visit 8. At Week 18, all subjects returned to the site for Visit 9, regardless of smoking status.

Cigarette consumption was evaluated using self-report diaries, and carbon monoxide (CO) by measurement of exhaled CO, and saliva cotinine concentration with a NicAlert test strip. Withdrawal symptoms were assessed using The Minnesota Nicotine Withdrawal Scale at each

study visit. The Sensory Questionnaire and the Fagerström Test of Nicotine Dependence were administered at study Visits 1 to 5. Safety was assessed by evaluation of AEs, physical examinations, clinical laboratory studies, concomitant medications, and measurement of heart rate, blood pressure, and body weight at each study visit. Table VIII.D-22 shows the schedule of assessments.

Table VIII.D-22. Schedule of study visits and assessments. (see next page)

| Assessments | Screen | Treatment | | | | | | | Abstinence | | | | Follow-up | | |
|--|---------|---------------|-----------------|--------------|-----------------|--------------|-----------------|------------------------------|-----------------|---------------------------|-----------------|-----------------------------|----------------------------|----------------------|---------------|
| | Visit 1 | Visit 2 | TC ^e | Visit 3 | TC ^e | Visit 4 | TC ^e | Visit 5 Quit ^h | TC ^e | Visit 6 | TC ^e | Visit 7/ ET ^j | TC ^e | Visit 8 ⁿ | Visit 9 |
| | Day -7 | Day 0 ±2 d | Wk 1 ±2 d | Wk 2 ±2 d | Wk 3 ±2 d | Wk 4 ±2 d | Wk 5 ±2 d | Wk 6 ±2 d | Wk 7 ±2 d | Wk 8 ±2 d ⁱ | Wk 9 ±2 d | Wk 10 +4 d ^k | Wk 13 +3 d ^m | Wk 14 ±2 d | Wk 18 ±2 d |
| Informed Consent | X | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | |
| Plan to Quit Smoking Query | X | | | | | | | | | | | | | | |
| Urine Drug Screen | X | | | | | | | | | | | | | | |
| Clinical Laboratory Tests ^a | X | | | | | | | X | | | | X (ET only) ^l | | | |
| Electrocardiogram | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Smoking History | X | | | | | | | | | | | | | | |
| Dispense Behavioral Support ^b | | | | | | X | | X | | X | | | | | X |
| Concomitant Medications | X | X | | X | | X | | X | | X | | X | | X | X |
| Physical Examination ^c | X | | | | | | | | | | | X | | | |
| Urine Pregnancy Test ^d | X | | | | | | | | | | | X | | | |
| Alcohol Intake | X | | | | | | | | | | | | | | |
| Blood Pressure and Heart Rate | X | X | | X | | X | | X | | X | | X | | X | X |
| Height | X | | | | | | | | | | | | | | |
| Weight | X | X | | X | | X | | X | | X | | X | | X | X |
| Carbon Monoxide Level | X | X | | X | | X | | X | | X | | X | | X | X |
| Saliva Cotinine Level | X | X | | X | | X | | X | | X | | X | | X | X |
| Randomization | | X | | | | | | | | | | | | | |
| Sensory Questionnaire | X | X | | X | | X | | X | | | | | | | |
| Withdrawal Questionnaire | X | X | | X | | X | | X | | X | | X | | X | X |
| FTND | X | X | | X | | X | | X | | | | | | | |
| Self-report Diary | X | X | | X | | X | | X | | X | | X | | X | X |
| Dispense Study Product | | X | | X | | X | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---------------------------------------|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Return Unused Study Product | | | | X | | X | | X | | | | | | | |
| Check Supply of Study Product | | | X | | X | | X | | | | | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Telephone Call ^e | | | X | | X | | X | | X | | X | | X | | |
| Treatment Guess ^f | | | | | | | | | | | | X | | | |
| Smoking Abstinence Query ^g | | | | | | | | | | X | | X | X | X | X |

AE=adverse events; d=days; ET=early termination; FTND= Fagerström Test of Nicotine Dependence; TC=telephone call; Wk=week

a Complete blood count and differential and clinical chemistries.

b Behavioral support included ~15-minute smoking cessation counseling sessions and supporting printed materials appropriate to the phase of the study.

c Physical examination included measurement of respiratory rate and temperature.

d Woman of childbearing potential only.

e The site called each subject between site visits During the Treatment Phase at Weeks 1, 3, and 5 to ensure that the subject had an adequate supply of investigational product and to obtain information regarding AEs. During the Abstinence Phase, at Weeks 7 and 9, the site called each subject to obtain information regarding AEs. During Follow-up, at Week 14, the site called each subject and question them about their smoking status; subjects who have smoked were questioned about AEs; subjects who have not smoked within the past 7 days were asked to come to the site within 1 week. The site also called each subject the day before each site visit to remind the subject of their appointment.

f Each subject was asked to guess which treatment group they were assigned to.

g All subjects were asked if they have smoked since the last visit and if they have smoked within the last 7 days.

h Visit 5 was the "Quit Date" (all subjects quit smoking at midnight on the night before Visit 5).

i Visit 6/Week 8 occurred between 12 to 16 days after the Quit date.

j Visit 7 assessments were performed for subjects who terminate the study early.

k Visit 7/Week 10 occurred between 28 to 32 days after the Quit date.

l Subjects who drop out of the study prior to Visit 5 also had laboratory studies completed at the Early Termination Visit. Subjects who completed Visit 5 did not need additional laboratory studies completed at Visit 7.

m The Week 13 telephone took place 4 to 7 days prior to Week 14.

n Only subjects who reported during their Week 13 telephone call that they had not smoked in the previous week completed Visit 8.

Table VIII.D-23 shows the weekly study and total cigarette consumption (includes all cigarettes smoked, both study and non-study). There was a trend for decreased cigarette consumption for the X-22 group. Total cigarette consumption did not appear different between X-22 and the active control. Weeks 8 and 10 were the cessation period. There were no differences between X-22 and the active control during the cessation phase. It appeared that there was more non-compliance (smoking non-study cigarettes) in the X-22 group than the active control. Median salivary levels of cotinine appeared decreased in the X-22 group. It appeared that there was significant consumption of non-study cigarettes during the study that impacted the results (Table VIII.D-23). By week 18 cotinine and exhaled CO indicated that there was no difference in the

abstinence rates for X-22 compared to the active control. The study was considered a failure in terms of cessation efficacy and no final report was written.

Table VIII.D-23. Cigarettes per week, compliance, and nicotine consumption (22nd Century Group 2012 [pg297]).

| Week | Study Cigarettes Smoked per Week (mean) | | Total No. of Cigarettes smoked per week (mean (SD)) | | Non-Study Cigarettes Smoked per Week (% of total) | | Median Salivary Cotinine NicAlert Score (mean (SD)) | | Exhaled CO (mean (SD)) | |
|------|---|----------------|---|-----------------|---|----------------|---|----------------|------------------------|----------------|
| | X-22 | Active Control | X-22 | Active Control | X-22 | Active Control | X-22 | Active Control | X-22 | Active Control |
| 0 | | | 126.3 (38.9) | 123.8 (38.8) | | | 3.7 (1.09) | 3.7 (1.10) | 24.2 (10.5) | 26.2 (10.3) |
| 2 | 155.0 | 151.2 | 170.1 (77.6) | 155.1 (64.4) | 8.9% | 2.5% | 2.6 (1.41) | 3.5 (1.15) | 25.5 (12.8) | 23.3 (9.7) |
| 4 | 129.6 | 146.5 | 135.3 (75.6) | 147.2 (64.0) | 6.2% | 0.5% | 2.6 (1.47) | 3.5 (1.15) | 22.9 (14.0) | 22.2 (10.9) |
| 6 | 117.3 | 138.6 | 122.4 (69.7) | 139.3 (51.3) | 6.2% | 0.5% | 2.6 (1.66) | 3.4 (1.12) | 14.6 (10.8) | 15.5 (10.2) |
| 8 | | | 28.1 (34.8) | 30.6 (34.9) | | | 2.7 (1.65) | 3.0 (1.51) | 16.5 (14.0) | 15.5 (11.7) |
| 10 | | | 34.9 (42.7) | 33.8 (37.5) | | | 2.9 (1.63) | 3.3 (1.55) | 16.6 (15.0) | 16.5 (11.3) |
| 14 | | | | | | | 1.8 (1.82) | 2.2 (1.76) | 5.1 (4.8) | 9.2 (10.7) |
| 18 | | | | | | | 3.0 (1.72) | 2.9 (1.72) | 16.9 (13.3) | 17.5 (11.8) |

Conclusion: Test CPD and salivary cotinine appeared to be reduced. Compliance was higher in test group than control. There was no effect on abstinence.

v. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation (IND 69,185).

A randomized, double-blind, active controlled, parallel group, multi-center phase II clinical trial was reported by Becker *et al.*, (2008) [pg297] to evaluate the efficacy of reduced-nicotine cigarettes as a novel smoking cessation treatment under IND 69,185. This is a published report of the IND filed by Vector for their Quest products (Vector Tobacco Inc. 2006 [pg304]). Treatment consisted of 6 weeks of smoking a series of cigarettes with progressively lower

nicotine content (Quest 1, Quest 2, and Quest 3, with smoking yields of 0.6, 0.3 and ≤ 0.05 mg nicotine/cigarette, respectively), either in combination with nicotine patch therapy (NRT) or placebo patches. Three hundred forty-six smokers of non-menthol cigarettes who were motivated to quit were randomized to one of 3 treatments:

- Group 1: Quest plus NRT patch,
- Group 2: Quest plus placebo patch, or
- Group 3: active control (conventional cigarette) plus NRT patch.

The design of the study is presented in Table VIII.D-24 below.

Table VIII.D-24. Study Design (From Becker *et al.* 2008 [[pg297](#)]).

| | Weeks | | | | | | | | | | | | | | | | | | | | |
|-------|------------------------|----------------|---|----------------|---|----------------|---|---------------|---|---|------------------------------------|---------------|----|---------------|----|---------------|----|----|-----------------------------|-----|------------------------------|
| | | | | | | | | | | | Primary endpoint 4-week Abstinence | | | | | | | | | | |
| Group | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | --- | 32 |
| 1 | Usual Brand all groups | Quest 1 | | Quest 2 | | Quest 3 | | 21 mg patch | | | | 14 mg patch | | 7 mg patch | | placebo patch | | | 3-month post-quit follow-up | | 6 months post-quit follow-up |
| 2 | | Quest 1 | | Quest 2 | | Quest 3 | | placebo patch | | | | placebo patch | | placebo patch | | placebo patch | | | | | |
| 3 | | Active Control | | Active Control | | Active Control | | placebo patch | | | | 21 mg patch | | 14 mg patch | | 7 mg patch | | | | | |

The primary endpoint was 4 weeks of continuous abstinence (Weeks 7 to 10), with follow-up at 3 and 6 months. Group 1 had a higher continuous abstinence during weeks 7 - 10 than Group 3, 32.8% vs. 21.9% ($p = 0.04$). Group 2 had an abstinence rate similar to that of Group 3, 16.4% vs. 21.9% ($p = 0.89$). Abstinence rates at the 3-month follow-up were 17.2%, 10.3%, and 14.9% in Groups 1, 2, and 3, respectively. At the 6-month follow-up, abstinence rates were 11.2%, 7.8%, 9.6% in Groups 1, 2, and 3, respectively. The differences in abstinence among groups were not statistically significant at 3 months and 6 months. Mean exhaled CO levels increased moderately compared to baseline after subjects smoked Quest 1® (Group 1, +1.5 parts per million [ppm]; Group 2, +2.5 ppm) and Quest 2® (Group 1, +2.9 ppm; Group 2, +2.9 ppm), and

was reduced compared to baseline after smoking Quest 3® (Group 1, -5.4 ppm; Group 2, -3.0 ppm).

Conclusion: Stepdown reduction in nicotine consumption followed by NRT did not affect abstinence at 3 and 6 months when compared to usual brand followed by NRT.

vi. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation (NCT00777569).

Hatsukami, *et al.*, (2010) [\[pg300\]](#) compared the effects of smoking Quest cigarettes to the use of nicotine lozenges. After a 2-week period during which baseline measurements were collected while subjects smoked ad libitum, a total of 152 subjects were assigned to one of three conditions: (i) Quest 1 - 0.3 mg nicotine yield cigarette, (ii) Quest 3 - 0.05 mg nicotine yield cigarettes or (iii) nicotine lozenges (4 mg). Subjects assigned to the cigarette conditions were blinded as to which cigarette they received (i.e. 0.05 mg versus 0.3 mg). Subjects were instructed to use their assigned treatment for 6 weeks (after which time they were to discontinue product use) and to not use other nicotine or tobacco products during the treatment or any products during the follow-up period. Subjects were seen weekly during the 6-week treatment period and at 1, 2, 4 and 6 weeks after cessation. At each visit subjects assigned to either cigarette condition were provided a supply equivalent to 150% of their baseline smoking rate and were told to smoke ad libitum to allow for compensatory smoking, Subjects assigned to receive the 4 mg nicotine lozenge were asked to quit smoking and to use at least six to eight pieces per day (the mean number of lozenges used among smokers enrolled in a clinical trial). If side effects suggested that the dose was too high, the 2 mg nicotine lozenge was substituted at that time. Subjects maintained a daily smoking diary in which they recorded any cigarettes smoked (either those

assigned to them or their own). If they smoked cigarettes other than those assigned, they were to note when that cigarette was smoked. They were not penalized for smoking that cigarette but told that they were discouraged from smoking cigarettes other than those assigned, and that it was crucial to the study that they indicate to us whenever they smoked any other cigarettes.

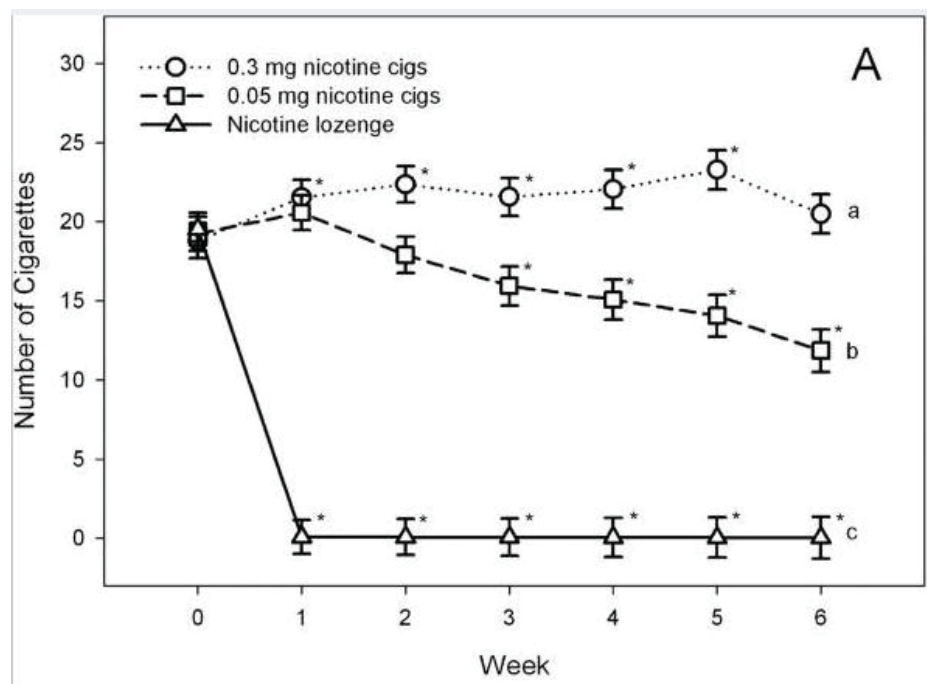
Brief (approximately 10 minutes) standardized counseling was provided at each of the visits during the treatment phase of the study. Subjects assigned to the cigarette conditions were counseled to consider the use of these products as a step towards quitting. They discussed any difficulties they experienced with switching cigarettes and behavioral strategies to resist smoking other (non-Quest) cigarettes. Subjects assigned to the nicotine lozenge condition were provided with treatment tools recommended by the U.S. Clinical Practice Guideline. During the abstinence phase, all subjects received counseling similar to that received by the subjects assigned to the nicotine lozenge condition. Therefore, all three treatment groups received similar amounts of behavioral support.

Biomarkers of tobacco toxicant exposure measures included: (i) urinary cotinine plus cotinine–glucuronide (total cotinine); (ii) alveolar carbon monoxide (CO); (iii) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL); [17]); (iv) urinary N'-nitrosonornicotine and its glucuronide (total NNN); (v) urinary 1-hydroxypyrene and its glucuronide and sulfate (total 1-HOP);(vi) urinary 3-hydroxypropylmercapturic acid (3-HPMA); and (vii) S-phenylmercapturic acid (S-PMA). All measures were assessed at baseline. Additionally, carbon monoxide was assessed at each treatment clinic visit, cotinine at weeks 2 and 6 of treatment and at follow-up visits (except at 1- week post-treatment) and biomarkers for other exposure measures at weeks 2 and 6 of treatment.

Subjective measures included: (i) a tobacco use questionnaire that asked about current tobacco use status (cigarettes and other tobacco products), number of ≥ 24 -hour quit attempts and duration of abstinence during these quit attempts; (ii) a daily diary detailing the number of cigarettes smoked; (iii) the Minnesota Nicotine Withdrawal Scale; (iv) the Fagerstrom Test for Nicotine Dependence. All these measures were assessed at baseline. Cigarette or product use was assessed daily, the tobacco use questionnaire and Minnesota Nicotine Withdrawal Scale at each clinic visit, and the FTND and perceived health risk at weeks 2 and 6.

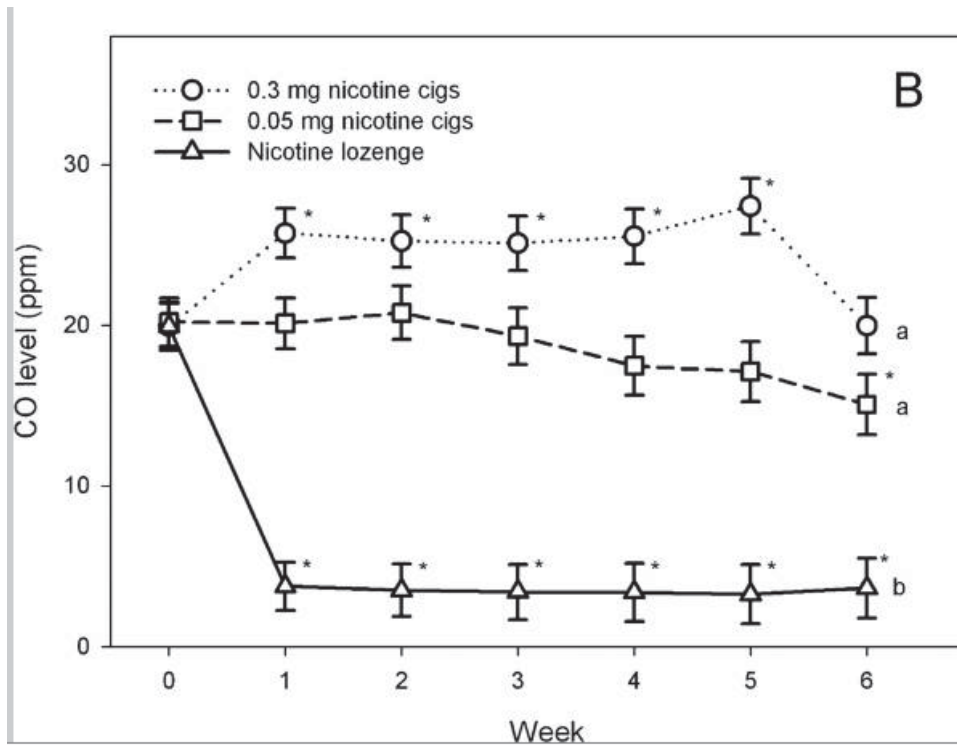
Cigarette consumption was reduced from baseline after 3 weeks of use (Figure VIII.D-13).

Figure VIII.D-13. CPD (From Hatsukami *et al.* 2010 [pg300]).



There was no CO boost after using the 0.05 mg product indicating no compensation (Figure VIII.D-14).

Figure VIII.D-14. CO level (From Hatsukami *et al.* 2010 [pg300]).



Biomarkers of exposure were reduced after 6 weeks for the 0.05 mg nicotine cigarette group (Table VIII.D-25).

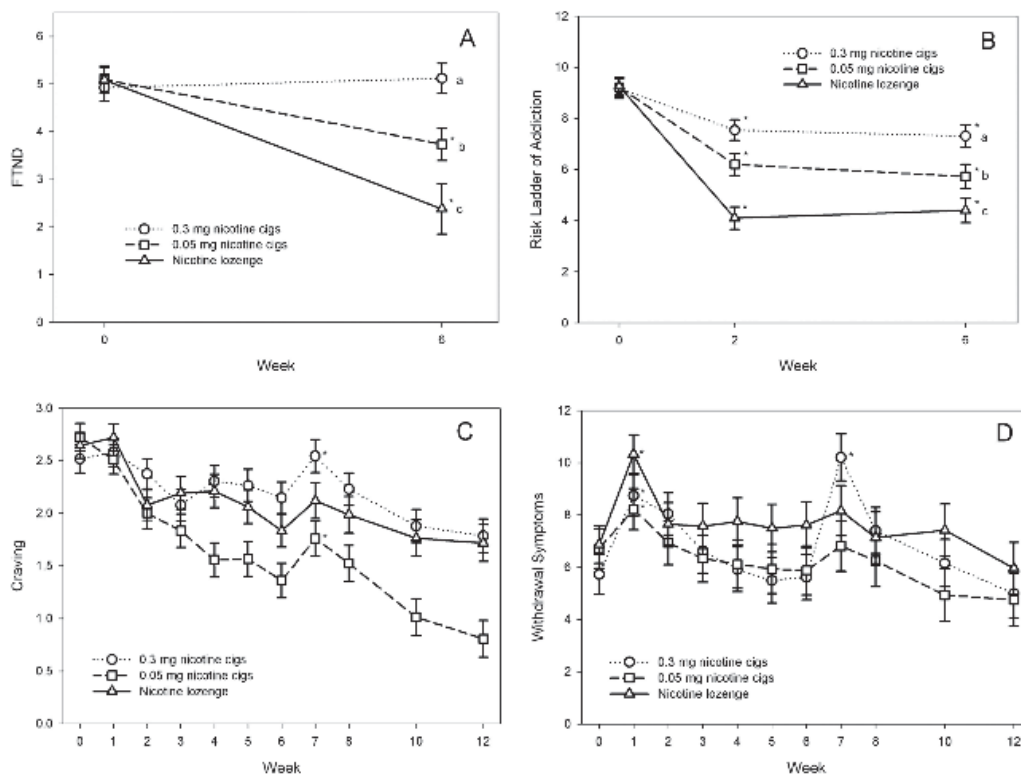
Table VIII.D-25. BOE (From Hatsukami *et al.* 2010 [pg300]).

| Biomarkers | Geometric mean (95% confidence interval) | | |
|-----------------------------|--|---------------------|---------------------------------|
| | Baseline | Week 2 | Week 6 |
| Total cotinine ¹ | | | |
| 0.3 mg cigarettes | 4057 (3323, 4952) | 2150 (1696, 2725) * | 2093 (1611, 2719) ^a |
| 0.05 mg cigarettes | 4216 (3492, 5090) | 278 (174, 442) * | 188 (111, 319) ^b |
| Nicotine lozenge | 3917 (3399, 4514) | 2291 (1708, 3073) * | 2154 (1312, 3536) ^a |
| Total NNAL ² | | | |
| 0.3 mg cigarettes | 0.96 (0.73, 1.26) | 0.54 (0.41, 0.69) * | 0.47 (0.30, 0.73) ^a |
| 0.05 mg cigarettes | 0.92 (0.70, 1.21) | 0.34 (0.20, 0.57) * | 0.20 (0.11, 0.34) ^b |
| Nicotine lozenge | 1.06 (0.84, 1.35) | 0.24 (0.18, 0.32) * | 0.14 (0.07, 0.26) ^b |
| Total NNN ² | | | |
| 0.3 mg cigarettes | 0.10 (0.06, 0.16) | 0.09 (0.06, 0.14) | 0.06 (0.04, 0.10) ^a |
| 0.05 mg cigarettes | 0.09 (0.05, 0.15) | 0.06 (0.04, 0.11) | 0.03 (0.02, 0.07) ^{ab} |
| Nicotine lozenge | 0.08 (0.05, 0.12) | 0.02 (0.01, 0.04) * | 0.02 (0.01, 0.04) ^b |
| Total 1-HOP ² | | | |
| 0.3 mg cigarettes | 0.84 (0.70, 1.02) | 0.95 (0.58, 1.53) | 0.73 (0.59, 0.90) ^a |
| 0.05 mg cigarettes | 0.89 (0.71, 1.12) | 0.75 (0.56, 1.01) | 0.57 (0.42, 0.78) ^a |
| Nicotine lozenge | 0.94 (0.71, 1.24) | 0.40 (0.29, 0.56) * | 0.34 (0.21, 0.57) ^b |
| 3-HPMA ² | | | |
| 0.3 mg cigarettes | 3662 (2868, 4674) | 2838 (2226, 3619) | 2738 (2110, 3537) ^a |
| 0.05 mg cigarettes | 3320 (2667, 4134) | 1639 (1215, 2211) * | 1453 (1039, 2032) ^b |
| Nicotine lozenge | 3445 (2539, 4673) | 911 (670, 1239) * | 1062 (749, 1508) ^b |
| S-PMA ² | | | |
| 0.3 mg cigarettes | 2.21 (1.54, 3.18) | 1.30 (0.88, 1.92) * | 1.35 (0.94, 1.93) ^a |
| 0.05 mg cigarettes | 2.46 (1.68, 3.62) | 1.54 (1.03, 2.31) * | 0.76 (0.48, 1.20) ^b |
| Nicotine lozenge | 2.69 (1.95, 3.72) | 0.33 (0.22, 0.49) * | 0.48 (0.30, 0.78) ^b |

Subjective evaluations suggested that the subjects were less addicted after 6 weeks as measured by the Fagerström index. Nicotine craving and withdrawal symptoms at the time of switching to products (week 1) and cessation from products (week 7) were examined. Upon cessation of usual brand cigarettes and switching to the products, there was a significant increase in withdrawal symptoms and no significant change in craving in all three treatment groups. Increase in nicotine withdrawal scores upon cessation of usual brand cigarettes (week 1

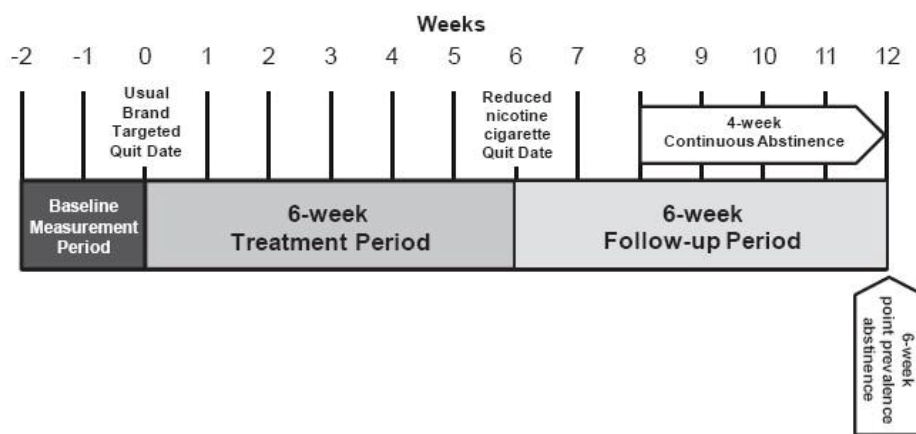
compared to baseline) was significantly smaller for the group assigned to 0.05 mg cigarettes compared to the group assigned nicotine lozenges nearly significantly than for those assigned to 0.3 mg cigarettes. Upon cessation of the product (week 7 compared to week 6), significant increase in craving and withdrawal symptoms were observed for the 0.3 mg cigarette group. In those discontinuing the 0.05 mg cigarettes, craving increased significantly but withdrawal symptoms did not. In those discontinuing the nicotine lozenge, neither changes in craving nor withdrawal symptoms were increased significantly. Change in withdrawal symptoms was significantly lower in those discontinuing 0.05 mg cigarettes or nicotine lozenges compared to those discontinuing 0.3 mg cigarettes, with no significant differences in craving observed between groups (Figure VIII.D-15).

Figure VIII.D-15 (From Hatsukami *et al.* 2010 [pg300]).



Four-week continuous abstinence was measured after the treatment period, as shown in the figure below, rather than during the last four weeks of the treatment period (Figure VIII.D-16).

Figure VIII.D-16. Study Design (From Hatsukami *et al.* 2010 [pg300]).



Continuous abstinence 4-weeks post-treatment was 43% for the 0.05 mg cigarette group, 35% for the nicotine lozenge group, and 21% for the 0.3 mg cigarette group. Point abstinence rates at 6 weeks post-treatment were 47% for the 0.05 mg cigarette group, 37% for the nicotine lozenge group, and 23% for the 0.3 mg group. The 0.05 mg cigarette led to a significantly higher rate of cessation than the 0.3 mg nicotine cigarette and a similar rate as nicotine lozenge.

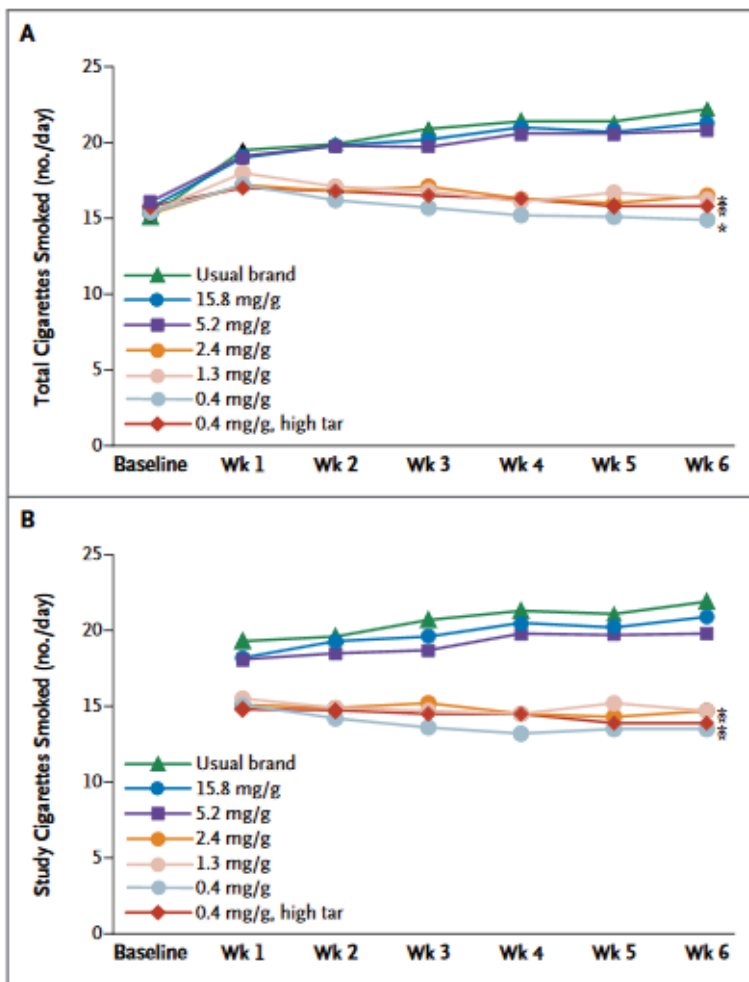
Conclusions: The 0.05 mg cigarettes were not associated with compensatory smoking behaviors. Furthermore, the 0.05 mg cigarettes were associated with reduced cigarette consumption, carcinogen exposure, nicotine dependence and product withdrawal scores. The 0.05 mg cigarette was associated with greater relief of withdrawal from usual brand cigarettes than the nicotine lozenge. The 0.05 mg cigarette led to a similar rate of cessation as the nicotine lozenge.

vii. *Randomized trial of reduced-nicotine standards for cigarettes (NCT01681875).*

Donny *et al.*, (2015) [\[pg299\]](#) conducted a double-blind, parallel, randomized clinical trial at 10 sites enrolling 840 subjects. Subjects were randomly assigned to smoke either their usual brand of cigarettes or one of six types SPECTRUM® cigarettes, provided free, for 6 weeks. The investigational cigarettes had nicotine content ranging from 0.4 mg per gram of tobacco to 15.8 mg per gram (typical of commercial brands). The primary outcome was the number of cigarettes smoked per day during week 6. Subjective measures of dependence, withdrawal, and smoking urges were collected. Biomarkers of exposure and were measured in urine at 2- and 6-weeks. Topography was also measured at 2- and 6-weeks. Abstinence (no smoking for ≥ 18 hours) was measured after 6 weeks of product use.

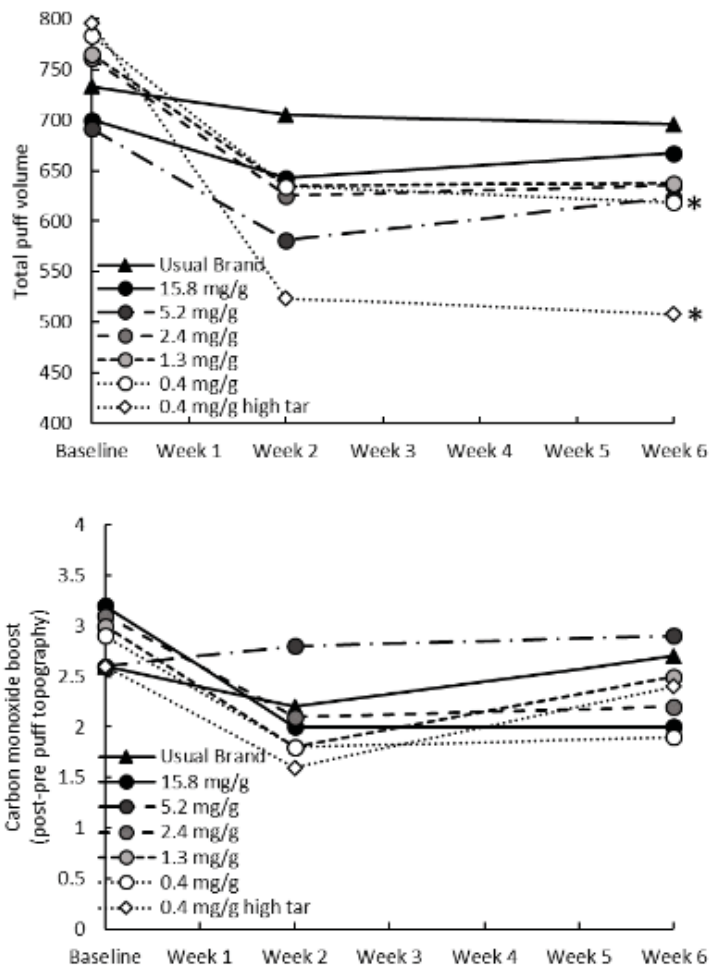
Study and total cigarette (study cigarettes and non-study cigarettes) consumption was reduced in 0.4 mg group (Figure VIII.D-17).

Figure VIII.D-17. CPD (From Donny *et al.*, 2015 [pg299]).



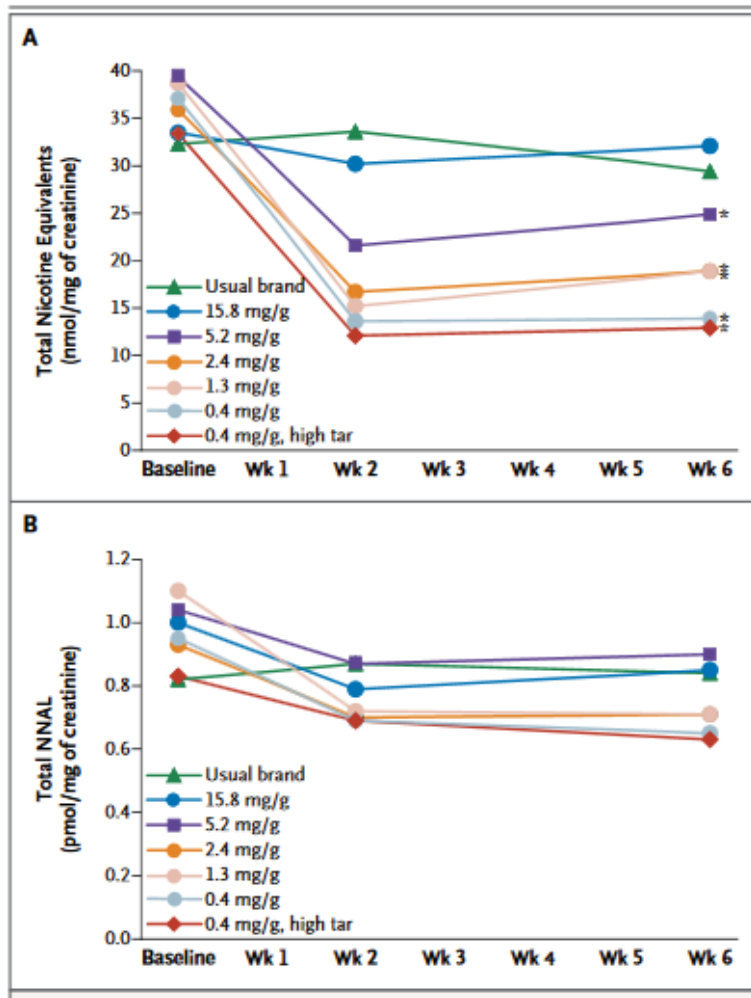
Total puff volume decreased and there was no CO boost indicating there was no compensation (Figure VIII.D-18).

Figure VIII.D-18. Topography (From Donny *et al.*, 2015 [pg299]).



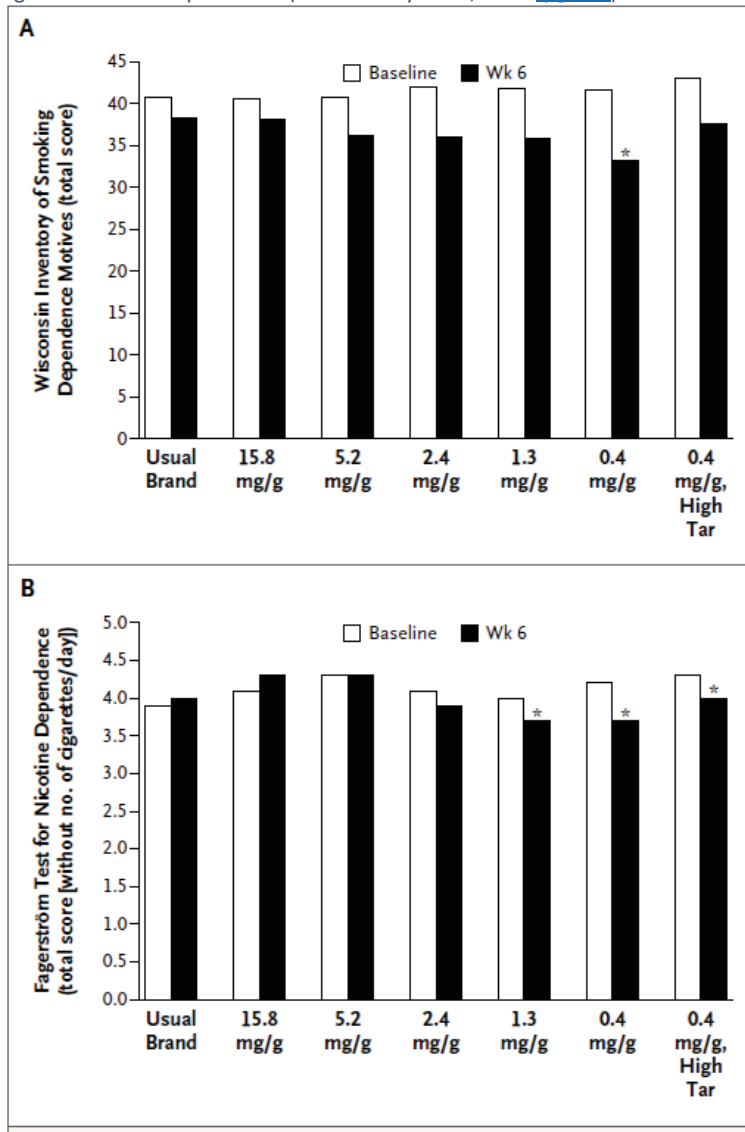
Total urine nicotine equivalents were statistically reduced after 6 weeks. NNAL was also reduced (not significant) (Figure VIII.D-19).

Figure VIII.D-19. TNE (From Donny *et al.*, 2015 [pg299]).



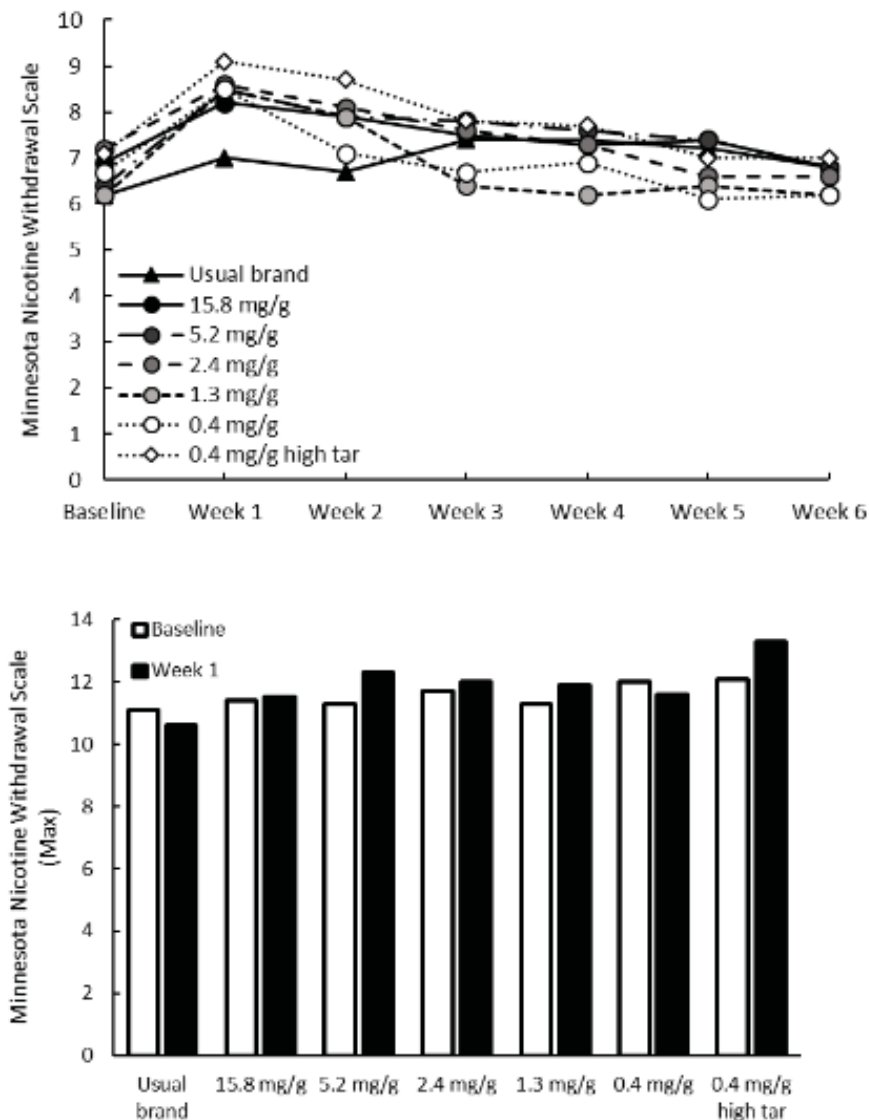
Dependence, as assessed on the basis of the total score on the Wisconsin Inventory of Smoking Dependence Motives, was significantly lower at week 6 among participants smoking cigarettes with 0.4 mg of nicotine per gram than among those smoking cigarettes with 15.8 mg of nicotine per gram. The score on the Fagerström Test for Nicotine Dependence at week 6 was lower among smokers assigned to cigarettes with 2.4 mg of nicotine or less per gram than among those assigned to cigarettes with 15.8 mg per gram (Figure VIII.D-20).

Figure VIII.D-20. Dependence (From Donny *et al.*, 2015 [pg299]).



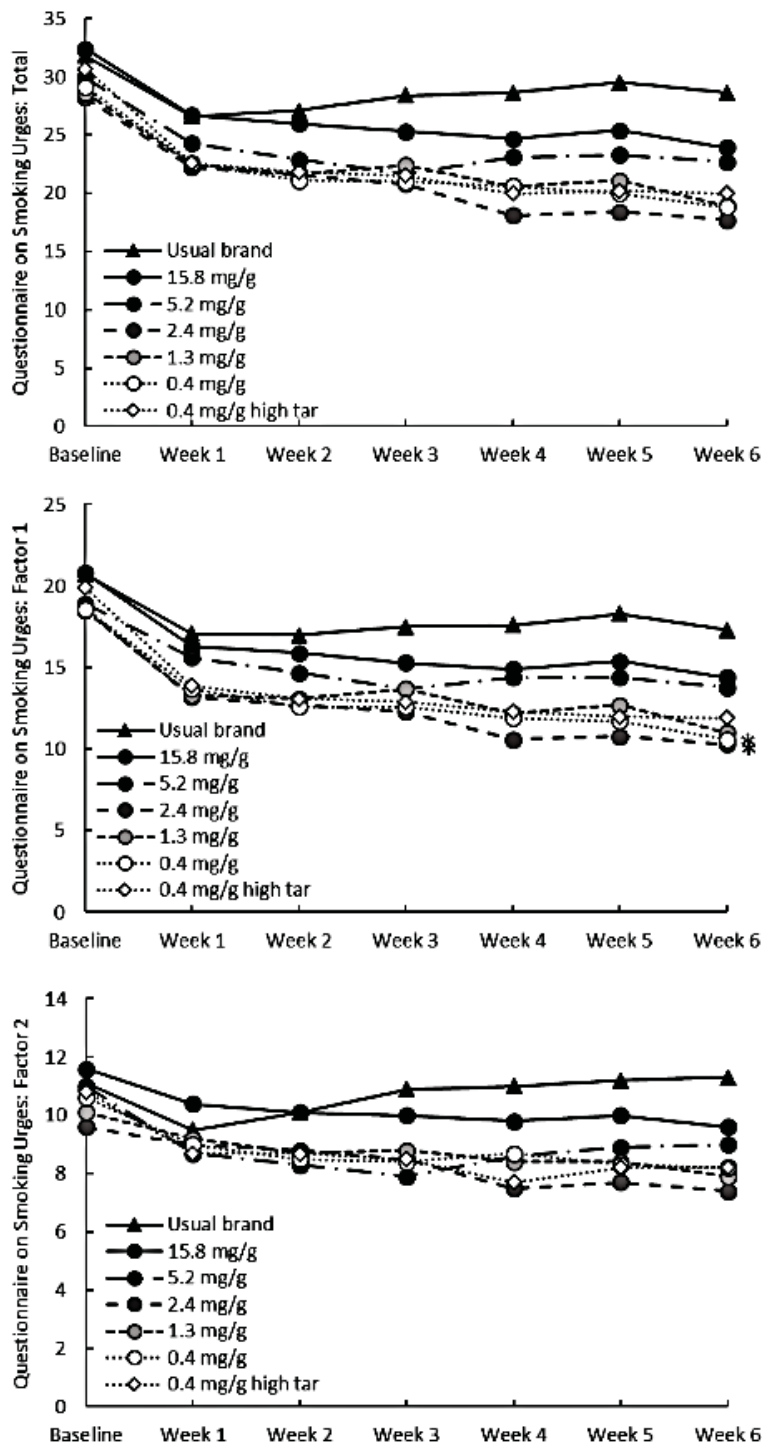
As compared with cigarettes containing 15.8 mg of nicotine per gram, cigarettes with 5.2 mg or less did not significantly increase peak daily withdrawal during week 6 (Figure VIII.D-21).

Figure VIII.D-21. Withdrawal (From Donny *et al.*, 2015 [pg299]).



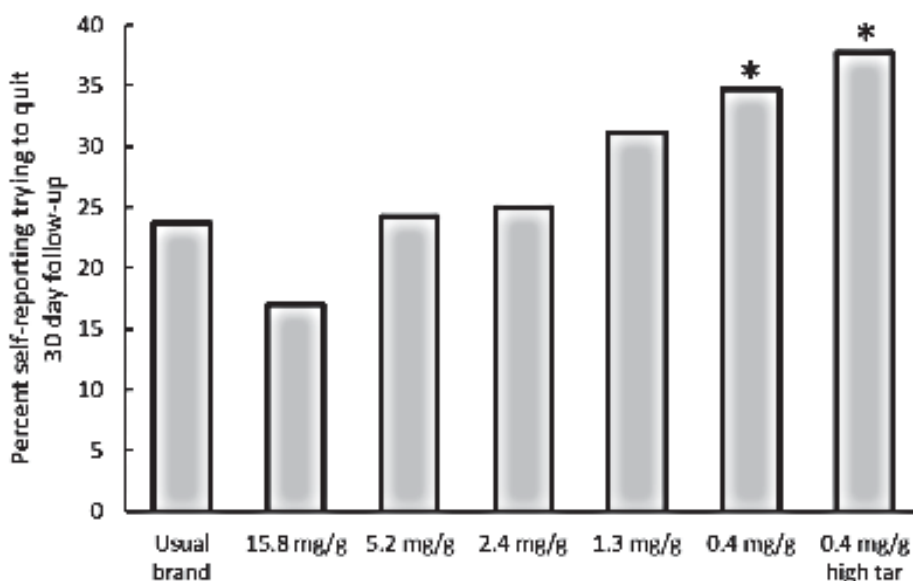
Less craving was observed at week 6 with cigarettes containing 2.4 or 0.4 mg of nicotine per gram than with the control cigarettes. Scores on the Questionnaire of Smoking Urges reported as total score (Upper panel), Factor 1 (intention to smoke) (Middle panel) and Factor 2 (relief from negative affect and urgent desire to smoke) (Lower panel) (Figure VIII.D-22).

Figure VIII.D-22. Smoking Urges (From Donny *et al.*, 2015 [pg299]).



Eighty-one percent of participants completed the telephone follow-up 30 days after the 6-week randomized smoking phase. Participants assigned to cigarettes with 0.4 mg of nicotine per gram were more likely to report attempts to quit than were those assigned to cigarettes with 15.8 mg per gram (Figure VIII.D-23).

Figure VIII.D-23. Quit Results (From Donny *et al.*, 2015 [\[pg299\]](#)).



Conclusions: Cigarette consumption and nicotine exposure were reduced. The subjects did not compensate. Dependence was reduced. Quit attempts increased.

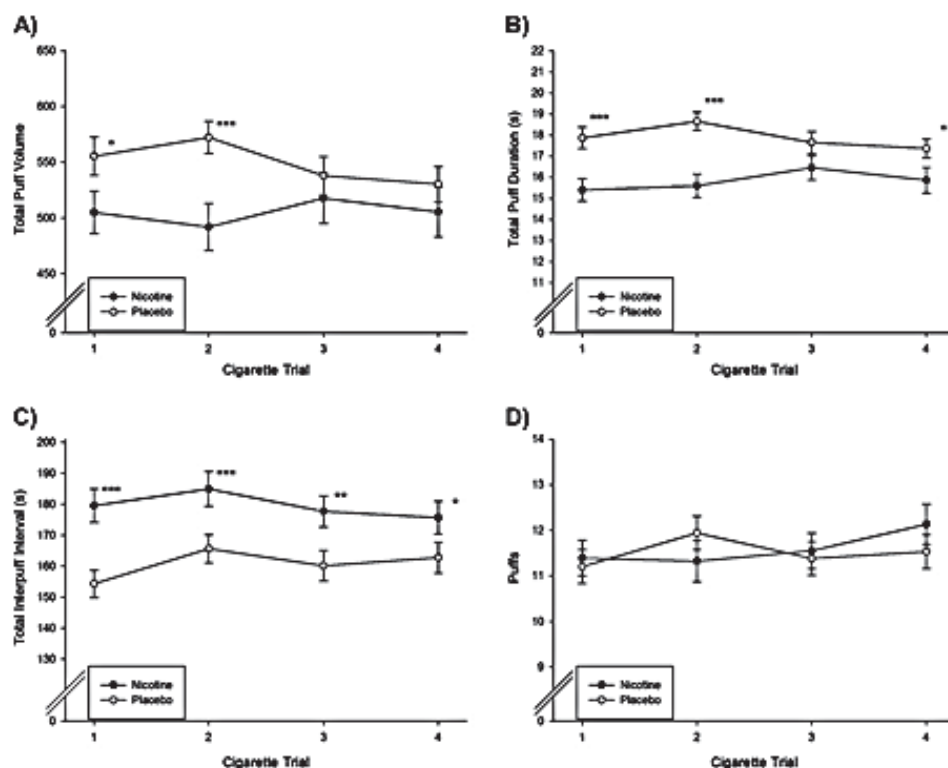
viii. Transient compensatory smoking in response to placebo cigarettes.

MacQueen *et al.*, (2012) [\[pg301\]](#) conducted a study with Quest cigarettes. Eighty-three smokers were recruited. Participants completed two separate 2.5-h experimental sessions (scheduled 3 to 14 days apart). Sessions were double-blinded, counterbalanced, and only differed in the nicotine content of the cigarettes administered: Quest 1 (8.9 mg) or Quest 3 (1.0 mg)

(placebo). Participants smoked the first of four cigarettes at their own pace through a smoking topography device. Each subsequent cigarette was smoked 40 min following initiation of the previous cigarette, and all cigarettes were followed immediately by completion of a subjective questionnaire (Modified Cigarette Evaluation Questionnaire; contains 12 items and assesses five domains: smoking satisfaction, psychological reward, aversion (e.g., dizziness and nausea), sensory feelings, and reduction in craving). Smoking topography measures included total puff volume, total puff duration, total interpuff interval, total number of puffs, and average maximum peak air velocity per cigarette.

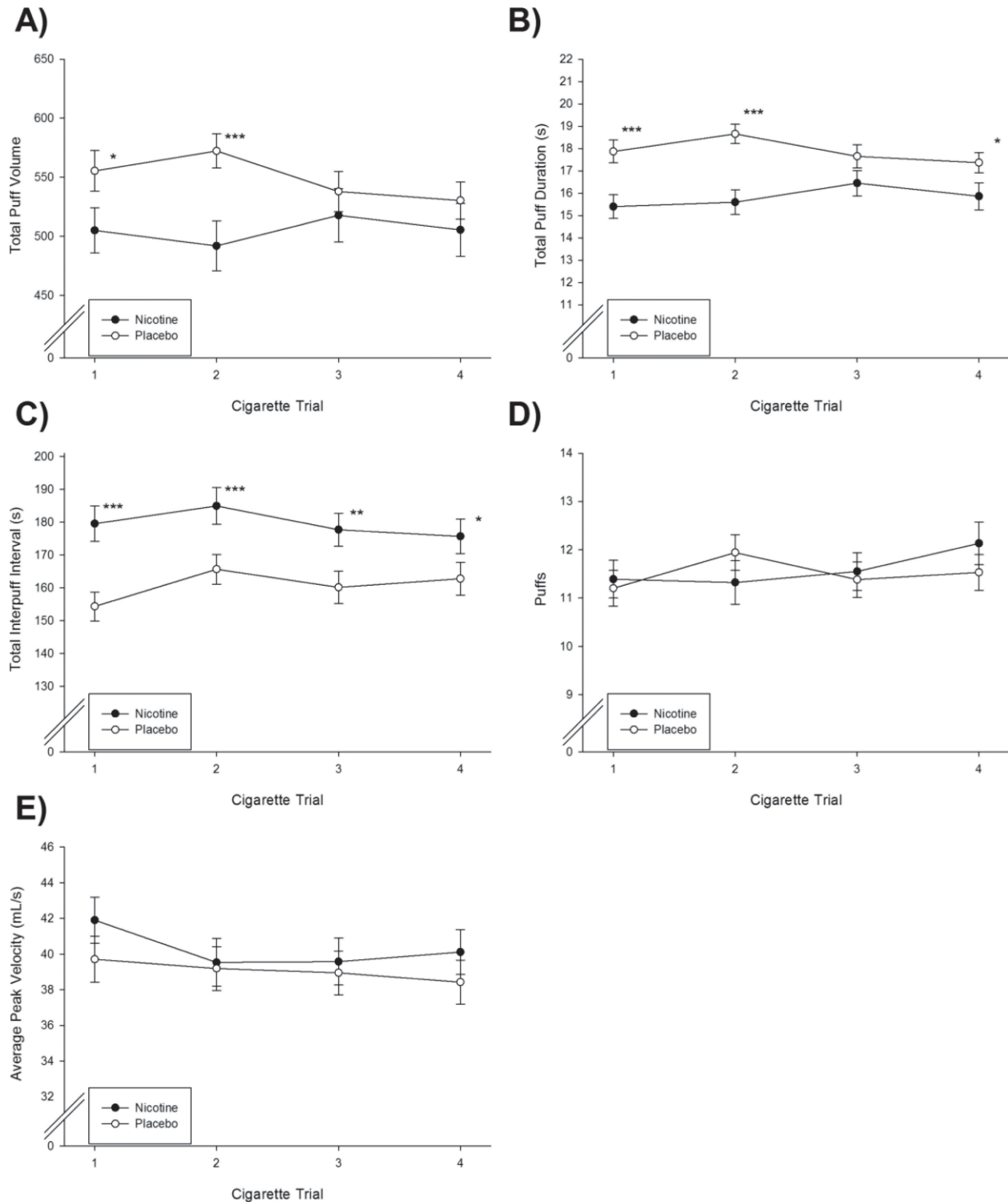
This study measured the effects of first smoking of the cigarette. Each subject smoked one cigarette 4 times over a day. Puff volume was initially increased, and total puff duration increased. Interpuff interval was decreased. Differences in total puff volume and duration generally dissipated across smoking bouts, with differences in total puff volume nonexistent by the third and fourth bouts. Placebo cigarettes produce compensatory smoking during initial exposures; however, these effects appear to be short lived (Figure VIII.D-24).

Figure VIII.D-24. Topography (From MacQueen *et al.*, 2012 [pg301]).



Smoking satisfaction and sensory feelings were greater in the high nicotine group. These subjective ratings also showed reduction across cigarette trial. Participants rated cigarettes with higher nicotine content as more satisfying and indicated that they enjoyed the sensory aspects to a higher degree than when smoking cigarettes with lower nicotine content; these effects diminished across smoking trials, regardless of nicotine content. The nicotine-containing cigarettes were also found to reduce cravings to a greater extent than low nicotine cigarettes. Psychological reward and aversion ratings were significantly affected by nicotine content, cigarette trial, and their interaction. Smoking was generally more rewarding and aversive (i.e., caused a higher degree of dizziness and nausea) for higher dose cigarettes, but these differences attenuated across smoking sessions (Figure VIII.D-25).

Figure VIII.D-25. Topography (From MacQueen *et al.*, 2012 [pg301]).



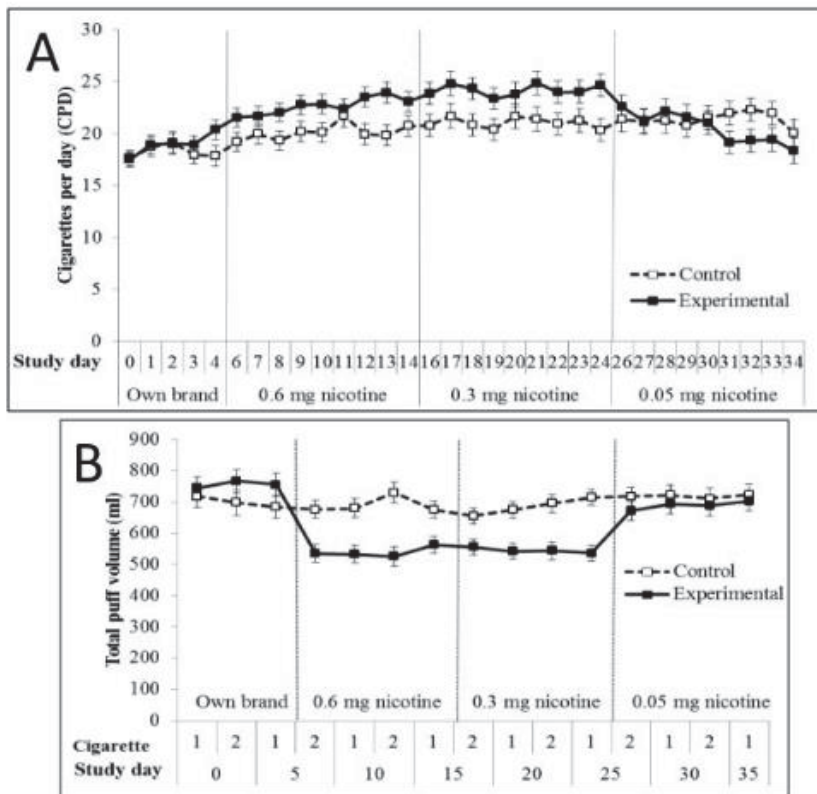
Conclusions: It appears that smokers attempt to compensate after one use of very low nicotine cigarettes. The effect seems to diminish after just a few cigarettes.

ix. A Randomized Controlled Trial of Progressively Reduced Nicotine Content Cigarettes on Smoking Behaviors, Biomarkers of Exposure, and Subjective Ratings.

Mercincavage, *et al.*, (2016) [\[pg301\]](#) studied 158 daily, non-treatment-seeking smokers in a 35-day randomized, unblinded, parallel study. After a 5-day baseline period, participants were randomly assigned to an experimental group (n= 80) that smoked progressively decreasing reduced nicotine content Quest cigarettes for three 10-day periods, or control group (n=78) that smoked their own brand throughout the study.

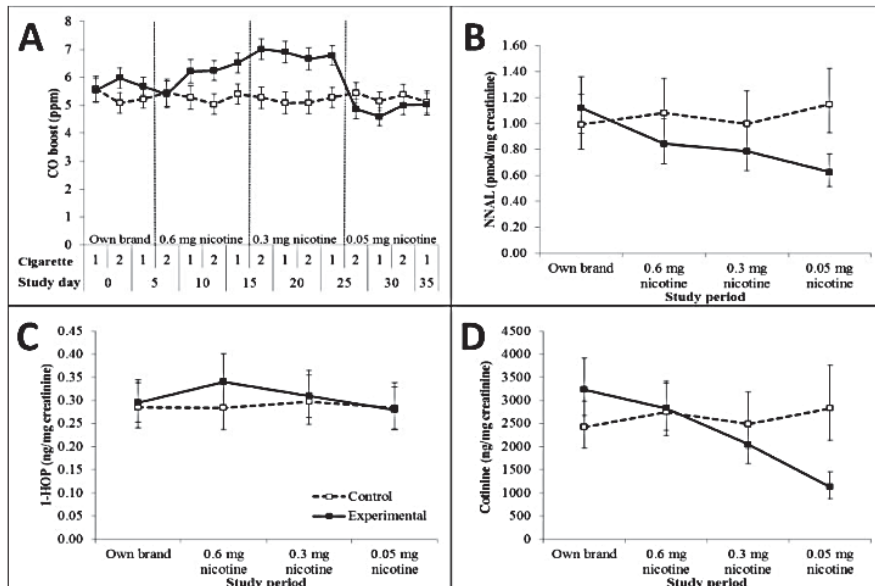
Daily cigarette consumption and total puff volume was not affected in the 0.05 mg nicotine group (Quest 3). CO boost was not affected indicating no compensation.

Figure VIII.D-26. CPD (From Mercincavage, *et al.*, 2016 [\[pg301\]](#))



As expected NNAL and cotinine were reduced and there was no effect on 1-HOP (Figure VIII.D-27). Subjective ratings indicated that the participants perceived the Quest 3 as being weaker, less satisfying and milder than usual brand.

Figure VIII.D-27. BOE (From Mercincavage, *et al.*, 2016 [pg301])



Conclusions: After 10 days of use there was no effect on cigarette consumption or compensation in the 0.05 mg nicotine group. Cotinine and NNAL were decreased.

x. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure.

Strasser, *et al.*, (2007) [pg303] conducted a study to test the hypothesis that compensatory smoking will occur as nicotine levels of cigarettes decrease, increasing exposure to tobacco toxins. In this study, 50 adult smokers participated in a single laboratory session. Subjects first smoked one of their own brand cigarettes through a topography device. Thirty minutes after smoking their own brand cigarette, participants smoked the first of three Quest cigarettes (Quest 1 [nicotine content 0.6 mg], Quest 2 [nicotine content 0.3 mg] or Quest 3 [nicotine content ≤ 0.05 mg]) with a 30-minute interval between cigarettes. The Quest cigarettes were presented in a randomized order, counter-balanced across participants to minimize potential order effects. Subjects and researcher were blind to nicotine level. Puff volume was measured using the topography device. Prior to and 4 minutes after smoking each cigarette, participants provided

breath CO samples. Upon extinguishing each cigarette, participants completed a 14-item subjective rating of the cigarette they had just finished smoking, including which had the most and least amount of nicotine.

Puff volume was not changed but number of puffs was decreased with the 0.05 mg nicotine cigarette when compared to own brand. This caused a reduction in the total puff volume. CO boost was not changed. Strength of cigarette, satisfaction from smoking, and smoke strength differed significantly by nicotine level (Table VIII.D-26).

Table VIII.D-26. Topography (From Strasser, *et al.*, 2007 [pg303]).

| | Cigarette type (mg of nicotine) | | | |
|---|---------------------------------|-------------------------------|-------------------------------|--------------------------------|
| | Own brand (various) | Quest [®] 1 (0.6 mg) | Quest [®] 2 (0.3 mg) | Quest [®] 3 (0.05 mg) |
| Biochemical measure | | | | |
| CO boost (ppm) | 5.5 (4.8–6.3) | 4.7 (4.0–5.5) | 5.8 (5.1–6.6) | 5.3 (4.6–6.0) |
| Smoking topography measures | | | | |
| Total puff volume (ml) | 832.0 (737–926) | 540.3 (500–580) | 518.1 (478–558) | 570.5 (527–614) |
| Number of puffs | 14.3 (12.8–15.7) | 9.8 (9.0–10.5) | 9.9 (8.9–10.9) | 10.0 (9.1–10.9) |
| Puff duration (s) | 1.8 (1.6–1.9) | 1.8 (1.6–1.9) | 1.7 (1.5–1.8) | 1.8 (1.6–1.9) |
| Puff volume (ml) | 60.5 (55.2–65.7) | 58.1 (53.3–62.8) | 55.9 (51.0–60.8) | 59.4 (54.6–64.3) |
| Puff velocity (ml/s) | 35.5 (22.3–37.8) | 34.5 (32.0–37.0) | 34.4 (31.9–37.0) | 35.1 (32.5–37.8) |
| Interpuff interval (s) | 21.6 (19.1–24.1) | 21.6 (19.0–24.2) | 19.6 (16.9–22.3) | 18.6 (15.7–21.6) |
| Subjective ratings | | | | |
| Strength-very weak/very strong | 60.7 (53.7–67.8) | 44.4 (38.4–50.5) | 40.3 (32.9–47.6) | 28.3 (21.1–35.6) |
| Harshness-very mild/very harsh | 29.6 (23.3–35.9) | 33.7 (27.3–40.1) | 35.9 (28.1–43.7) | 27.8 (20.2–35.4) |
| Heat-no heat/very hot | 19.0 (13.7–24.2) | 24.5 (18.9–30.1) | 27.6 (20.2–35.1) | 26.4 (19.6–33.2) |
| Draw-easy/difficult | 46.5 (7.8–85.2) | 26.3 (19.9–32.7) | 46.9 (8.1–85.6) | 28.3 (20.8–35.8) |
| Taste-very bad/very good | 70.0 (62.7–78.0) | 44.6 (30.1–43.6) | 36.8 (30.1–43.6) | 53.3 (14.7–91.8) |
| Satisfaction from smoking-unsatisfying/satisfying | 70.3 (62.7–78.0) | 44.3 (36.3–52.2) | 36.8 (29.3–44.3) | 24.4 (18.3–30.5) |
| Burned/did not burn too fast in too few puffs | 86.7 (49.4–100.0) | 26.0 (19.3–32.7) | 22.3 (17.0–27.6) | 21.8 (15.5–28.2) |
| Mild taste/not mild taste | 46.7 (38.8–54.7) | 33.2 (26.3–40.2) | 35.5 (27.8–43.2) | 33.2 (25.5–41.0) |
| It was/was not too mild for me | 71.4 (64.0–78.8) | 42.4 (33.5–51.4) | 41.1 (31.7–50.5) | 31.4 (23.0–39.8) |
| Smoke seemed/did not seem harsh | 75.3 (68.8–81.8) | 56.2 (47.7–64.8) | 57.6 (48.9–66.3) | 61.6 (52.6–70.5) |
| Did not leave/left a good aftertaste in my mouth | 54.1 (45.5–62.7) | 59.7 (21.3–98.1) | 35.0 (27.4–42.5) | 44.4 (5.6–83.1) |
| Somehow it seemed/did not seem stale | 84.1 (79.1–89.1) | 59.4 (51.5–67.3) | 58.0 (49.9–66.1) | 53.7 (44.4–63.0) |
| Smoke seemed very weak/very strong | 62.4 (55.4–69.4) | 44.6 (37.7–51.4) | 37.8 (30.8–44.8) | 31.9 (24.2–39.5) |
| Smoke smell-unpleasant/pleasant | 65.0 (58.4–71.6) | 50.2 (43.1–57.3) | 48.4 (41.4–55.3) | 46.0 (39.4–52.7) |

Data presented as mean (±95% confidence interval).

Conclusion: There was no compensation after a single use of 0.05 mg nicotine cigarettes.

xi. The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers

This study by Barrett and Darredeau (2012) [pg297] evaluated the effect of pre-use of a quick release nicotine lozenge on denicotinized cigarette smoking behavior. Twenty-seven subjects were randomized in a double-blind study design. Subjects were given a nicotine lozenge or a placebo lozenge and 30 minutes later allowed to smoke a single Quest 3 cigarette. Subjective state was assessed using the Questionnaire of Smoking Urges-Brief.

Relative to the placebo lozenge, use of the nicotine lozenge reduced the levels of Quest 3 self-administration. The use of a single Quest 3 cigarette was followed by a reduction in craving irrespective of the type of lozenge (nicotine or placebo). Quest 3 usage was associated with increased ratings of 'pleasant,' 'satisfied,' 'stimulated,' and 'relaxed,' as well as with decreased ratings of 'anxious,' independent of the type of lozenge.

Conclusion: This study suggests that there are factors other than nicotine in tobacco that may be contributing to the addictive factors of smoking.

xii. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers.

This study by Barrett (2010) [pg297] examined the acute subjective effects of nicotine in the absence of tobacco (through nicotine inhalers and placebo inhalers), tobacco with greatly reduced nicotine (Quest 3 cigarettes), and nicotine-containing tobacco (Quest 1 cigarettes), and their effects on subsequent smoking behavior. A total of 22 smokers (12 male, 10 females; 11 low dependent, 11 high dependent) were enrolled. During 4 randomized blinded sessions, participants self-administered inhaled nicotine, inhaled placebo, Quest 1 cigarettes, or Quest 3 cigarettes and assessed their effects using Visual Analogue Scales and the Brief Questionnaire of

Smoking Urges. They could then self-administer their preferred brand of cigarettes using a progressive ratio task. Quest 1 cigarettes and Quest 3 cigarettes were each associated with increased satisfaction and relaxation as well as decreased craving relative to the inhalers, and Quest 1 cigarettes increased ratings of stimulation relative to each of the other products. Both Quest 1 and Quest 3 cigarettes delayed the onset of preferred tobacco self-administration relative to inhaled nicotine and inhaled placebo, but only Quest 3 cigarettes reduced the total amount of nicotine self-administered.

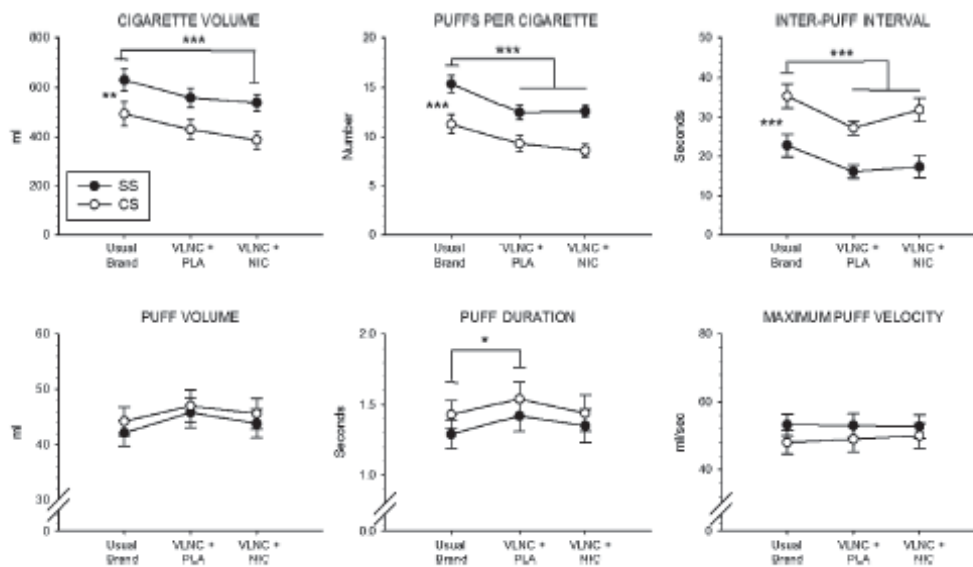
Conclusion: Quest 3 can reduce craving.

xiii. Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without Nicotine Replacement, in Smokers with Schizophrenia and Controls.

Tidey *et al.*, (2016) [\[pg304\]](#) investigated the effects of Quest 3 cigarettes on smoking topography in 27 schizophrenics (SS) and 23 control smokers (CS). The hypothesis was that schizophrenics may be prone to changing their smoking topography in response to lower nicotine levels. The study was a within-subject, counter balanced design. SS and CS smoked usual brand, Quest 3 cigarettes while wearing a placebo nicotine patch, or Quest 3 while wearing a 42 mg nicotine patch. The subjects smoked through a topography device during 5-hour ad libitum smoking sessions.

Across all conditions, SS smoked more puffs per session and per cigarette, had higher cigarette volumes, and had shorter inter-puff intervals than CS ($P_s < .01$). During VLNC cigarette sessions, puff duration increased and time between puffs decreased, but participants smoked fewer puffs, resulting in a net decrease in cigarette and total session volume ($P_s < .001$). There were no significant interactions between group and condition (Figure VIII.D-28).

Figure VIII.D-28. Topography (From Tidey *et al.*, 2016 [pg304])



Conclusions: This study indicates that acute use of Quest 3 cigarettes does not increase the intensity of smoking in schizophrenics. There was no compensation in CS smokers. Use of the nicotine patch did not affect smoking behavior.

xiv. The impact of smoking very low nicotine content cigarettes on alcohol use.

Dermody *et al.*, (2016) [pg299] were interested in the effect of SPECTRUM® cigarette usage on alcohol intake over time. This study was an analysis of a subset of a 7-arm, double-blind, randomized clinical trial conducted at 10 U.S. sites. Daily smokers not currently interested in quitting (n = 839) were assigned to equally sized groups to smoke for 6 weeks cigarettes containing either normal nicotine content (NNC; 15.8 mg/g, 9 mg tar), moderate nicotine content (MNC; 5.2 mg/g nicotine, 9 mg tar), or very low nicotine content (VLNC; 0.4 to 2.4 mg/g, 9 to 13 mg tar). This investigation focused on a subsample of current drinkers (n = 403). Each reduced nicotine content cigarette condition was compared to the NNC control condition with respect to trajectories over the 6-week period of average daily alcohol use and occurrence of binge drinking.

Moderating variables were considered. Mediation analyses tested potential explanatory processes including changes in nicotine exposure, cigarettes per day, and withdrawal.

This study modeled drinking and smoking behaviors and investigated the interactions between them. Table VIII.D-27. *Effect on Alcohol Use* (From shows some of the results of the analysis. All results are compared to the NNC group. Slope 1 is over the first two weeks and Slope 2 is over the 2- to 6-week period. Over time, reduced nicotine exposure and smoking rate mediated effects of VLNC cigarette use on reduced alcohol use. There was no evidence of compensatory drinking in response to nicotine reduction or nicotine withdrawal, even among subgroups expected to be at greater risk (e.g., relatively heavier drinkers, highly nicotine-dependent individuals). Reduced CPD was associated with reduced alcohol consumption. Changes in CPD were unrelated to binge drinking.

Table VIII.D-27. Effect on Alcohol Use (From Dermody *et al.*, 2016 [[pg299](#)])

| | 5.2 mg/g | 2.4 mg/g | 1.3 mg/g | 0.4 mg/g |
|------------------------------|-----------------------|---------------------|----------------------|---------------------|
| Unadjusted estimates | | | | |
| Alcohol use | | | | |
| Slope 1 | -0.18* (-0.36, -0.04) | -0.08 (-0.28, 0.15) | -0.14 (-0.32, 0.02) | -0.16 (-0.34, 0.04) |
| Slope 2 | 0.09 (-0.02, 0.21) | -0.03 (-0.14, 0.08) | 0.03 (-0.08, 0.14) | 0.03 (-0.07, 0.14) |
| Binge drinking | | | | |
| Slope 1 | 0.12 (-0.09, 0.34) | -0.13 (-0.34, 0.08) | -0.004 (-0.19, 0.18) | 0.13 (-0.06, 0.38) |
| Covariate-adjusted estimates | | | | |
| Alcohol use | | | | |
| Slope 1 | -0.19* (-0.35, -0.03) | -0.08 (-0.30, 0.12) | -0.13 (-0.32, 0.02) | -0.16 (-0.39, 0.03) |
| Slope 2 | 0.089 (-0.02, 0.21) | -0.04 (-0.15, 0.08) | 0.03 (-0.08, 0.14) | 0.04 (-0.06, 0.15) |
| Binge drinking | | | | |
| Slope 1 | 0.13 (-0.08, 0.33) | -0.12 (-0.33, 0.08) | 0.04 (-0.16, 0.20) | 0.16 (-0.02, 0.35) |

Conclusion: The findings suggest that compensatory drinking is unlikely to occur in response to switching to VLNC cigarettes. In contrast, reducing the nicotine content of cigarettes may reduce alcohol use.

xv. Nondaily smokers' changes in cigarette consumption with very low-nicotine-content cigarettes. A randomized double-blind clinical trial (NCT02228824).

Shiffman, *et al.*, (2018) [pg303] conducted a cigarette consumption study in nondaily smokers. This was a 12-week randomized, controlled, double-blind intervention trial. After a 2-week baseline period when participants smoked their own brand of cigarettes, participants were randomized (1:1, block size of 10, stratified by own-brand menthol preference) to receive SPECTRUM 0.07 mg nicotine / g tobacco cigarettes (VLNCs) or normal-nicotine-content cigarettes (NNCs), blinded (identical in appearance), which they were to smoke exclusively for 10 weeks. Cigarette consumption was the primary outcome and was assessed using 3 different methods: (1) timeline follow-back reports of the number of research and conventional cigarettes smoked each day since the prior visit (retrospective reports entered in calendar format); (2) counts of cigarette butts stored in plastic bags issued for each day; and (3) reports from participants each time they smoked via calls to an interactive voice response system. Daily, participants received a call to report cigarettes not reported in real time. The 3 methods were highly concordant, yielding a highly reliable composite (mean) measure of daily consumption. Mean CPD was computed during 2-week blocks, relative to time of randomization. Abstinence for the final 2-week block was also assessed, with biochemical validation via urinary total cotinine (<100 ng/mL; carbon monoxide, <8 ppm). In intent-to-treat (ITT) analyses, smoking was assumed for participants lost to observation. On exit from the study, participants were asked to rate their intention to quit

smoking (1 indicating not at all and 5 indicating completely) in the succeeding month and in 6 months.

The VLNC cigarette group reduced consumption by 1.51 CPD throughout 10 weeks (Figure VIII.D-29). Analysis throughout 2-week periods showed that CPD decreased significantly more in the VLNC group over time (Figure VIII.D-30). There were no differences in CPD changes after week 5. Treatment group differences were not moderated by sex, race/ethnicity, or history of daily smoking. Abstinence was not different between VLNC and NNCC in weeks 9 to 10. This is not surprising since over 70% of the participants reported FTND score of 0 indicating that they were not addicted to smoking.

Conclusions: CPD are reduced in intermittent smokers. Abstinence is not affected.

Figure VIII.D-29. CPD (From Shiffman *et al.* 2018 [pg303])

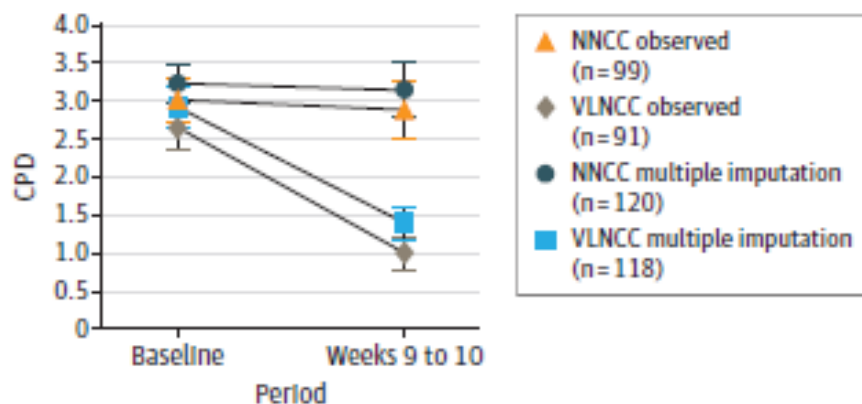
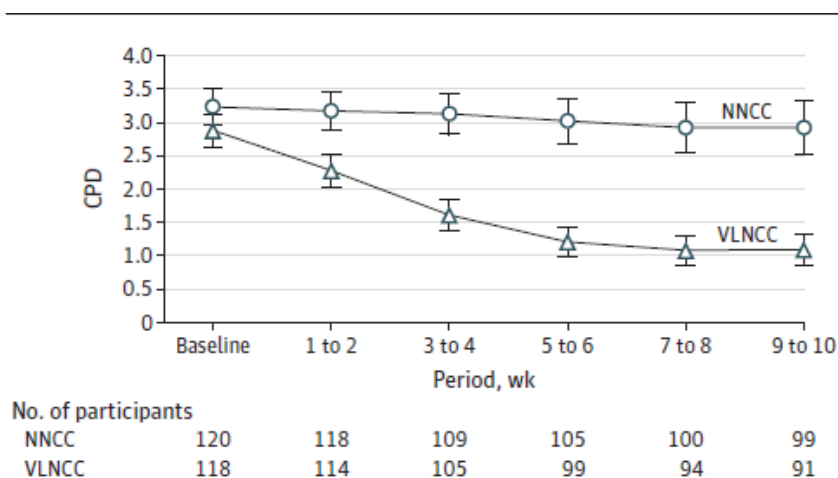


Figure VIII.D-30. CPD (From Shiffman *et al.* 2018 [pg303])



xvi. Response to varying the nicotine content of cigarettes in vulnerable populations: An initial experimental examination of acute effects.

Higgins, *et al.*, (2017, Psychopharmacology) [pg300] were interested in the effect of VLNC cigarettes in vulnerable populations. Twenty-six adult, daily cigarette smokers were from one of three populations: economically disadvantaged women of reproductive age ($n = 9$), opioid-dependent individuals ($n = 11$), individuals with affective disorders ($n = 6$). Participants completed fourteen 2 – 4 hour experimental sessions in a within-subjects research design. Sessions were conducted following brief smoking abstinence. Four SPECTRUM® research cigarettes varying in nicotine content (0.4, 2.4, 5.2, 15.8 mg/g) were studied under double-blind conditions, assessing smoking topography, subjective effects, and relative reinforcing effects of varying doses in concurrent choice tests.

Number of puffs was reduced in the 0.4 mg/g group when compared to the 15.8 mg/g group. Mean puff volume was not changed. Reduced number of puffs caused a reduction in total puff volume. These changes were not significant (Table VIII.D-28. Topography (From). The authors concluded that there were no discernable differences in smoking topography. All test cigarettes

were effective in reducing nicotine withdrawal (Figure VIII.D-31). Ratings of satisfaction were lower in the 0.4 mg/g group than 15.8 mg/g group (Table VIII.D-29. Craving).

Conclusions: There was no compensation in vulnerable populations. The 0.4 mg/g cigarette was effective in reducing withdrawal.

Table VIII.D-28. Topography (From Higgins *et al.* 2017, Psychopharmacology [pg300]).

| Smoking Topography Indices | Investigational Cigarettes | | | |
|----------------------------|----------------------------|-----------------|-----------------|-----------------|
| | 0.4 mg/g | 2.4 mg/g | 5.2 mg/g | 15.8 mg/g |
| Total Puff Volume | 411.88 ± 184.23 | 444.35 ± 200.09 | 370.72 ± 212.15 | 463.82 ± 211.94 |
| Mean Puff Volume | 38.62 ± 12.50 | 41.50 ± 12.60 | 35.58 ± 16.10 | 38.86 ± 15.12 |
| Puff Duration | 1.38 ± 0.36 | 1.39 ± 0.38 | 1.23 ± 0.45 | 1.35 ± 0.40 |
| Inter-puff Interval | 21.29 ± 6.12 | 20.95 ± 8.24 | 27.77 ± 24.19 | 19.88 ± 9.34 |
| Max Flow Rate | 31.71 ± 9.00 | 34.33 ± 10.75 | 31.76 ± 11.87 | 34.14 ± 13.87 |
| Puff Number | 11.67 ± 3.12 | 11.25 ± 3.24 | 12.00 ± 4.98 | 15.00 ± 8.32 |

Figure VIII.D-31. Withdrawal and urges (From Higgins *et al.* 2017, Psychopharmacology [pg300])

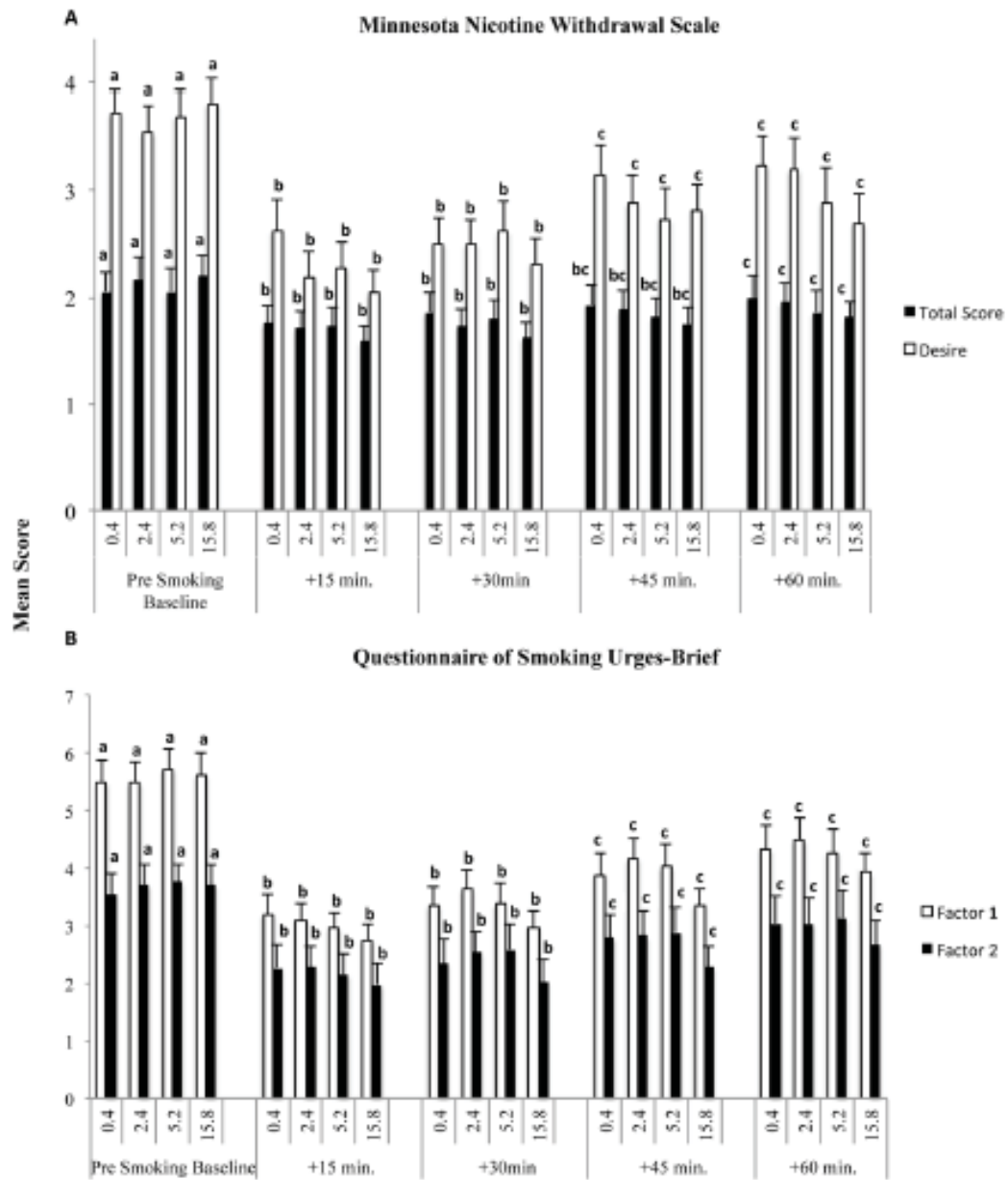


Table VIII.D-29. Craving (From Higgins *et al.* 2017, Psychopharmacology [pg300])

| Modified Cigarette Evaluation Questionnaire Subscales | Investigational Cigarettes | | | |
|---|----------------------------|---------------------------|---------------------------|--------------------------|
| | 0.4 mg/g | 2.4 mg/g | 5.2 mg/g | 15.8 mg/g |
| Smoking Satisfaction* | 3.28 ± 0.41 ^a | 3.68 ± 0.39 ^{ab} | 3.77 ± 0.38 ^{ab} | 4.17 ± 0.35 ^b |
| Psychological Reward | 2.68 ± 0.37 | 2.62 ± 0.34 | 2.74 ± 0.34 | 3.02 ± 0.35 |
| Aversion | 1.60 ± 0.13 | 1.88 ± 0.25 | 1.62 ± 0.12 | 2.04 ± 0.22 |
| Enjoyment of Respiratory Tract Sensations | 2.85 ± 0.35 | 3.08 ± 0.36 | 3.00 ± 0.33 | 3.42 ± 0.34 |
| Craving Reduction | 3.88 ± 0.41 | 3.85 ± 0.41 | 3.46 ± 0.36 | 4.19 ± 0.38 |

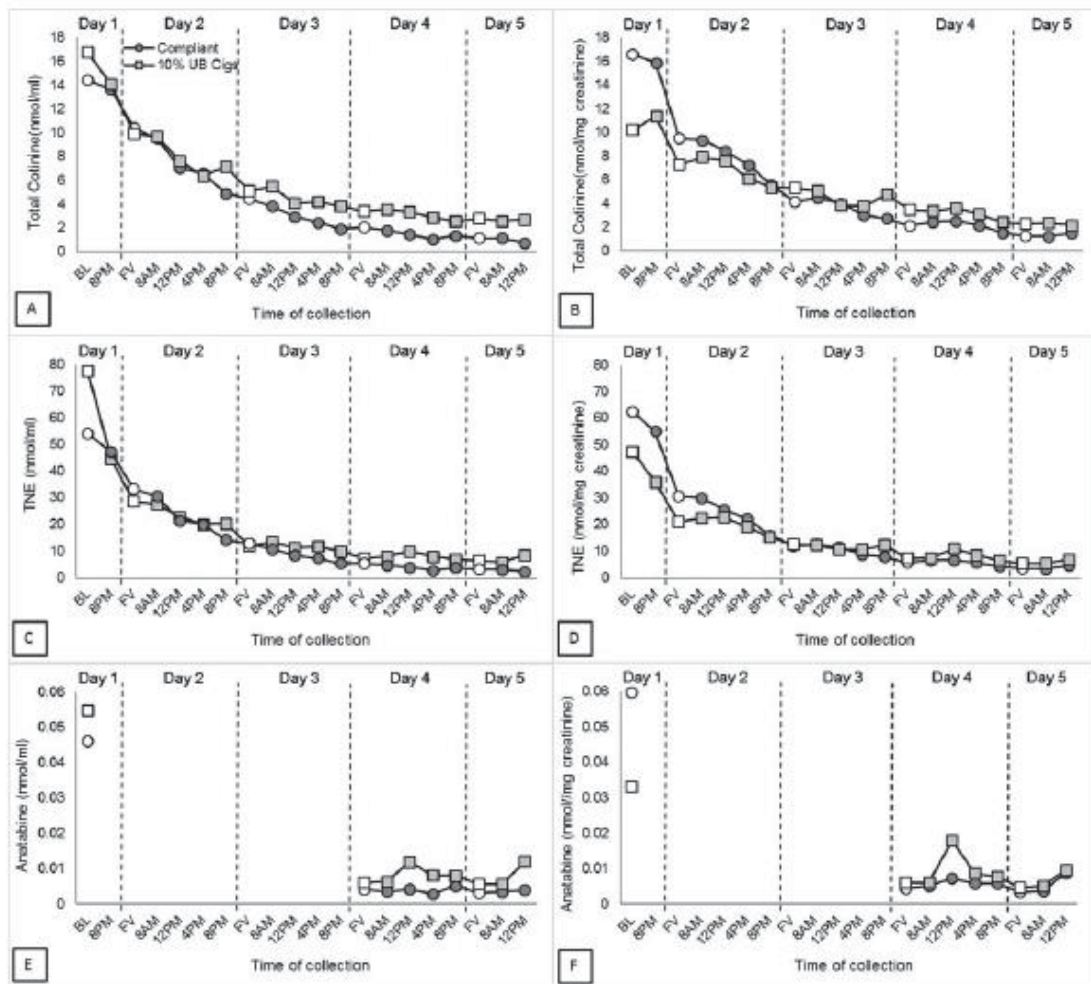
xvii. *Nicotine and Anatabine Exposure from Very Low Nicotine Content Cigarettes.*

Research using VLNC cigarettes has shown that participants under report use of non-study cigarettes. This study by Denlinger, *et al.*, (2016) [pg298] aimed to characterize biomarkers of nicotine exposure when participants exclusively used VLNC cigarettes. Twenty-three participants stayed in a hotel that permitted smoking for 5 days and 4 nights. They were provided 2 packs of SPECTRUM® cigarettes each day (0.4 mg of nicotine/g of tobacco) and did not have access to other tobacco products. 24-hour urine samples were collected to assess exposure to nicotine and anatabine. Anatabine levels in SPECTRUM® cigarettes are reduced compared to conventional cigarettes. The participants returned for a second week and were allowed to smoke one of their usual brand cigarettes each day in addition to the VLNC cigarettes. This group is referred to as “10% usual brand group”.

Figure VIII.D-32. BOE (From Denlinger *et al.* 2016 [pg298]) shows the geometric means for the urinary biomarkers. The concentrations of both total cotinine and total nicotine equivalents decreased markedly over the first two days. There was no difference between the exclusive VLNC group and the 10% usual brand group. Anatabine levels did not reveal any valuable data.

Conclusion: Cheaters are unlikely to significantly impact urinary biomarkers of nicotine exposure.

Figure VIII.D-32. BOE (From Denlinger *et al.* 2016 [pg298])



xviii. *Alcohol-induced increases in smoking behavior for nicotine and denicotinized cigarettes in men and women.*

Alcohol is known to increase smoking urges and smoking behavior. To evaluate if nicotine content of cigarettes or gender of subjects influences this effect, King *et al.*, (2009) [pg301] enrolled forty-two male and female smokers who were non-dependent heavy social drinkers in 2 double-blind laboratory sessions. Subjects were randomized to receive either an alcohol (n=29) or placebo (n=13) beverage and then smoked either Quest 3 (≤ 0.05 mg nicotine yield) or Quest 1 (0.60 mg nicotine yield) cigarettes over a 3-hour period. Results showed that alcohol, compared

with placebo beverage, increased both men's and women's smoking urge (Figure VIII.D-33), as well as subjective ratings of smoking reference puffs for either nicotine or VLNC cigarettes. The data are combined on cigarette type as there were no differences between Quest 3 and Quest 1. Regardless of cigarette type, alcohol (more than placebo) increased men's smoking behavior, including puff count, volume, and duration (Figure VIII.D-34). In contrast, for women, smoking topography measures did not differ between alcohol and placebo conditions. The authors concluded that the results indicate that the mechanisms underlying co-use of alcohol and tobacco in women may be more complex than in men.

Figure VIII.D-33. Smoking urges (From King *et al.* 2009 [pg301])

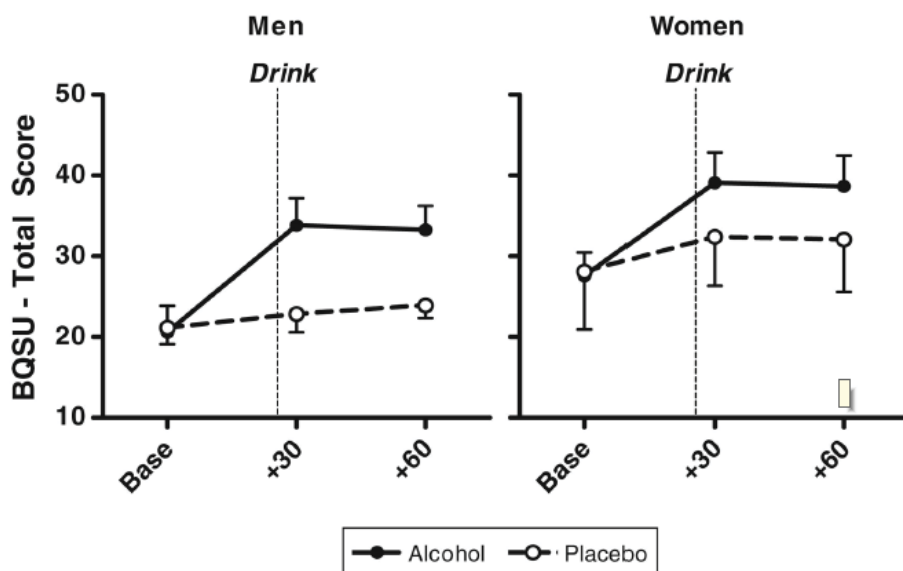
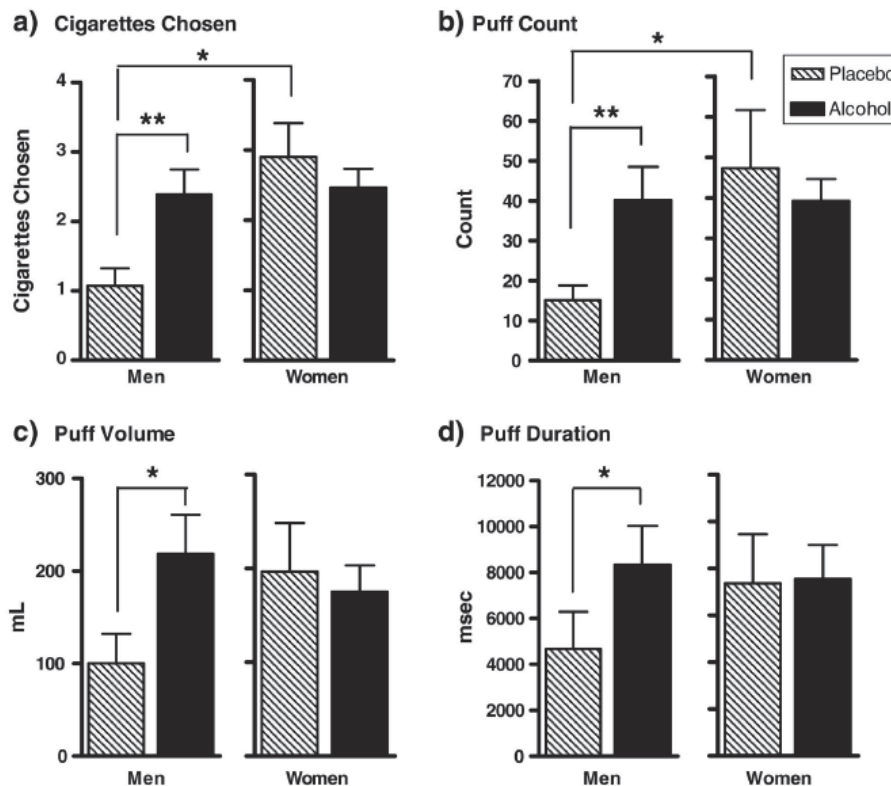


Figure VIII.D-34. Topography (From King *et al.* 2009 [pg301])



Conclusion: Alcohol increases smoking urge and puff count more in men than women.

xix. Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation.

This publication (Dermody *et al.* 2015 [pg298]) was a secondary data analysis of two analogous randomized trials of treatment-seeking, adult daily smokers (n=112) who were instructed to smoke VLNC cigarettes for 6 weeks and then make a quit attempt. Controlling for baseline demographic and smoking features, the association between reductions in nicotine exposure during the 6-week trial, assessed by urinary total cotinine, and biomarker-confirmed smoking abstinence one month later was tested. Subsequent analyses controlled for the effects of the frequency of VLNC and normal nicotine content cigarette use, and the nicotine yield of the VLNC cigarette (SPECTRUM® (0.05 mg) vs Xodus (0.09 mg)). Nicotine exposure at baseline, week

6, and week 12 was assessed by total urinary cotinine (urinary free cotinine plus cotinine N-glucuronide). Change in cotinine was examined in two ways: Week 6 cotinine level controlling for baseline cotinine level and percent change in cotinine level from baseline to week 6. The cotinine outcomes were natural log transformed due to positive skew. Abstinence at week 12 was defined as no VLNC or non-study cigarettes smoked during the past 7 days and carbon monoxide (CO) < 6 ng/ml. The analyses were replicated using cotinine (<35 ng/ml) to confirm self-reported abstinence.

At baseline, participants smoked 20.09 CPD and were moderately nicotine dependent (FTND=4.46). Lower urinary total cotinine level after smoking VLNC cigarettes for 6 weeks increased the odds of cessation 6 weeks later (Odds Ratio (OR)=0.52). This effect was replicated with percent change in cotinine (OR=0.46. Effects were not moderated by study or gender (i.e., non-significant interaction terms). Controlling for other covariates and sources of nicotine exposure, Week 6 urinary total cotinine level was significantly higher in the 2010 study, and among individuals who smoked 0.09 mg VLNC cigarettes, reported more non-study and VLNC CPD at Week 6, and marginally associated with non-compliance. Week 6 urinary total cotinine continued to predict abstinence (OR=0.44), after controlling for sources of nicotine exposure. Percent change in cotinine was significantly associated with non-study and VLNC CPD at Week 6. Percent change in cotinine remained significantly related to abstinence (OR=0.39), after controlling for sources of nicotine.

Conclusion: Greater reductions in nicotine exposure when smoking VLNC cigarettes were associated with increased cigarette abstinence.

xx. *Reduced nicotine content cigarettes and use of alternative nicotine products: Exploratory trial.*

The primary objective of this study was to evaluate the impact of alternative tobacco/nicotine products on smoking behaviors and biomarkers of exposure when smokers were switched to SPECTRUM® research cigarettes. Hatsukami, *et al.*, (2017) [\[pg300\]](#) studied one hundred thirty-five participants who were randomized to one of three conditions for eight weeks in a parallel arm study design: 1) SPECTRUM® cigarettes with access to non-cigarette combusted products and non-combusted tobacco and nicotine (including medicinal) products, referred to as VLNC1; 2) SPECTRUM® cigarettes with access to only non-combusted products, referred to as VLNC2; or 3) NNC cigarettes with access to non-cigarette combusted and non-combusted products, simulating the current marketplace, referred to as NNC. One of the primary comparisons was between VLNC1 and VLNC2 vs. NNC conditions to determine the effects of nicotine content in cigarettes on rate of use of alternative tobacco/nicotine products and the effects of cigarette type and use of these alternative products on smoking behaviors, smoking abstinence rates and biomarkers of tobacco exposure. Another primary comparison was between VLNC1 vs. VLNC2 to determine the effect of access to combusted and non-combusted products vs. non-combusted products alone on similar outcome measures.

Cigarette consumption decreased when compared to NNC cigarettes even when other tobacco products were consumed (Figure VIII.D-35). The mean number of combusted products used per day was decreased in the VLNC groups (Figure VIII.D-36). Biomarkers of exposure are shown in Table VIII.D-30. *BOE* (From Hatsukami *et al.* 2017 [\[pg300\]](#)). *TNE*, *NNAL* and *NNN* were reduced in the VLNC groups even though the subjects had access to alternative nicotine sources.

Conclusion: The use of alternative tobacco products does not mitigate the overall reduction in the usage of VLNC cigarettes or the biomarkers of exposure.

Figure VIII.D-35. CPD (From Hatsukami *et al.* 2017 [pg300])

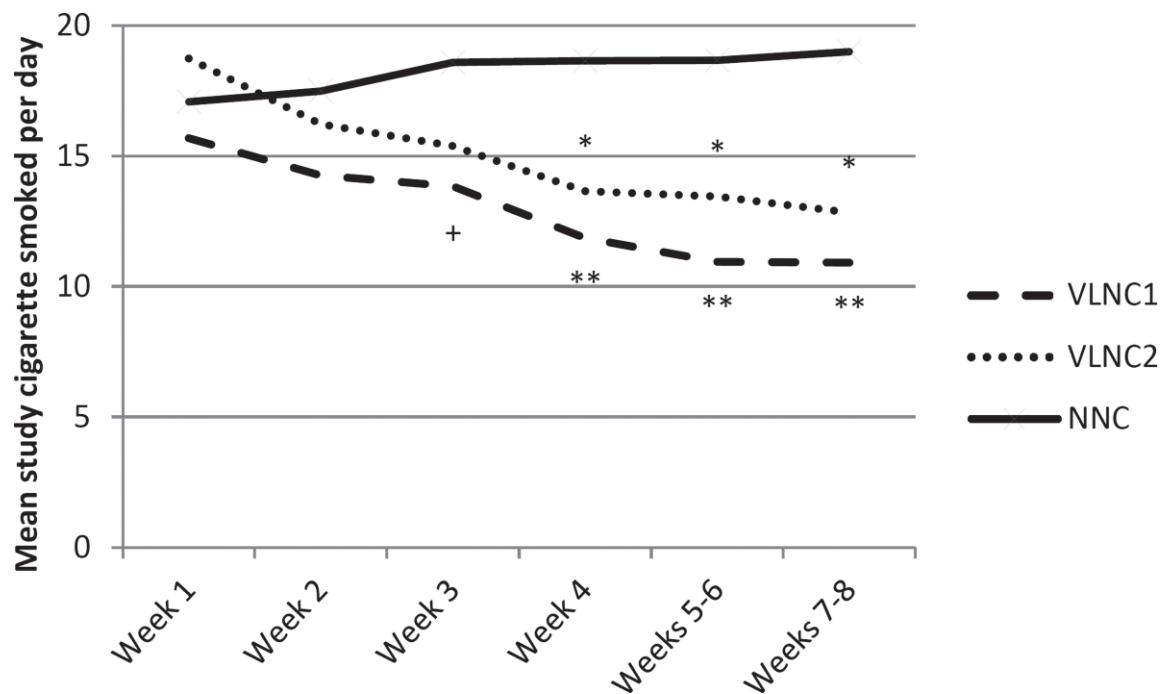


Figure VIII.D-36. Total CPD (From Hatsukami *et al.* 2017 [pg300])

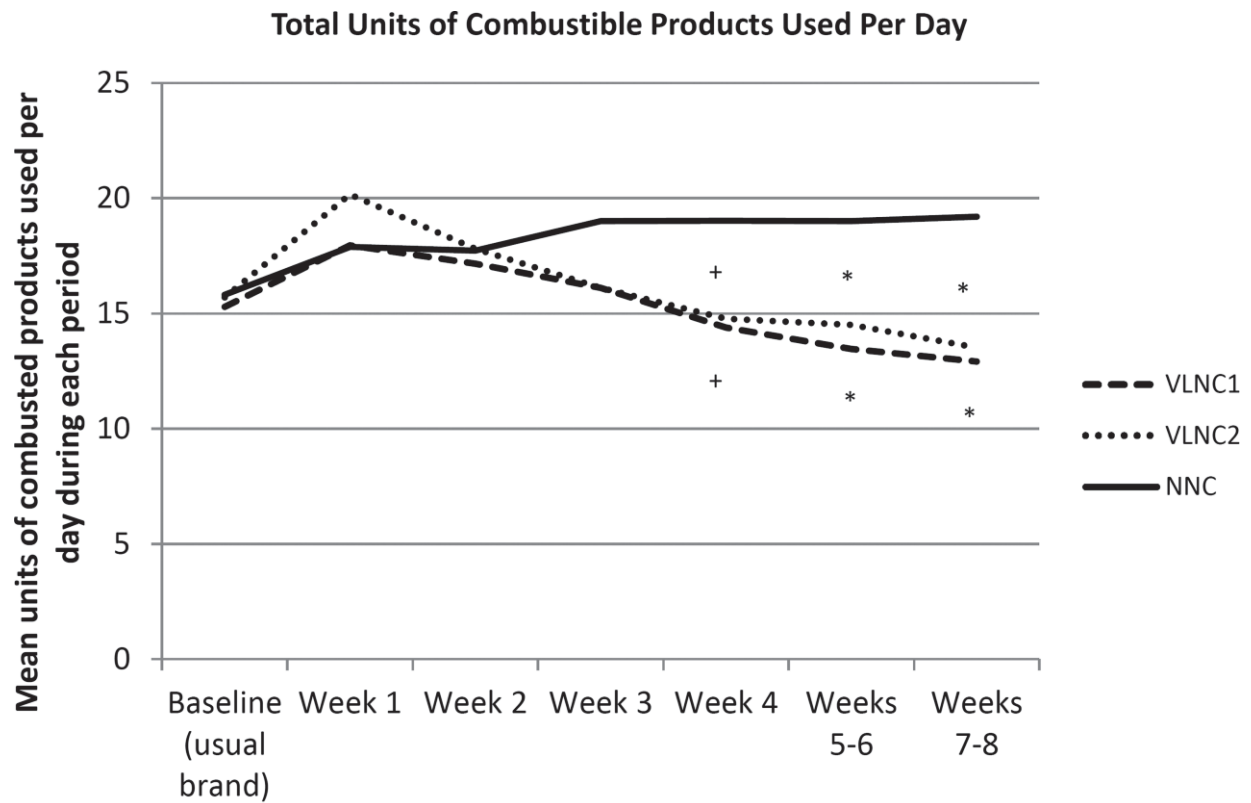


Table VIII.D-30. BOE (From Hatsukami *et al.* 2017 [pg300])

| | VLNC1 N=53 | VLNC2 N=56 | NNC N=27 | VLNC1 vs NNC | | VLNC2 vs NNC | | VLNC1 vs VLNC2 | |
|--|-------------------------------|-------------------------------|-------------------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|
| | Geometric mean (95% CI) | Geometric mean (95% CI) | Geometric mean (95% CI) | Unadjusted p-value | Adjusted p-value | Unadjusted p-value | Adjusted p-value | Unadjusted p-value | Adjusted p-value |
| TNE (nmol/mg creatinine) | | | | | | | | | |
| Baseline | 34.5 (28.5, 41.7) | 34.0 (28.9, 39.9) | 36.9 (29.2, 46.8) | | | | | | |
| Week 4 | 14.5 (9.4, 22.3) | 7.9 (5.4, 11.6) | 34.6 (27.7, 43.1) | 0.02 | 0.02 | <0.0001 | 0.02 | 0.02 | <0.0001 |
| Week 8 | 13.9 (7.9, 24.4) | 10.8 (7.0, 16.8) | 39.9 (32.5, 49.0) | <0.01 | <0.01 | <0.001 | <0.001 | | |
| Total NNAL (pmol/mg creatinine) | | | | | | | | | |
| Baseline | 1.33 (0.96, 1.83) | 1.17 (0.88, 1.56) | 1.54 (1.09, 2.17) | | | | | | |
| Week 4 | 0.99 (0.63, 1.54) | 0.50 (0.36, 0.70) | 1.22 (0.92, 1.63) | | | <0.01 | <0.01 | <0.01 | <0.01 |
| Week 8 | 0.71 (0.41, 1.23) | 0.51 (0.35, 0.74) | 1.22 (0.91, 1.65) | | | <0.01 | <0.01 | | |
| Total NNN (pmol/mg creatinine) | | | | | | | | | |
| Baseline | 0.039 (0.023, 0.064) | 0.022 (0.016, 0.031) | 0.031 (0.018, 0.051) | | | | | | |
| Week 4 | 0.025 (0.015, 0.040) | 0.020 (0.013, 0.031) | 0.035 (0.020, 0.063) | | | | | | |
| Week 8 | 0.025 (0.014, 0.046) | 0.015 (0.010, 0.022) | 0.035 (0.019, 0.068) | | | 0.02 | 0.04 | | |

VLNC1: Very low nicotine content cigarettes with access to non-cigarette combusted and non-combusted tobacco/nicotine products

VLNC2: Very low nicotine content cigarettes with access to only non-combusted tobacco/nicotine products

NNC: Normal nicotine content cigarettes with access to non-cigarette combusted and non-combusted tobacco/nicotine products

TNE: Total nicotine equivalents, biomarker for nicotine exposure

Total NNAL: Biomarker for exposure to carcinogen, NNK

Total NNN: Biomarker for exposure to carcinogen, NNN

Unadjusted: Linear mixed effects model with the covariates of study arm, week, and their interaction.

Adjusted: Linear mixed effects model with the covariates of study arm, week, and their interaction, adjusting for the baseline level of the corresponding biomarker.

xxi. Abrupt nicotine reduction as an endgame policy: A randomized trial.

This was a randomized, parallel-group trial conducted by Walker, *et al.*, (2014) [pg304] in New Zealand. Thirty-three dependent adult daily smokers unmotivated to quit were randomly allocated to an intervention group provided with 12 weeks supply of free very low nicotine content Magic cigarettes, or to a control group, who were free to purchase their usual cigarette brand over the same period. The primary outcome was change from baseline in the daily mean number of usual cigarettes smoked over the previous week, measured at 12 weeks. Secondary outcomes at 6 and 12 weeks included cigarettes smoked per week (also measured at weeks 1–6

and 9), salivary cotinine, tobacco dependence, smoking satisfaction/craving, behavioral addiction to smoking, autonomy over smoking, motivation to stop, quitting and adverse events.

The VLNC group reduced their cigarette consumption by half at all time points. Salivary cotinine was also reduced (Table VIII.D-31. *CPD* (From Walker *et al.* 2014 [pg304])). Overall, the participants in the intervention group smoked a similar total amount of CPD (usual plus VLNC) as participants in the control group over the 12-week period but replaced their usual brand with VLNC cigarettes (Figure VIII.D-37). Participants were heavily dependent at baseline but by 12-weeks dependence had reduced, more so in the VLNC group. The change from baseline to 12-weeks in motivation to stop smoking was not significantly different in the intervention group compared with the control group. However, participants in the intervention group were more likely to have made a quit attempt during the 12-week study period (seven participants), compared with those in the control group (one participant). In the intervention group, two participants had quit smoking usual cigarettes and no participants had quit smoking usual as well as VLNC cigarettes (7-day point prevalence abstinence at 12 weeks). In comparison, one participant had quit smoking usual cigarettes in the control group. In terms of continuous abstinence at 12 weeks, two participants in the intervention group had quit smoking usual cigarettes compared with one in the control group.

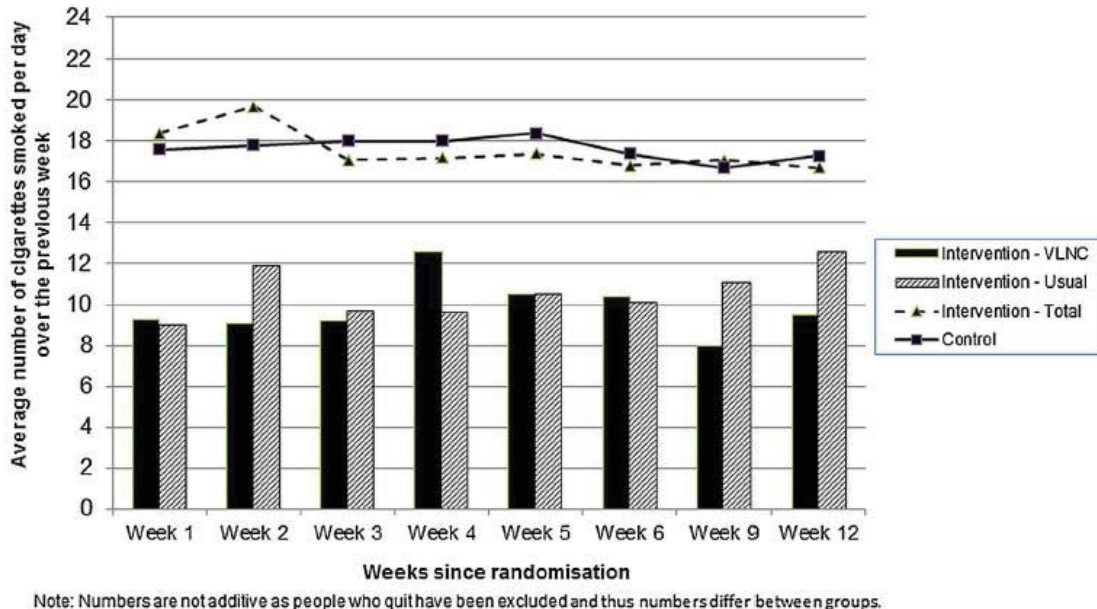
Conclusion: Smokers unmotivated to quit will reduce their usual cigarette consumption when VLNC cigarettes are available.

Table VIII.D-31. CPD (From Walker *et al.* 2014 [pg304])

| | Intervention (n=17) | Control (n=15) | p Value |
|--|-------------------------|-----------------------|---------|
| Change in number of usual CPD in the previous week | | | |
| 6 weeks (median, IQR) | -5.29 (-10.50 to -2.00) | -0.55 (-1.71 to 1.11) | 0.002* |
| 12 weeks (median, IQR) | -2.00 (-6.57 to -0.43) | -0.64 (-3.68 to 0.43) | 0.066* |
| Change in salivary cotinine (ng/mL)†‡ | | | |
| 6 weeks (mean, SD) | -9.5 (23.5) | 16.4 (32.4) | 0.022 |
| 12 weeks (mean, SD) | 10.9 (23.0) | 17.1 (22.1) | 0.495 |
| Change in mCEQ‡ (6 weeks) | | | |
| Satisfaction (median, IQR) | -0.50 (-1.00 to 0.33) | -0.33 (-0.67 to 0) | 0.922* |
| Psychological reward (mean, SD) | -0.41 (1.41) | -0.69 (0.92) | 0.520 |
| Aversion (median, IQR) | 0.5 (0 to 1.5) | 0 (-0.5 to 0) | 0.022* |
| Sensations (mean, SD) | 0 (-2 to 1) | 0 (0 to 1) | 0.346* |
| Craving (median, IQR) | 0 (-1.5 to 0.5) | 0 (-2 to 1) | 0.857* |
| Change in mCEQ‡ (12 weeks) | | | |
| Satisfaction (median, IQR) | -0.33 (-0.67 to 0.67) | -0.50 (-1 to 0) | 0.230* |
| Psychological reward (mean, SD) | -0.80 (1.46) | -0.63 (1.02) | 0.719 |
| Aversion (median, IQR) | 0 (-0.5 to 0) | 0 (-0.5 to 0) | 0.623* |
| Sensations (mean, SD) | -0.33 (2.61) | 0.50 (1.22) | 0.287 |
| Craving (median, IQR) | 0 (-1 to 0) | -1 (-1 to 1) | 0.036* |
| Change in GN-SBQ‡ | | | |
| 6 weeks (mean, SD) | -4 (-5 to 0) | -3 (-5 to -1) | 0.366* |
| 12 weeks (mean, SD) | -5.29 (4.89) | -1.71 (3.52) | 0.036 |
| Change in AUTOS‡ (6 weeks) | | | |
| Total score (mean, SD) | -4.5 (-7.0 to -2.5) | -3.0 (-6.0 to 0) | 0.259* |
| Withdrawal symptoms (mean, SD) | -2.0 (-3.0 to -0.5) | -1.0 (-3.0 to 0) | 0.416* |
| Psychological dependence (median, IQR) | -1.5 (-3.5 to 0) | -1.0 (-2.0 to 0) | 0.270* |
| Cue-induced cravings (mean, SD) | -2.0 (-2.5 to 0) | -1.0 (-2.0 to 0) | 0.293* |
| Change in AUTOS‡ (12 weeks) | | | |
| Total score (mean, SD) | -5.53 (5.55) | -2.00 (4.51) | 0.072 |
| Withdrawal symptoms (mean, SD) | -2.53 (2.56) | -0.64 (1.65) | 0.027 |
| Psychological dependence (median, IQR) | -2.00 (-3.00 to -1.00) | -1.00 (-2.00 to 0) | 0.162* |
| Cue-induced cravings (mean, SD) | -0.93 (1.49) | -0.50 (1.91) | 0.500 |

All tests of significance are between group comparisons and t tests (unless otherwise indicated).
 *Mann-Whitney test.
 †One baseline extreme outlier in the control group was excluded from analysis.
 ‡People who quit have been excluded (three quitters at 12 weeks: two in the intervention group and one in the control group; and one quitter in the intervention group was excluded at 6 weeks).
 AUTOS, Autonomy Over Tobacco Smoking Scale; CPD, cigarettes smoked per day; GN-SBQ, Glover Nilsson Smoking Behavioural Questionnaire; mCEQ, modified Cigarette Evaluation Questionnaire.

Figure VIII.D-37. CPD (From Walker *et al.* 2014 [pg304])



xxii. *Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use.*

This is a secondary analysis of a study examining the effect of nicotine content on smoking behavior performed by Donny, *et al.*, (2015) [pg299]. Pacek, *et al.*, (2106) [pg302] performed a linear regression assessing whether baseline cannabis use moderated behavioral, subjective, or physiological effects of smoking very low nicotine content (VLNC) versus normal nicotine content (NNC) cigarettes. Repeated measures analysis of associations between nicotine condition and prevalence and frequency of cannabis use was completed using generalized estimating equations (GEE).

At baseline, 28.9% of the study subjects were current cannabis users. VLNC cigarettes significantly decreased CPD, FTND scores, QSU scores and TNE in cannabis users and non-users (Table VIII.D-32). VLNC cigarettes significantly decreased WISDM, total NNAL, total puff count, and total puff volume among non-cannabis users, while significantly decreasing PANAS positive affect scores among cannabis users. Cannabis use significantly moderated the effect of VLNC cigarettes

on QSU Factor 1 scores: cannabis users exhibited greater decreases in QSU Factor 1 scores than non-cannabis users. Assignment to VLNC versus NNC cigarettes was not associated with days of cannabis use.

Table VIII.D-32. CPD and smoking urges (From Pacek *et al.* 2016 [pg302])

| Outcome | Unadjusted Model ^a | | | Adjusted Model ^b | | |
|-----------------------|-------------------------------|-------------------------|---------------------|-----------------------------|-------------------------|---------------------|
| | No Cannabis Use | Cannabis Use | Interaction p-value | No Cannabis Use | Cannabis Use | Interaction p-value |
| FTND | -0.92 (-1.22, -0.62) | -0.57 (-1.00, -0.13) | 0.202 | -0.94 (-1.25, -0.64) | -0.58 (-1.01, -0.14) | 0.246 |
| QSU total score | -4.53 (-6.90, -2.15) | -9.14 (-12.56, -5.73) | 0.072 | -4.49 (-6.92, -2.07) | -8.96 (-12.49, -5.42) | 0.069 |
| QSU Factor 1 | -3.29 (-4.75, -1.84) | -5.93 (-8.10, -3.75) | 0.065 | -3.22 (-4.70, -1.73) | -5.89 (-8.12, -3.66) | 0.049 |
| QSU Factor 2 | -1.36 (-2.41, -0.31) | -3.21 (-4.73, -1.69) | 0.124 | -1.40 (-2.47, -0.32) | -3.04 (-4.62, -1.46) | 0.166 |
| MNWS | -0.61 (-1.45, 0.23) | -0.05 (-1.26, 1.16) | 0.457 | -0.74 (-1.58, 0.10) | -0.14 (-1.43, 1.14) | 0.511 |
| CESD | -0.36 (-1.81, 1.08) | 0.09 (-2.22, 2.40) | 0.732 | -0.54 (-2.01, 0.92) | 0.35 (-2.09, 2.78) | 0.564 |
| PSS | -0.22 (-0.72, 0.29) | -0.02 (-0.82, 0.78) | 0.685 | -0.22 (-0.74, 0.29) | 0.02 (-0.80, 0.83) | 0.631 |
| PANAS positive affect | -0.24 (-1.56, 1.09) | -1.85 (-3.90, 0.21) | 0.181 | -0.28 (-1.63, 1.06) | -2.25 (-4.33, -0.17) | 0.106 |
| PANAS negative affect | 0.05 (-0.96, 1.07) | -0.65 (-2.34, 1.04) | 0.512 | -0.14 (-1.14, 0.86) | -0.61 (-2.36, 1.15) | 0.559 |
| WISDM | -4.13 (-6.00, -2.26) | -0.51 (-3.38, 2.35) | 0.042 | -4.37 (-6.20, -2.53) | -0.94 (-3.84, 1.96) | 0.074 |
| CO | -0.64 (-2.07, 0.78) | -1.49 (-3.64, 0.67) | 0.377 | -0.56 (-2.01, 0.89) | -1.69 (-3.93, 0.55) | 0.298 |
| CPD | -6.08 (-7.51, -4.64) | -6.68 (-8.89, -4.48) | 0.734 | -6.19 (-7.63, -4.74) | -6.54 (-8.82, -4.26) | 0.748 |
| TNE ^c | -0.80 (-1.04, -0.56) | -0.61 (-1.00, -0.22) | 0.395 | -0.76 (-1.00, -0.52) | -0.61 (-1.02, -0.20) | 0.458 |
| NNAL ^c | -0.30 (-0.46, -0.13) | -0.22 (-0.48, 0.04) | 0.641 | -0.28 (-0.45, -0.11) | -0.19 (-0.46, 0.08) | 0.560 |
| Puff count | -1.55 (-2.38, -0.73) | -0.97 (-2.44, 0.51) | 0.468 | -1.58 (-2.42, -0.73) | -1.04 (-2.6, 0.52) | 0.572 |
| Total puff volume | -107.85 (-154.73, -60.98) | -51.48 (-123.92, 20.96) | 0.250 | -97.81 (-145.25, -50.37) | -66.96 (-144.26, 10.34) | 0.574 |
| Mean puff volume | -1.12 (-4.02, 1.79) | -0.8 (-5.40, 3.81) | 0.853 | -0.57 (-3.51, 2.36) | -1.39 (-6.34, 3.16) | 0.773 |

Note: Bolded text indicates statistically significant findings p<0.05

Outcomes are expressed as differences between the VLNC and NNC conditions. Negative values indicate that those in the VLNC condition reported lower scores on a measure relative to those in the NNC condition.

Abbreviations: NNC=normal nicotine content; VLNC=very low nicotine content; CESD=Centers for Epidemiological Studies of Depression Scale; PSS=Perceived Stress Scale; PANAS=Positive and Negative Affect Scale; CPD=cigarettes per day; FTND=Fagerstrom Test for Nicotine Dependence; CO=carbon monoxide; QSU=Questionnaire of Smoking Urges; MNWS=Minnesota Nicotine Withdrawal Scale; WISDM=Wisconsin Inventory of Smoking Dependence Motives; TNE=total nicotine equivalents; NNAL=a biomarker of [NNK] exposure

^a Adjusted for baseline value only

^b Adjusted for age, race, sex, education, and NMR, along with baseline value

Conclusion: Cannabis use is unlikely to affect VLNC use and VLNC use is unlikely to affect cannabis use.

xxiii. *Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings?*

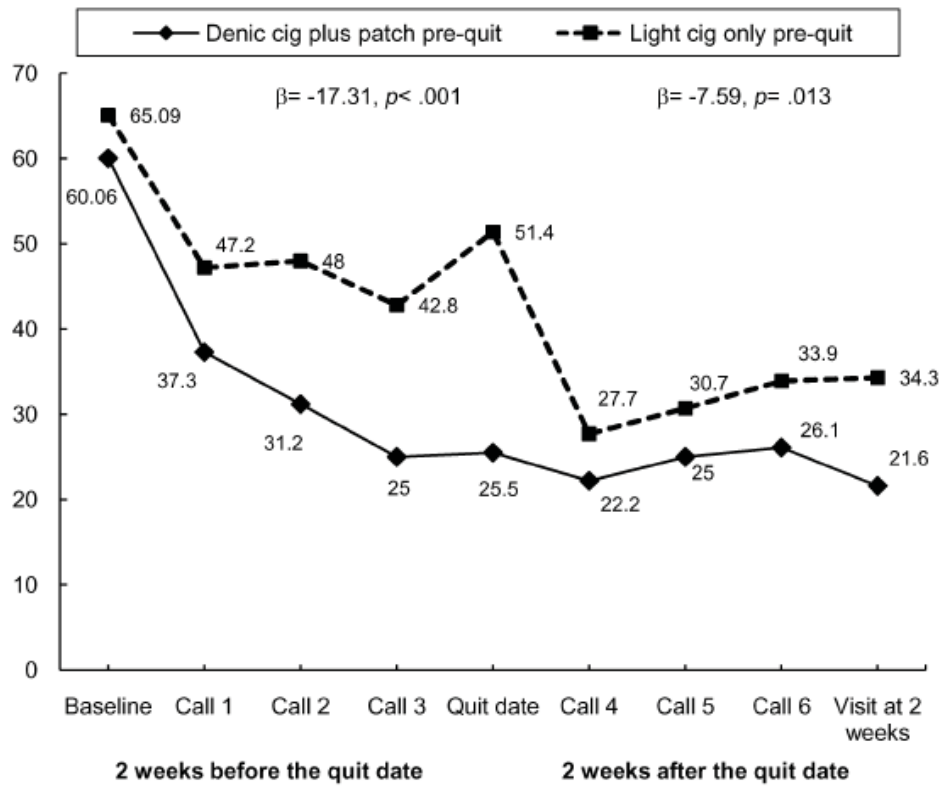
Rezaishiraz, *et al.*, (2007) [pg303] investigated whether treatment with the combination of denicotinized cigarettes and 21-mg nicotine patch for 2 weeks before a designated quit date could lessen cravings for smoking, thereby helping smokers abstain from smoking. The study was a randomized controlled clinical trial with 98 adult heavy smokers (using 20 or more cigarettes/day). Half of the subjects received 2 weeks of combination of denicotinized cigarettes

(Quest 3) and 21-mg nicotine patch for 2 weeks before the quit date. The remaining smokers were switched to light cigarettes (Quest 1) during the 2 weeks before the quit date. After the quit date, all subjects received counseling for smoking cessation and were provided nicotine patches for up to 8 weeks after the quit date. Self-reported cravings for smoking, withdrawal symptoms, and smoking abstinence were measured at predetermined intervals using phone-based surveys and in clinical visits.

The group that used denicotinized cigarettes and nicotine patch before quitting reported less frequent and less intense cravings for cigarettes in the 2 weeks before and after the designated quit date (Figure VIII.D-38). Self-reported withdrawal symptoms and quit rates did not differ significantly between the groups (Figure VIII.D-39). Self-reported quit rates at 3 and 6 months were not different (both groups had NRT for up to 8-weeks post quit date) (Figure VIII.D-40).

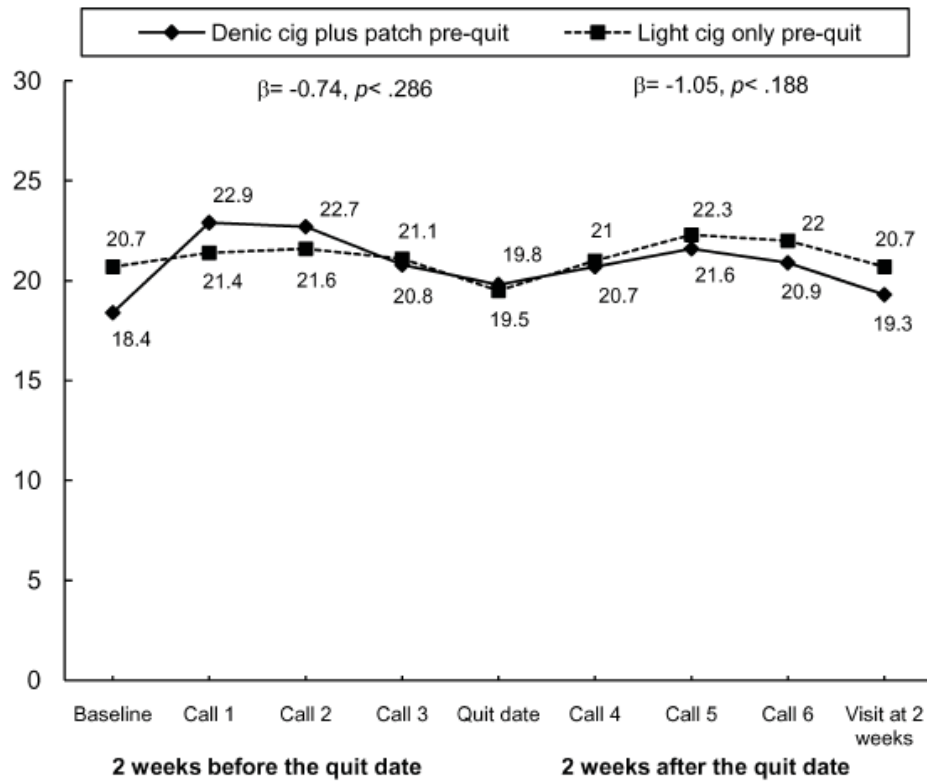
Conclusion: VLNC may be effective in helping reduce cravings prior quit date.

Figure VIII.D-38. Craving (From Rezaishiraz, *et al.*, 2007 [pg303])



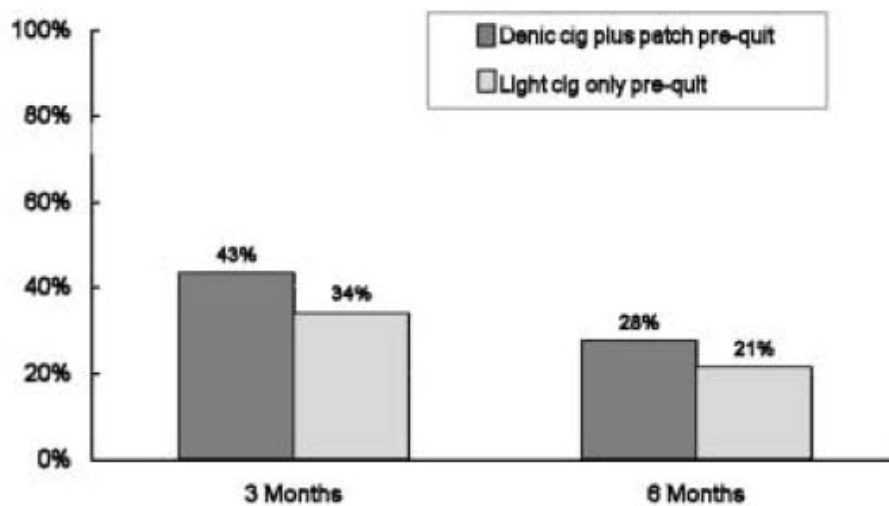
Combined craving score by treatment ($N=98$). Score=severity of craving \times frequency of craving. Beta and p values obtained from mixed-model analysis.

Figure VIII.D-39. Withdrawal (From Rezaishiraz, *et al.*, 2007 [pg303])



Withdrawal score by treatment ($n=98$). Score=sum of scores for anger+nervousness+distractibility+impatience+appetite+insomnia+depression+desire to smoke (Koeltzow & Vezina, 2005). Beta and p values obtained from mixed-model analysis (adjusted for baseline values).

Figure VIII.D-40. Quit rates (From Rezaishiraz, *et al.*, 2007 [pg303])



Self-reported quit rates by treatment arm at 3 and 6 months ($N=98$). Quitting defined as abstinence from smoking during the 7 days preceding the assessment.

xxiv. Effects of 6-week use of reduced-nicotine content cigarettes in smokers with and without elevated depressive symptoms.

This is a secondary analysis of a study examining the effect of SPECTRUM® cigarettes with varying nicotine content on smoking behavior performed by Donny, *et al.*, (2015) [pg299]. Tidey, *et al.*, (2017) [pg303] used linear regression to examine whether baseline depressive symptom severity (scores on the Center for Epidemiologic Studies Depression Scale [CES-D]) moderated the effects of reduced-nicotine content (RNC) cigarettes, relative to normal-nicotine content (NNC) cigarettes, on smoking rates, depressive symptom severity, and related subjective and physiological measures.

Of the 717 participants included in this analysis, 109 (15.2%) had CES-D scores ≥ 16 , indicative of possible clinical depression. Relative to NNC cigarettes, RNC cigarettes reduced smoking rates, nicotine dependence, and cigarette craving, and these effects were not

significantly moderated by baseline CES-D score. A significant interaction between baseline CES-D score and cigarette condition on week 6 CES-D score was observed ($p < .05$); among those with CES-D scores ≥ 16 at baseline, those assigned to RNC cigarettes had lower week 6 CES-D scores than those assigned to NNC cigarettes (Table VIII.D-33). Among those in the lowest nicotine content (0.4 mg nicotine/g tobacco) conditions, biochemically confirmed compliance with the RNC cigarettes was associated with an increase in CES-D score for those with baseline CES-D scores < 16 and no change in CES-D score for those with baseline CES-D scores ≥ 16 .

Conclusion: Reduced nicotine cigarettes may reduce smoking, without worsening depressive symptoms, in subjects with elevated depressive symptoms.

Table VIII.D-33. CPD (Tidey et al. 2017 [pg303])

| Outcome | Interaction tests | | | | CES-D < 16 | | | | CES-D ≥ 16 | | | |
|----------------------------------|-------------------------------|-----|-----------------------------|---|-------------------------------|-------|-----------------------------|-------|-------------------------------|-------|-----------------------------|------|
| | Unadjusted model ^b | | Adjusted model ^b | | Unadjusted model ^b | | Adjusted model ^b | | Unadjusted model ^b | | Adjusted model ^b | |
| | p | p | p | p | Mean difference | p | Mean difference | p | Mean difference | p | Mean difference | p |
| Drinks per day (75th percentile) | .35 | .30 | | | 0.1 (-0.3, 0.4) | .48 | 0.01 (-0.22, 0.25) | .96 | 0.6 (-0.4, 1.7) | 1 | 0.5 (-0.2, 1.2) | 1 |
| Cannabis use ^c | .19 | .11 | | | 1.0 (0.9, 1.0) | .73 | 1.0 (0.9, 1.1) | .81 | 1.1 (0.9, 1.3) | .27 | 1.1 (1.0, 1.3) | .15 |
| CFO | .44 | .47 | | | -6.4 (-7.7, -5.1) | <.001 | -6.3 (-7.6, -5) | <.001 | -5.1 (-6.2, -3.9) | .002 | -5.5 (-6.7, -4.4) | .001 |
| TNPs | .40 | .41 | | | 0.5 (0.4, 0.6) | <.001 | 0.5 (0.41, 0.62) | <.001 | 0.4 (0.2, 0.6) | <.001 | 0.4 (0.3, 0.7) | .001 |
| Breath CO | .52 | .42 | | | -0.71 (-2, 0.6) | .27 | -0.6 (-1.9, 0.7) | .36 | -2.2 (-5.1, 0.7) | .14 | -2.1 (-5.1, 0.9) | .17 |
| FTND | .99 | .88 | | | -0.8 (-1.1, -0.6) | <.001 | -0.8 (-1.1, -0.5) | <.001 | -0.8 (-1.5, -0.1) | .03 | -1 (-1.7, -0.2) | .01 |
| Total puff volume | .06 | .10 | | | -309 (-353, -67) | <.001 | -303 (-344, -61) | <.001 | 18 (-108, 131) | .97 | -4.0 (-117, 109) | .95 |
| CES-D Total | .03 | .03 | | | 0.3 (-1.1, 1.7) | .64 | 0.2 (-1.2, 1.6) | .77 | -4.4 (-8.4, -0.4) | .03 | -4.8 (-8.7, -0.9) | .02 |
| Depressed | .03 | .03 | | | 0.3 (-0.2, 0.8) | .23 | 0.3 (-0.3, 0.8) | .35 | -1.4 (-3, 0.2) | .10 | -1.8 (-3.3, -0.2) | .08 |
| Positive | .85 | .99 | | | 0.1 (-0.4, 0.5) | .92 | 0.1 (-0.5, 0.8) | .99 | 0.3 (-1, 1.6) | .69 | 0.2 (-1.2, 1.6) | .77 |
| Somatic | .01 | .01 | | | 0.1 (-0.5, 0.6) | .90 | 0.1 (-0.6, 0.9) | .88 | -1.9 (-3.5, -0.3) | .02 | -2.1 (-3.7, -0.6) | .01 |
| Interpersonal | .19 | .18 | | | 0.1 (-0.1, 0.2) | .75 | 0.1 (-0.2, 0.2) | .88 | -0.3 (-0.9, 0.3) | .36 | -0.3 (-1, 0.3) | .29 |
| WISDM total | .66 | .66 | | | -3.2 (-5, -1.5) | <.001 | -3.6 (-5.3, -1.9) | <.001 | -1.8 (-5.9, 2.2) | .38 | -2.9 (-6.7, 1) | .15 |
| QSU Fiance 1 | .91 | .99 | | | -4 (-5.3, -2.7) | <.001 | -4 (-5.3, -2.7) | <.001 | -4 (-7.6, -0.4) | .03 | -4.3 (-8, -0.5) | .08 |
| QSU Fiance 2 | .26 | .30 | | | -1.6 (-2.6, -0.7) | .001 | -1.6 (-2.6, -0.7) | .001 | -3.4 (-5.9, -0.9) | .01 | -3.7 (-6.3, -1.1) | .01 |
| MNWS | .87 | .67 | | | -0.5 (-1.2, 0.3) | .22 | -0.5 (-1.3, 0.2) | .14 | -0.7 (-2.8, 1.4) | .52 | -1.3 (-3.4, 0.7) | .20 |
| PANAS positive | .73 | .52 | | | -0.7 (-1.9, 0.5) | .27 | -0.7 (-1.9, 0.5) | .26 | -0.5 (-3.5, 2.9) | .76 | -0.2 (-3.3, 3) | .91 |
| PANAS negative | .09 | .06 | | | 0.2 (-0.7, 1.1) | .74 | 0.1 (-0.9, 0.9) | .96 | -2.2 (-4.9, 0.6) | .13 | -2.7 (-5.3, -0.2) | .04 |
| Noncompliance ^d | .12 | .15 | | | 1.3 (1.2, 1.4) | <.001 | 1.3 (1.2, 1.4) | <.001 | 1.1 (0.9, 1.4) | .34 | 1.1 (0.9, 1.4) | .029 |
| Quit attempt ^e | .96 | .90 | | | 1.9 (1.2, 2.9) | .01 | 1.9 (1.2, 2.9) | .01 | 1.9 (0.7, 5.6) | .23 | 2.9 (0.8, 10.2) | .10 |

Bold values are statistically significant. CES-D is a Center for Epidemiologic Studies Depression Scale; CO is carbon monoxide; CFO is cigarettes per day; FTND is Fagerstrom Test of Nicotine Dependence; MNWS is Minnesota Nicotine Withdrawal Scale; NNC is a normal baseline control; PANAS is Positive and Negative Affect Scale; QSU is Questionnaire on Smoking Urges; RNC is reduced nicotine unit; TNPs is total nicotine equivalents; WISDM is Wisconsin Inventory of Smoking Dependence Motives.

^aAdjusted for baseline value only.

^bAdjusted for age, race (white, African American, other), sex, education (<12 vs. ≥12 yr), and nicotine metabolite ratio, along with baseline value.

^cTreatment effect represented by odds ratios.

^dTreatment effect represented by ratio of geometric means.

xxv. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of Quest alone and in combination with nicotine replacement therapy as a smoking cessation aid (IND 69,185).

This study was performed for Vector Tobacco Company using 22nd Century VLN™ tobacco. 22nd Century has the right to cite Vector's data. 22nd Century does not have any additional records related to the study other than the ones included with this application for IND69185. Original records may be found in the IND submissions.

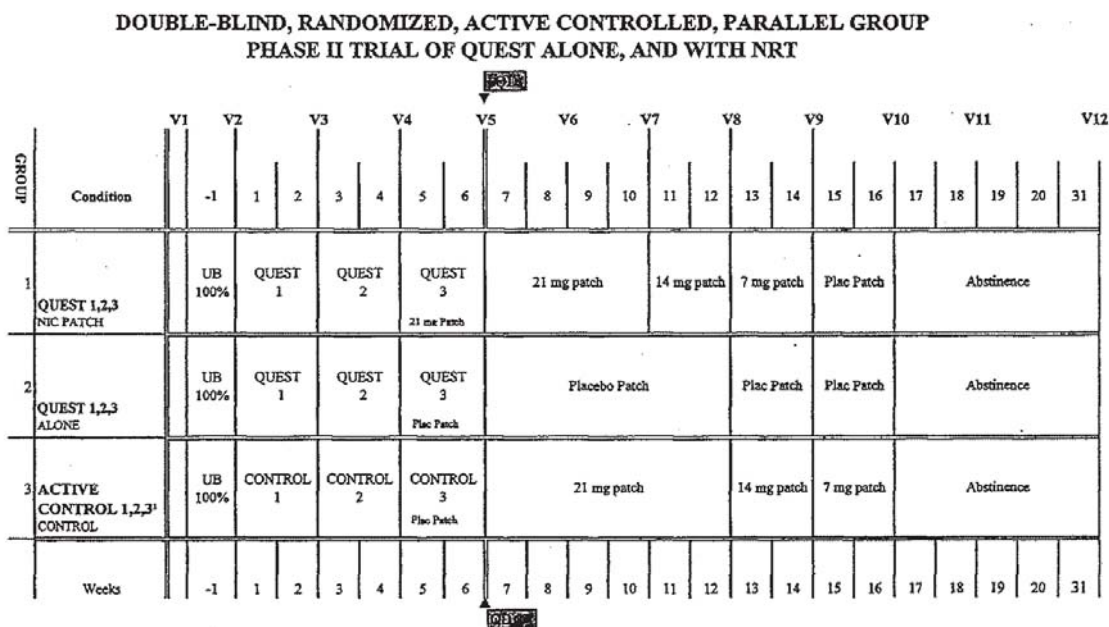
This study (Vector Tobacco Inc. 2006, IND69185 [[pg304](#)]) was a randomized trial of 346 subjects motivated to quit subjects. The subjects were randomized to one of three treatments:

- Group 1: Quest 1, Quest 2, Quest 3 plus NRT patch
- Group 2: Quest 1, Quest 2, Quest 3 plus placebo patch
- Group 3: Active control cigarettes plus NRT patch

Figure VIII.D-41 shows the study design. Subjects were followed over 8 months at five clinical sites. Subjects in group 1 and 2 transitioned from Quest 1 to Quest 3 over 5 weeks. At week 5, groups 1 and 2 received their respective NRT patches. The end of week 6 was the quit date. Endpoints included abstinence, quit rates, subjective questionnaires and cigarettes per day.

Four-week abstinence data (ITT population) was 43.2% in group 1, 24.1% in group 2 and 26.3% in group 3. This study demonstrated that Quest was as effective as standard of care NRT treatment in achieving abstinence at four weeks and suggests that Quest alone may be as effective as standard of care NRT. No statistically significant differences were observed in three- or six-month quit rates.

Figure VIII.D-41. Study design (From Vector IND 69,185 November 22, 2004 Update)



QD - Quit All Smoking

¹ Active Control Cigarettes: Conventional, American blended and Sham-faded

Conclusion: Quest was effective for abstinence.

xxvi. Sex differences in acute relief of abstinence-induced withdrawal and negative affect due to nicotine content in cigarettes.

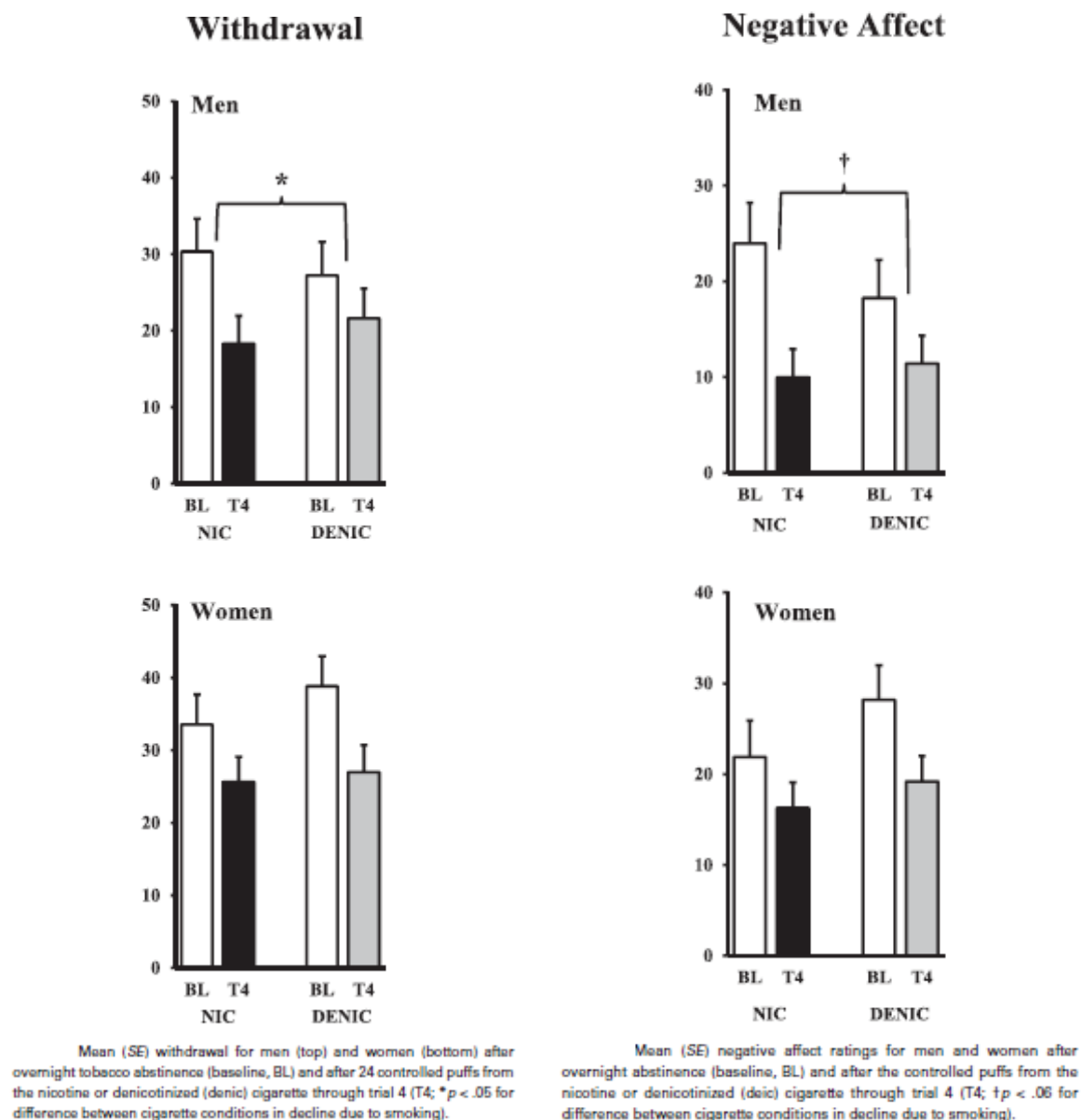
This study by Perkins and Karelitz (2015) [pg302] used a within-subjects design to assess acute effects of intermittently smoking nicotine versus denicotinized cigarettes on relief of withdrawal and negative affect in 21 male and 22 female dependent smokers who were abstinent overnight. Each Quest cigarette was administered to participants blind to brand markings and nicotine content, with the amount of smoking intake (i.e. topography) controlled (24 puffs over 2 hours). Withdrawal symptoms were obtained before and after smoking, and negative affect was assessed after each period of cigarette exposure consisting of 6 puffs every 25 min.

Men and women did not differ in baseline withdrawal and negative affect due to overnight abstinence, but reductions in each symptom were significantly influenced by the

interaction of sex X nicotine/denicotinized cigarette. In men, but not in women, each symptom was generally decreased more by the nicotine versus denicotinized cigarette, and the nicotine cigarette reduced each to a greater degree in men versus women. Puff volume was less but CO boost and perceived nicotine amount were greater for the nicotine versus denicotinized cigarette. Yet, men and women did not differ at all in these relative responses to the two different cigarettes, in sharp contrast to their differential affective responses.

Conclusion: Nicotine appears to be less rewarding in women than men.

Figure VIII.D-42. Withdrawal (From Perkins and Karelitz 2015 [pg302])



xxvii. Reduced Nicotine Content Cigarettes and Nicotine Patch.

Hatsukami, *et al.*, (2013, *Cancer Epidemiology...*) [pg300] was interested in examining the feasibility of using Quest cigarettes as a method to significantly reduce smoking behavior and the effects of adding the nicotine patch in augmenting beneficial effects from VLNC cigarettes. Seventy-nine smokers interested in quitting were enrolled in the study. After a two-week period

during which baseline measurements were collected while subjects smoked their usual brand ad libitum, subjects were assigned to one of three conditions: a) 0.05-0.09 mg nicotine yield cigarettes (Quest 3), that is very low nicotine content cigarettes, b) 21 mg nicotine patch (NP), or c) combination of both. Subjects were initially assigned Quest 3 cigarettes. These cigarettes were no longer available after randomizing 27% of the subjects, so the study was switched to Xodus³⁹. Subjects were instructed to use only assigned products for six weeks, after which time they were to discontinue all product use. Subjects were seen weekly during the 6-week product assignment period and an additional 6 weeks at weeks 7, 8, 10 and 12 for continued behavioral treatment. At each visit, subjects assigned to either cigarette condition were provided a supply equivalent to 150% of their baseline smoking rate (to allow for compensatory smoking) and were told to smoke these VLNC cigarettes ad libitum, that is, as they would smoke their usual cigarettes. Subjects assigned to receive nicotine patch were informed to replace the old patch with the new patch each morning. Subjects maintained a daily smoking diary where they recorded any cigarettes smoked (either those assigned to them or their usual brand). They were not penalized for smoking unassigned cigarettes but told that although we do not encourage them to smoke cigarettes other than those assigned, it is crucial to the study that they accurately report all cigarette use. Follow-up visits occurred at 16, 24 and 36 weeks.

Biomarkers of tobacco exposure measures included a) urinary total nicotine equivalents (TNE) b) urinary total cotinine, c) alveolar carbon monoxide and d) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL). All measures

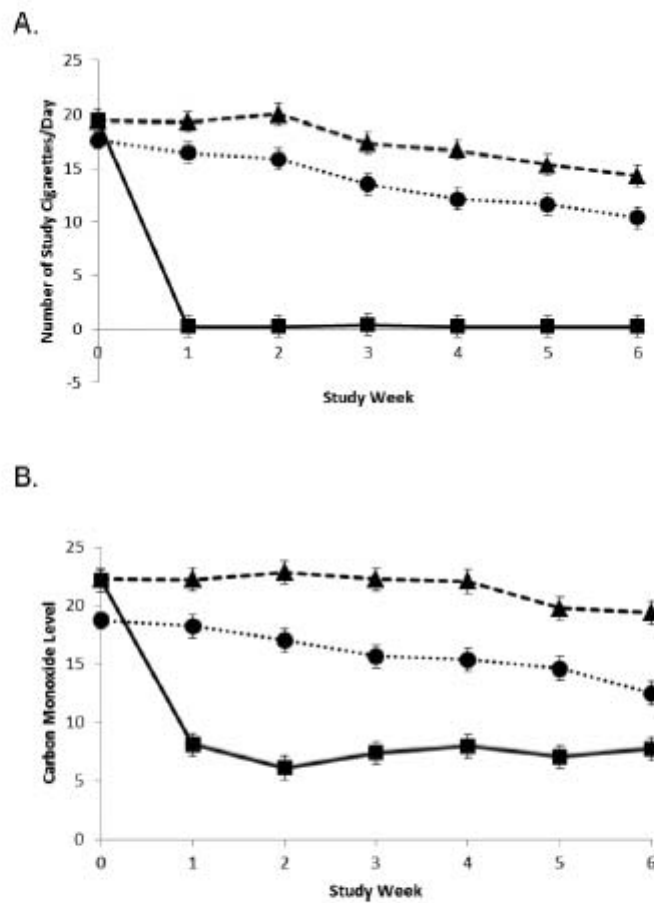
³⁹ Xodus cigarettes were manufactured by 22nd Century. They contained 1.89 mg nicotine /g tobacco (dry weight) (blend of VLN™ and non-VLN™ tobacco) and yielded 0.09 mg nicotine/cigarette and 10.8 mg tar in the smoke.

were assessed at baseline. Additionally, carbon monoxide was assessed at each clinic visit, cotinine at weeks 2, 6 and 12 of intervention and at follow-up visits, and biomarkers for other exposures at week 6 of intervention. Subjective measures included: a) a Tobacco Use Questionnaire asking about current tobacco use status (cigarettes and other tobacco products); b) a daily diary detailing the number of assigned products used and usual cigarettes smoked; c) the Minnesota Nicotine Withdrawal Scale, d) Fagerstrom Test for Nicotine Dependence (FTND); e) Centers for Epidemiological Studies 20-item scale (CES-D) assessing current symptoms of depression and f) Perceived Health Risk. All of these measures were assessed at baseline. Cigarette or product use was assessed daily, the Tobacco Use Questionnaire and Minnesota Nicotine Withdrawal Scale at each clinic visit and Perceived Health Risk at weeks 2 and 6.

The number of cigarettes smoked per day was reduced in both VLNC and VLNC plus patch groups. Exhaled CO followed a pattern similar to cigarettes (Figure VIII.D-43). TNE and urinary cotinine were reduced in all groups (Table VIII.D-34). Craving and nicotine withdrawal were not affected by treatment. After completion of treatment there was no difference in abstinence rates (~ 18%) after 36 weeks (Table VIII.D-35).

Conclusions: Use of VLNC cigarettes reduced CPD and nicotine exposure. Addition of a nicotine patch to the VLNC cigarette produced a larger decrease in CPD. Thirty-six-week abstinence was about 18%. Addition of a nicotine patch did not increase abstinence rates.

Figure VIII.D-43. CPD (From Hatsukami, *et al.*, 2013, Cancer Epidemiology... [pg300]



Least squares (LS) mean (\pm SE) of number of study cigarettes smoked per day (Panel A) and exhaled carbon monoxide (Panel B). Diamond represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch (NP) alone; circle represents VLNC + NP.

Table VIII.D-34. BOE (From Hatsukami, *et al.*, 2013, Cancer Epidemiology... [pg300])

| Biomarkers | Baseline | | Week 6 | |
|------------------------------------|----------|-------------------------|--------|-------------------------|
| | N | Geometric Mean (95% CI) | N | Geometric Mean (95% CI) |
| <u>Total TNE</u> ¹ | | | | |
| VLNC Cigarette | 54 | 55.70 (48.42, 64.07) | 54 | 6.89 (4.26, 11.02) |
| Patch | 59 | 49.90 (43.82, 57.40) | 58 | 23.10 (14.59, 36.60) |
| VLNC Cigarette + Patch | 58 | 53.52 (46.99, 61.56) | 58 | 27.39 (17.29, 43.38) |
| <u>Total Cotinine</u> ¹ | | | | |
| VLNC Cigarette | 54 | 17.12 (14.44, 20.09) | 54 | 2.03 (1.20, 3.45) |
| Patch | 59 | 16.78 (14.30, 19.69) | 59 | 5.50 (3.31, 9.13) |
| VLNC Cigarette + Patch | 58 | 17.99 (15.33, 21.12) | 58 | 7.65 (4.59, 12.76) |
| <u>Total NNAL</u> ² | | | | |
| VLNC Cigarette | 53 | 1.20 (1.00, 1.43) | 52 | 0.40 (0.29, 0.55) |
| Patch | 59 | 1.29 (1.09, 1.53) | 59 | 0.25 (0.18, 0.34) |
| VLNC Cigarette + Patch | 57 | 1.09 (0.92, 1.30) | 55 | 0.26 (0.19, 0.36) |

¹ nmol/mg creatinine

² pmol/mg creatinine

Table VIII.D-35. CO (From Hatsukami, *et al.*, 2013, Cancer Epidemiology... [pg300])

| <u>CO and Cotinine Verified Continuous Abstinence</u> | | | | | | | |
|--|------------------------------|----------|------------------------------|----------|-------------------------|----------|----------------|
| <i>Week</i> | Treatments | | | | | | <i>p-value</i> |
| | <i>VLNC cigarette (n=79)</i> | | <i>Nicotine Patch (n=80)</i> | | <i>VLNC + NP (n=76)</i> | | |
| | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | |
| 12 | 11 | 13.9 | 11 | 13.8 | 8 | 10.5 | 0.776 |
| 24 | 9 | 11.4 | 10 | 12.5 | 6 | 7.9 | 0.625 |
| 36 | 8 | 10.1 | 8 | 10.0 | 6 | 7.9 | 0.867 |

| <u>CO Verified Point Prevalence Abstinence</u> | | | | | | | |
|---|------------------------------|----------|------------------------------|----------|---------------------------|----------|----------------|
| <i>Week</i> | Treatments | | | | | | <i>p-value</i> |
| | <i>VLNC cigarette (n=79)</i> | | <i>Nicotine Patch (n=80)</i> | | <i>Combination (n=76)</i> | | |
| | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | |
| 12 | 21 | 26.6 | 24 | 30.0 | 22 | 29.0 | 0.888 |
| 16 | 21 | 26.6 | 20 | 25.0 | 23 | 30.3 | 0.752 |
| 24 | 18 | 22.8 | 17 | 21.3 | 16 | 21.1 | 0.959 |
| 36 | 15 | 19.0 | 19 | 23.8 | 16 | 21.1 | 0.763 |

| <u>CO and Cotinine Verified Point Prevalence Abstinence</u> | | | | | | | |
|--|------------------------------|----------|------------------------------|----------|---------------------------|----------|----------------|
| <i>Week</i> | Treatments | | | | | | <i>p-value</i> |
| | <i>VLNC cigarette (n=79)</i> | | <i>Nicotine Patch (n=80)</i> | | <i>Combination (n=76)</i> | | |
| | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | <i># abstinent</i> | <i>%</i> | |
| 12 | 19 | 24.1 | 19 | 23.8 | 18 | 23.7 | 0.998 |
| 24 | 15 | 19.0 | 16 | 20.0 | 13 | 17.1 | 0.896 |
| 36 | 14 | 17.7 | 15 | 18.8 | 15 | 19.7 | 0.950 |

xxviii. Reduced nicotine cigarettes: Smoking behavior and biomarkers of exposure in smokers not intending to quit.

Seventy-two adult smokers completed an unblinded trial of reduced nicotine cigarettes (Quest) (Hammond and O'Connor 2014 [pg300]). Participants completed a 7-day baseline period during which they smoked their usual cigarette brand, followed by consecutive 7-day periods smoking cigarettes with progressively lower nicotine levels (0.6, 0.3, and 0.05 mg Quest

cigarettes). Nicotine dependence and withdrawal, smoking behavior, and biomarkers of exposure were assessed for each 7-day period.

There was no difference in CPD between groups. Puff number and as a result total puff volume was decreased in the Quest 3 group (Table VIII.D-36). There was no CO boost and cotinine was reduced in the Quest 3 group (Table VIII.D-37). There was no difference in smoking urges and cravings between usual brand and Quest 3 (Table VIII.D-38).

Table VIII.D-36. Topography and CPD (Hammond and O'Connor 2014 [pg300])

| | Own brand (N = 72) | Quest 1 (N = 71) | Quest 2 (N = 71) | Quest 3 (N = 72) |
|---|-------------------------------|-----------------------------|-----------------------------|-----------------------------|
| Puff number | | | | |
| Mean | 16.1 | 14.5 | 13.8 | 13.2 |
| SD | (6.3) | (4.6) | (4.3) | (4.5) |
| Puff volume (mL) | | | | |
| Mean | 63.5 | 64.3 | 64.2 | 69.3 |
| SD | (22.4) | (22.3) | (17.2) | (18.8) |
| Total puff volume per cigarette (mL) | | | | |
| Mean | 977.9 | 910.1 | 834.2 | 890.7 |
| SD | (420.8) | (520.3) | (190.4) | (353.6) |
| CPD | | | | |
| Mean | 20.0 | 19.9 | 21.8 | 20.3 |
| (SD) | (8.9) | (8.4) | (9.4) | (10.2) |

Table VIII.D-37. BOE (From Hammond and O'Connor 2014 [pg300])

| | Own brand | Quest 1 | Quest 2 | Quest 3 |
|-------------------------------|-----------|----------|----------|----------|
| Exhaled CO | | | | |
| CO precigarette ppm | | | | |
| Mean | 21.6 | 19.9 | 23.2 | 22.9 |
| SD | (9.60) | (9.80) | (11.78) | (12.55) |
| CO postcigarette ppm | | | | |
| Mean | 26.2 | 23.3 | 28.3 | 26.2 |
| SD | (10.5) | (10.4) | (12.6) | (12.2) |
| CO boost ppm | | | | |
| Mean | 4.6 | 3.3 | 5.0 | 3.3 |
| SD | (3.13) | (2.55) | (2.95) | (3.00) |
| Cotinine (pmol/mg creatinine) | | | | |
| Cotinine (ng/mL) | | | | |
| Mean | 12,127.1 | 11,937.3 | 7,938.2 | 5,366.0 |
| SD | (7102.5) | (7371.4) | (6019.6) | (5560.6) |
| 1-HOP (pmol/mg creatinine) | | | | |
| Mean | 1.28 | 1.24 | 1.12 | 1.06 |
| SD | (0.9) | (0.9) | (0.9) | (0.8) |

Abbreviation: ppm, parts per million.

Table VIII.D-38. Smoking urges (From Hammond and O'Connor 2014 [pg300])

| | Own brand | Quest 1 | Quest 2 | Quest 3 | Differences |
|--|-------------|-------------|-------------|-------------|------------------------------|
| QSU | | | | | |
| QSU—factor 1 | | | | | $F_{131.4} = 0.7; P = 0.545$ |
| Expectations of positive outcomes from smoking | 4.29 (1.49) | 4.52 (1.42) | 4.59 (1.45) | 4.63 (1.55) | |
| QSU—factor 2 | | | | | $F_{126.6} = 1.2; P = 0.313$ |
| Expectations of relief from negative effect of smoking | 3.06 (1.29) | 3.20 (1.36) | 3.28 (1.28) | 3.50 (1.55) | |
| QSU—overall | 3.68 (1.31) | 3.86 (1.29) | 3.93 (1.28) | 4.07 (1.48) | $F_{129.0} = 1.0; P = 0.394$ |
| FTND | | | | | |
| FTND—overall | 4.9 (2.3) | 4.8 (2.2) | 4.8 (2.1) | 4.4 (2.3) | $F_{129.7} = 0.7; P = 0.547$ |
| NDSS (raw scores) | | | | | |
| NDSS—overall | 2.47 (0.47) | 2.41 (0.52) | 2.41 (0.52) | 2.34 (0.52) | $F_{133.8} = 0.9; P = 0.450$ |
| NDSS—drive | 3.13 (0.88) | 3.02 (0.91) | 2.97 (0.98) | 2.85 (0.96) | $F_{132.2} = 1.1; P = 0.348$ |
| NDSS—priority | 1.75 (0.60) | 1.69 (0.59) | 1.71 (0.66) | 1.63 (0.60) | $F_{135.4} = 0.5; P = 0.695$ |
| NDSS—tolerance | 2.64 (0.68) | 2.69 (0.68) | 2.60 (0.70) | 2.70 (0.79) | $F_{128.6} = 0.3; P = 0.845$ |
| NDSS—continuity | 2.66 (0.93) | 2.56 (0.98) | 2.54 (0.94) | 2.49 (1.05) | $F_{129.7} = 0.4; P = 0.747$ |
| NDSS—stereotypy | 3.66 (0.85) | 3.31 (0.88) | 3.37 (0.94) | 3.35 (0.93) | $F_{131.7} = 2.5; P = 0.060$ |
| | | | | | V2 vs. V3; $P = 0.015$ |
| | | | | | V2 vs. V5; $P = 0.037$ |

Conclusions: Surprisingly, CPD was not affected by smoking Quest 3 cigarettes. There was no compensation and nicotine exposure were decreased. Quest 3 was as effective as usual brand in suppressing urge to smoke and withdrawal symptoms.

xxix. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine.

Donny and Jones (2009) [pg299] conducted a multi-dose, placebo-controlled, double-blind experiment in 68 subjects. The subjects received either a placebo patch and normal nicotine cigarettes (0/NC), a 7 mg nicotine patch and Quest 3 cigarettes (7/DN), a 14 mg patch and Quest 3 (14/DN), or 21 mg patch and Quest 3 (21/DN). The subjects smoked the products over 9 days. Smoking topography, subjective questionnaires, and exhaled CO were monitored. Topography was measured under controlled puffing and ad libitum conditions (Table VIII.D-39).

There was no difference in CPD between the normal cigarette and Quest 3 cigarettes. Addition of the nicotine patches reduced CPD (Figure VIII.D-44). Total puff volume was reduced in the Quest 3 groups (Figure VIII.D-44). Puff number was not affected. CO boost was not different between the NC and DN groups. Salivary cotinine levels at Day 10 for 0/NC, 0/DN, 7/DN, and 21/DN were 263 (± 30) ng/ml, 33 (± 9) ng/ml, 194 (± 27) ng/ml, and 355 (± 32) ng/ml, respectively. DN cigarettes were rated as having high negative and low positive subjective effects. Transdermal nicotine attenuated the withdrawal symptoms.

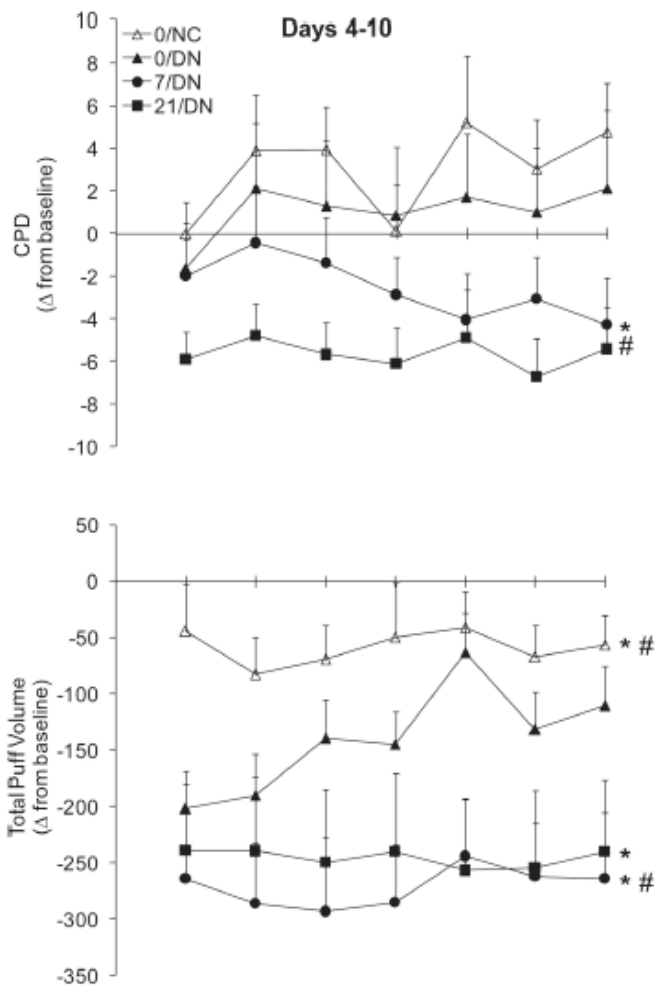
Conclusions: Quest 3 cigarettes did not affect CPD, however cotinine was reduced. There was no CO boost or increase in puff volume indicating no compensation.

Table VIII.D-39. Study Design (From Donny and Jones 2009 [pg299])

| | Day | | | | | | | | | | | |
|---|-----|---|---|---|---|---|---|---|---|----|----|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Conditions | | | | | | | | | | | | |
| Unrestricted smoking of preferred brand | X | X | | | | | | | | | | |
| Naturalistic smoking of research cigarettes | | | | X | X | X | X | X | X | X | | |
| Restricted smoking of research cigarettes | | | X | | | | | | | | X | |
| Patch administration | | | X | X | X | X | X | X | X | X | X | |
| Sessions | | | | | | | | | | | | |
| Orientation and Training Session | X | | | | | | | | | | | |
| Daily Smoking Assessment | | X | | X | X | X | X | X | X | X | | |
| Smoking in the natural environment | | X | | X | X | X | X | X | X | X | | |
| CO | | X | | X | X | X | X | X | X | X | | |
| Withdrawal and mood | | X | | X | X | X | X | X | X | X | | |
| Puff topography | | X | | X | X | X | X | X | X | X | | |
| Cigarette subjective effects | | X | | X | X | X | X | X | X | X | | |
| Extended Laboratory Sessions | | | X | | | | | | | | X | |
| CO | | | X | | | | | | | | X | |
| Puff topography | | | X | | | | | | | | X | |
| Cigarette subjective effects | | | X | | | | | | | | X | |
| Self-administration | | | X | | | | | | | | X | |
| Brief abstinence Verification Sessions | | | | X | | | | | | | | X |
| CO & urine sample | | | | X | | | | | | | | X |

The time line of major experimental conditions is displayed at the top of the table. The time line for experimental sessions is presented in the bottom section of the table. Over the course of 12 days, participants attended 1 orientation and training session, 8 daily afternoon smoking assessment sessions, 2 extended laboratory sessions, and 2 morning sessions verifying overnight abstinence. Italics indicate the major constructs/measures assessed during each session.

Figure VIII.D-44. CPD (From Donny and Jones 2009 [pg299])



xxx. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial (ACTRN126080004103580).

Walker, *et al.*, (2012) [pg304] was interested in the combined effect of VLNC cigarettes and usual Quitline care (NRT and counselling) on abstinence. A total of 1,410 subjects were randomized into a single-blind, parallel trial. Half of the subjects received Quest 3 for 6 weeks ad libitum and NRT and the other half just received NRT and counselling. The primary outcome was total abstinence for 7 days six months after the quit date. Other endpoints included CPD, subjective questionnaires, alcohol use, and adverse events.

Quest cigarette consumption declined during the treatment period (Table VIII.D-40). There was no significant difference between the intervention group and the usual care group in the average amount of NRT used in abstainers at any time point (Table VIII.D-41) or in the proportion of participants who had reduced their daily consumption of regular cigarettes by at least 25% at 6 months.

Seven-day point-prevalence 6-month abstinence rates were significantly greater in the intervention group compared to the usual care group (Table VIII.D-42). Results were similar when only participants with complete smoking data were included. Subgroup analyses showed no difference in the primary outcome according to age, sex, ethnicity, socio-economic status, type of cigarettes smoked, alcohol use at baseline, level of nicotine dependence or whether at least one quit attempt had been made in the last 12 months. Using continuous abstinence as the measure of outcome showed that 160 (23%) participants from the intervention group and 107 (15%) in the usual care group were abstinent at 6 months.

Table VIII.D-40. CPD (From Walker *et al.* 2012 [pg304])

| <i>Number of VLNC cigarettes smoked each week</i> | | |
|--|--|--------------------------------------|
| | <i>Mean (SD)</i> | <i>Median, range</i> |
| Week 1 (<i>n</i> = 662) | 26 (31) | 20, 0–200 |
| Week 2 (<i>n</i> = 662) | 20 (26) | 10, 0–120 |
| Week 3 (<i>n</i> = 662) | 13 (21) | 3, 0–140 |
| Week 4 (<i>n</i> = 619) | 10 (19) | 0, 0–200 |
| Week 5 (<i>n</i> = 618) | 8 (16) | 0, 0–100 |
| Week 6 (<i>n</i> = 618) | 6 (13) | 0, 0–80 |
| <i>Use of the VLNC cigarettes, with NRT and regular cigarettes</i> | | |
| | <i>Intervention <i>n</i> = 619 (%)</i> | <i>Usual care <i>n</i> = 617 (%)</i> |
| Smoked VLNC cigarettes and regular cigarettes, and used NRT | 235 (38%) | – |
| Smoked VLNC cigarettes and used NRT | 149 (24%) | – |
| Smoked VLNC cigarettes and regular cigarettes | 135 (22%) | – |
| Smoked VLNC cigarettes only | 64 (10%) | – |
| Used NRT only | 13 (2%) | 106 (17%) |
| Smoked regular cigarettes only | 13 (2%) | 187 (30%) |
| Used nothing | 8 (1%) | 33 (5%) |
| Smoked regular cigarettes and used NRT | 2 (0.3%) | 291 (47%) |

SD: standard deviation; NRT: nicotine replacement therapy. No definition of 'smoked VLNC cigarettes' was provided, thus users may have had only a few puffs or more than one cigarette. 'Smoked regular cigarettes' was defined as having smoked more than one nicotine-containing cigarette. No ethnic differences in the data were observed.

Table VIII.D-41. NRT use (From Walker *et al.* 2012 [pg304])

| <i>Time-period</i> | <i>Mean NRT used in mg/day (SD)</i> | <i>Median</i> | <i>P-value^a</i> |
|--------------------------------|---|---------------|----------------------------|
| Three weeks | | | |
| Intervention (<i>n</i> = 231) | 15.3 (12.2) | 21 | 0.89 |
| Usual care (<i>n</i> = 195) | 15.6 (12.5) | 21 | |
| Six weeks | | | |
| Intervention (<i>n</i> = 231) | 11.7 (11.9) | 11 | 0.87 |
| Usual care (<i>n</i> = 195) | 11.7 (13.1) | 6 | |
| Three months | | | |
| Intervention (<i>n</i> = 231) | 3.2 (7.5) | 0 | 0.15 |
| Usual care (<i>n</i> = 195) | 4.4 (8.3) | 0 | |
| Six months | | | |
| Intervention (<i>n</i> = 231) | 2.1 (5.9) | 0 | 0.83 |
| Usual care (<i>n</i> = 195) | 1.6 (5.0) | 0 | |

SD: standard deviation. ^aFrom Wilcoxon's Mann-Whitney *U*-test.Table VIII.D-42. Abstinence (From Walker *et al.* 2012 [pg304])

| | <i>Intervention n = 705 (%)</i> | <i>Usual care n = 705 (%)</i> | <i>Relative risk (95% CI)</i> | <i>P-value</i> |
|--|-------------------------------------|-----------------------------------|-----------------------------------|----------------|
| Seven-day point-prevalence abstinence | | | | |
| Three-week quit rate ^a | 378 (54) | 256 (36) | 1.48 (1.31–1.66) | <0.0001 |
| Six-week quit rate ^a | 333 (47) | 232 (33) | 1.44 (1.26–1.64) | <0.0001 |
| Three-month quit rate ^a | 280 (40) | 211 (30) | 1.33 (1.15–1.53) | 0.0001 |
| Six-month quit rate (primary outcome) ^a | 231 (33) | 195 (28) | 1.18 (1.01–1.39) | 0.037 |
| Sensitivity analyses for 6-month quit data | | | | |
| Complete cases only ^b | 231/537 (43) | 195/539 (36) | 1.19 (1.03–1.38) | 0.022 |
| Per protocol ^c | 224/512 (44) | 186/513 (36) | 1.21 (1.04–1.40) | 0.014 |
| Repeated-measures analyses^d | | | | |
| Overall treatment effect | – | – | 1.67 (1.39–2.00) | <0.0001 |
| Three-week effect | – | – | 2.06 (1.66–2.56) | <0.0001 |
| Six-week effect | – | – | 1.86 (1.49–2.31) | <0.0001 |
| Three-month effect | – | – | 1.56 (1.25–1.95) | <0.0001 |
| Six-month effect | – | – | 1.29 (1.02–1.62) | 0.03 |
| Continuous abstinence | | | | |
| Three-week quit rate ^a | 393 (56) | 275 (39) | 1.43 (1.28–1.60) | <0.0001 |
| Six-week quit rate ^a | 293 (42) | 203 (29) | 1.44 (1.25–1.67) | <0.0001 |
| Three-month quit rate ^a | 227 (32) | 148 (21) | 1.53 (1.28–1.83) | <0.0001 |
| Six-month quit rate ^a | 160 (23) | 107 (15) | 1.50 (1.20–1.87) | 0.0003 |

Six-month 7-day point-prevalence abstinence is the primary outcome. All other variables presented are secondary outcomes. CI: confidence interval.

^aAssumes all participants with missing smoking status were smoking (including those who withdrew). ^bOnly includes participants for whom data on smoking status was complete at 6 months (withdrawn participants excluded). ^cExcludes participants with missing 6-month data and protocol violations.^dAdjusted for gender, ethnicity and level of nicotine dependence.

There was no significant difference in the occurrence of serious adverse events between the intervention group (36 events in 36 participants, 5.1%) and usual care group (35 events in 35 participants, 5.0%, incidence rate ratio = 1.04, 95% CI: 0.65, 1.65, P = 0.9). Injuries to the body (eight versus four events) and mental and behavioral disorders (two versus no events) were more common in the intervention group than the usual care group, while in the usual care group more gastrointestinal events (four versus seven events) and symptoms and signs (one versus six events) occurred. All other events were similar in both groups. There were two deaths, one in each group, both due to cancer.

Conclusions: VLNC cigarette consumption declined during the quit attempt. Abstinence rate was higher in the group that received VLNC cigarettes and NRT compared to just NRT.

xxxi. Reduced-nicotine cigarettes in young smokers: Impact of nicotine metabolism on nicotine dose effects.

Faulkner, et al., (2017) [pg299] compared responses of 46 young adult smokers to SPECTRUM® research cigarettes, delivering 0.027 (= 0.4 mg/g), 0.110, 0.231, or 0.763 mg nicotine in smoke, and conventional cigarettes. On five separate days, craving, withdrawal, affect, and sustained attention were measured after overnight abstinence and again after smoking. Participants also rated each cigarette, and the nicotine metabolite ratio (NMR) was used to identify participants as normal or slow metabolizers.

There were no differences between the reduced-nicotine cigarettes, or between reduced-nicotine cigarettes and the preferred-brand cigarette, in puff count, average volume, intensity, or duration. Moreover, there were no differences between normal and slow metabolizers on any such measures when smoking reduced-nicotine cigarettes or the preferred-brand cigarette.

There were no differences between the plasma nicotine levels of slow and normal metabolizers after smoking reduced-nicotine cigarettes or preferred-brand cigarettes.

All cigarettes equally alleviated craving, withdrawal, and negative affect in the whole sample, but normal metabolizers reported greater reductions of craving and withdrawal than slow metabolizers, with dose-dependent effects (Figure VIII.D-45). All cigarettes increased positive affect and decreases negative effect (Figure VIII.D-46). Smokers liked their preferred brand more than the SPECTRUM cigarettes.

Only conventional cigarettes and, to a lesser degree, 0.763-mg nicotine research cigarettes, increased sustained attention. Finally, there were no differences between ratings of lower-dose cigarettes, but the 0.763-mg cigarettes and (even more so) conventional cigarettes were rated more favorably than lower-dose cigarettes. The findings indicate that smoking-induced relief of craving and withdrawal reflects primarily non-nicotine effects in slow metabolizers but depends on nicotine dose in normal metabolizers. By contrast, relief of withdrawal-related attentional deficits and cigarette ratings depend on nicotine dose regardless of metabolizer status. These suggest that normal and slow nicotine metabolizers would respond differently to nicotine reduction in cigarettes.

Figure VIII.D-45. Withdrawal and craving (From Faulkner *et al.* 2017 [pg299])

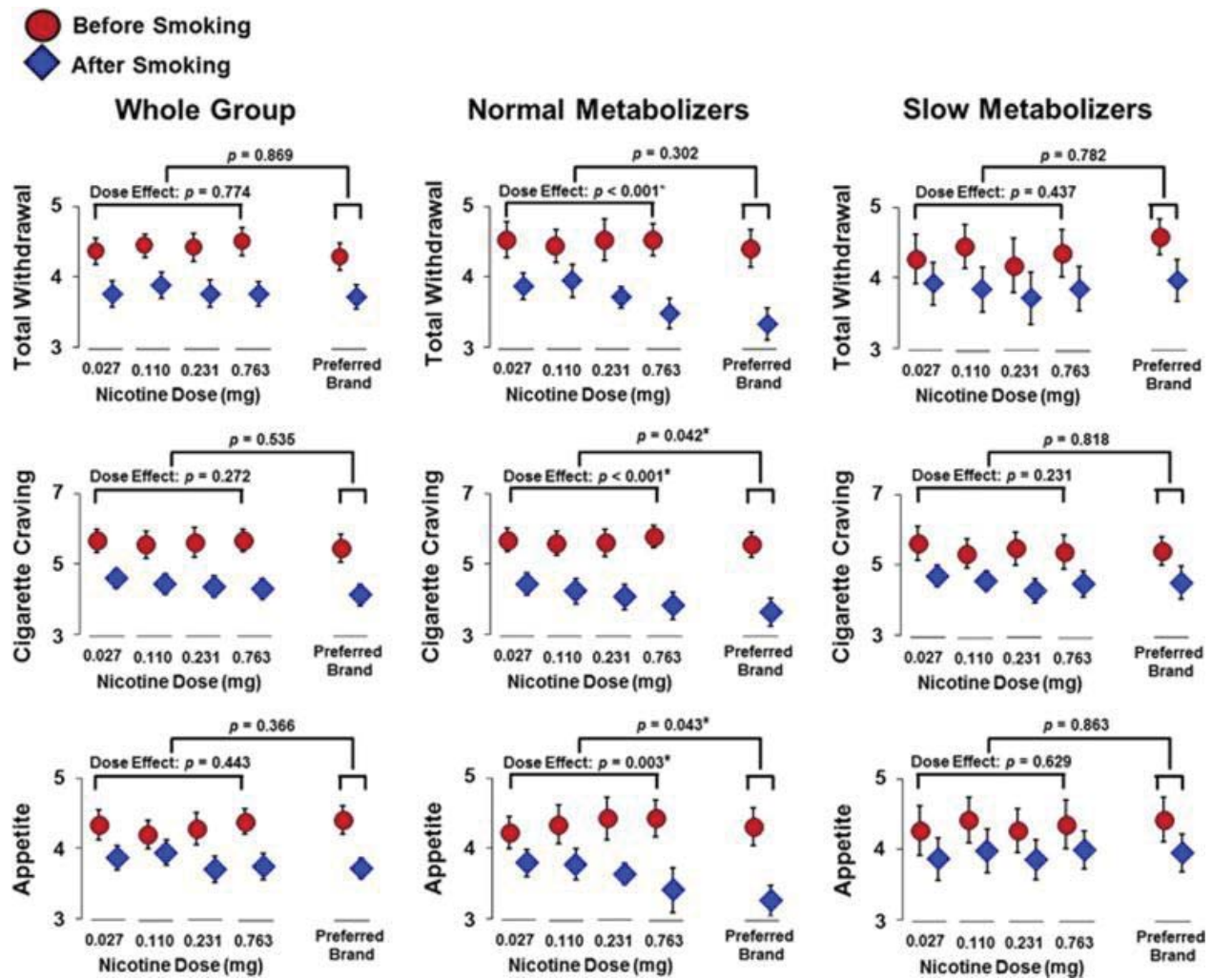
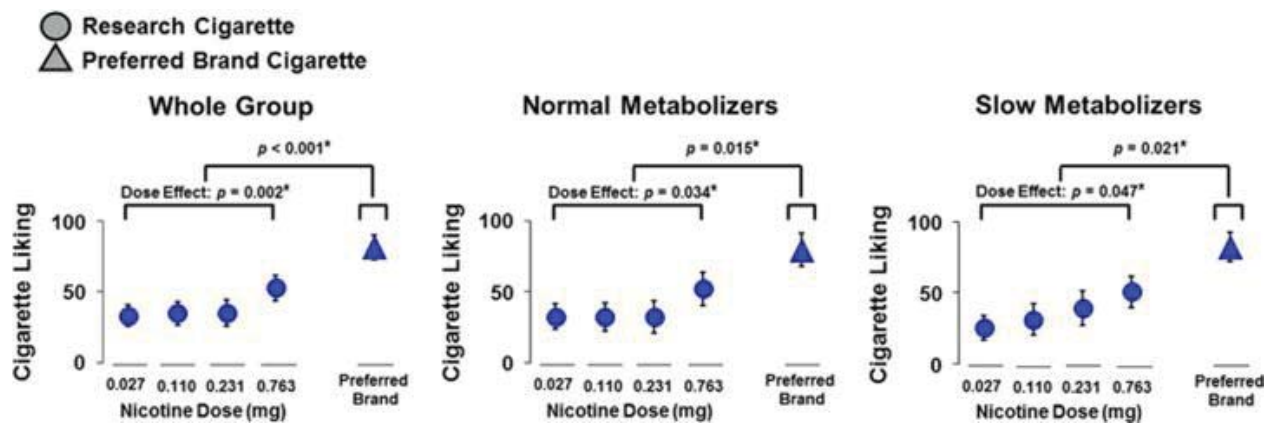


Figure VIII.D-46. Liking (From Faulkner *et al.* 2017 [pg299])



Conclusion: Results suggest that slow and normal metabolizers of nicotine may respond differently to VLNC cigarettes.

xxxii. Pharmacodynamic effects of new de-nicotinized cigarettes.

When Quest cigarettes were discontinued, NIDA contracted with Ultratech Inc. to develop and manufacture de-nicotinized tobacco cigarettes. The cigarettes used a normal blend of tobacco that was extracted with an alkaline solution removing the nicotine and reducing TSNAs. Pickworth, *et al.*, (1999) [pg303] compared these new cigarettes to conventional cigarettes. Nicotine was measured in plasma. Number of puffs was measured. Heart rate and blood pressure were measured after smoking. Subjective measures were also collected.

Table VIII.D-43. *Study design* (From Pickworth *et al.* 1999 [pg303]) shows the characteristics of the test cigarettes. The de-nicotinized full tar version had a nicotine content of 0.07 mg nicotine. Upon smoking the de-nicotinized cigarettes, plasma nicotine was decreased, and heart rate was increased (Figure VIII.D-47). The de-nicotinized cigarette was just as effective as standard cigarette in reducing withdrawal and urges (Figure VIII.D-48).

Conclusion: This new de-nicotinized cigarette was effective in reducing nicotine exposure, withdrawal, and urges to smoke.

Table VIII.D-43. Study design (From Pickworth *et al.* 1999 [pg303])

| | | FTC Nicotine (mg/cig) | FTC Tar (mg/cig) | Nicotine content (mg/cig) |
|-------------|----------------|-----------------------|------------------|---------------------------|
| Full Tar | Standard | 1.10 | 15.9 | 7.17 |
| | De-nicotinized | 0.07 | 17.3 | 0 |
| Reduced Tar | Standard | 0.60 | 10.0 | 5.58 |
| | De-nicotinized | 0.07 | 12.1 | 0 |

Figure VIII.D-47. BOE (From Pickworth *et al.* 1999 [pg303])

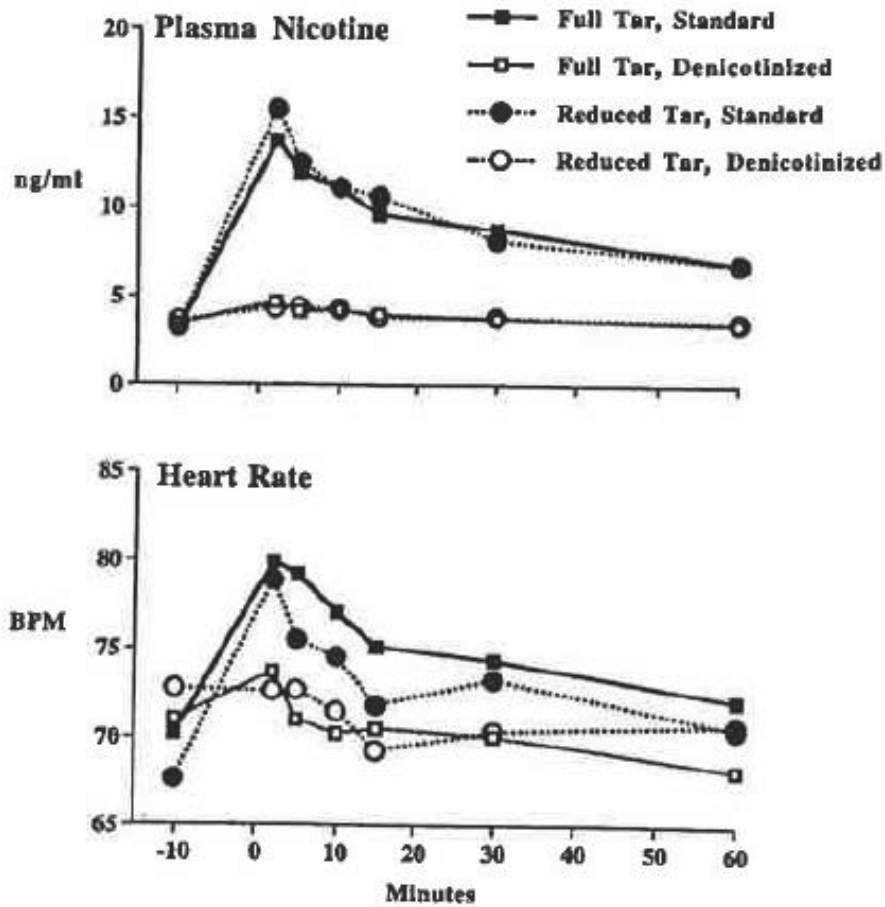
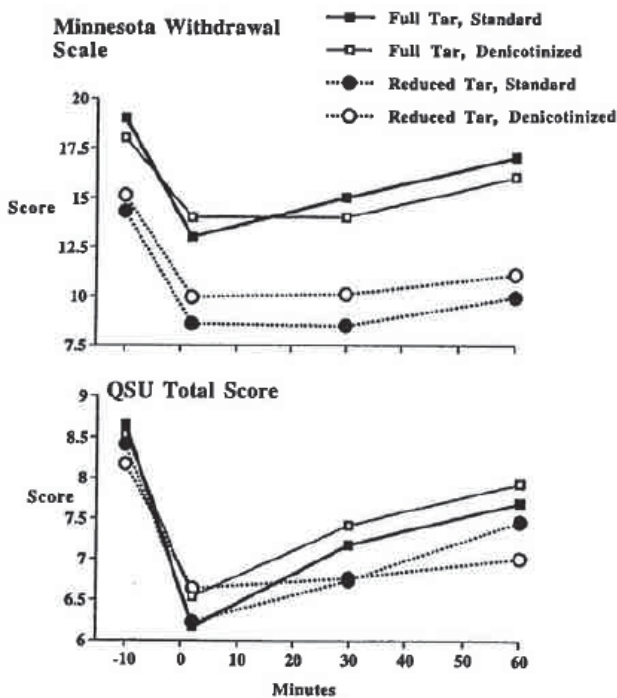


Figure VIII.D-48. Withdrawal (From Pickworth *et al.* 1999 [pg303])



xxxiii. Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers.

The objective of this study was to investigate smoking topography in 35 adolescents using high yield (HY) and Ultratech VLNC cigarettes (DN) (Kassel *et al.* 2007 [pg301]). The subjects were randomized into high yield or VLNC cigarettes. Topography and subjective assessments were performed. Puff number was increased in the VLNC cigarette group, but puff volume was not (Table VIII.D-44).

Conclusion: There appeared to be partial compensation with this new test cigarette.

Table VIII.D-44. Topography (From Kassel *et al.* 2007 [pg301])

Smoking topography indices

| | Full sample (n = 35) | HY nicotine group (n = 16) | DN nicotine group (n = 19) | t(33) |
|-------------------------|-------------------------|-------------------------------|-------------------------------|----------|
| Puff number | 17.51 (8.7) | 15.10 (6.3) | 23.20 (8.9) | -3.02** |
| Average volume (mL) | 43.07 (20.2) | 45.42 (22.2) | 40.10 (18.7) | .67 |
| Average duration (s) | 1.18 (.4) | 1.12 (.4) | 1.00 (.4) | .15 |
| Average IPI (s) | 23.54 (12.9) | 24.23 (12.9) | 23.00 (13.2) | .27 |
| Average flow (mL/s) | 55.23 (18.8) | 57.24 (18.9) | 53.40 (19.0) | .60 |
| Total volume (mL) | 862.92 (521.5) | 713.05 (461.8) | 988.80 (547.2) | -1.60 |
| Total duration (s) | 20.65 (10.6) | 16.70 (9.7) | 23.98 (11.5) | -2.00 |
| Total IPI (s) | 368.60 (113.7) | 289.50 (90.6) | 435.2 (130.5) | -3.76*** |
| Total flow ^a | 1117.33 (623.8) | 877.53 (490.4) | 1319.26 (744.2) | -2.03* |

HY = high yield cigarette; DN = denicotinized cigarette; IPI = inter-puff interval; CO = expired air carbon monoxide. Numbers in parentheses are standard deviations.

* $p < .05$; ** $p < .005$; *** $p < .001$.

^a Total flow is calculated by summing the flow (velocities) for each puff and, as such, is determined in great part by total puff number.

xxxiv. Sex differences in response to reduced nicotine content cigarettes.

Vogel, *et al.*, (2014) [pg304] assigned 235 subjects to one of three treatment conditions:

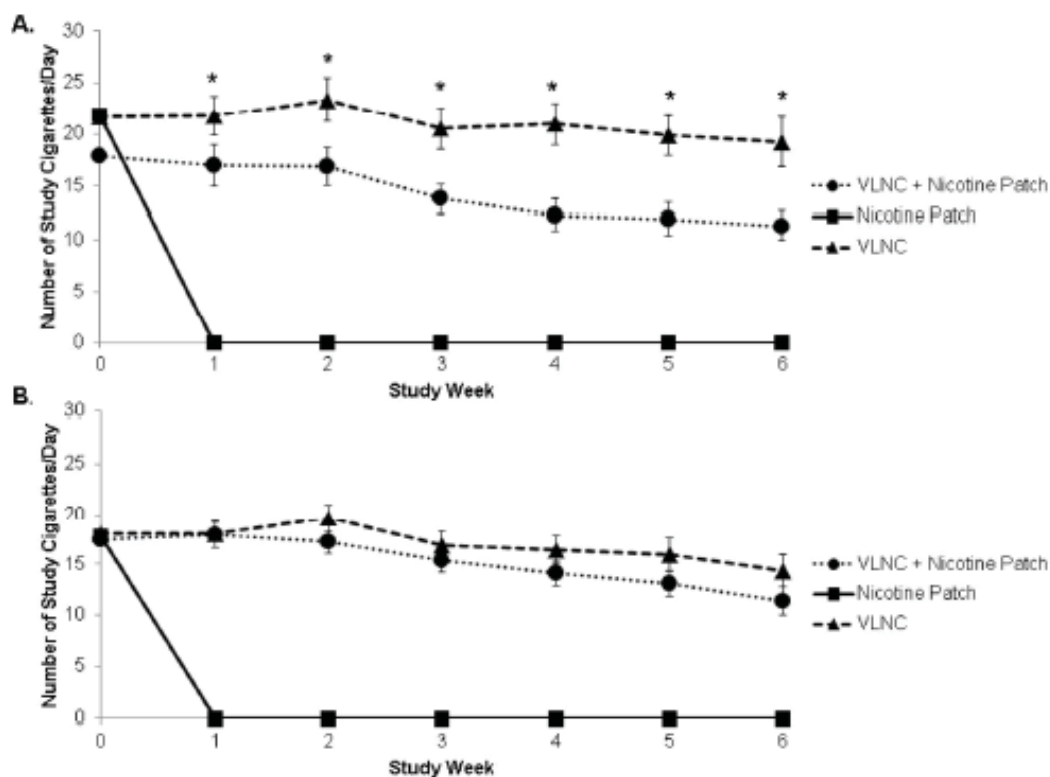
1) VLNC cigarettes only (0.05 mg nicotine yield [Quest 3] or 0.09 mg nicotine yield [Xodus] cigarettes; yields changed because Quest 3 went off the market during the study); 2) 21 mg nicotine patch only and 3) combination condition (VLNC cigarettes and nicotine patch) for a period of 6 weeks. At the end of the 6-week product use period, participants were asked to discontinue all product use and provided behavioral treatment for an additional 6 weeks. Follow-up occurred at 36 weeks from the initiation of the study.

The combination of VLNC cigarettes and nicotine patch was more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males than females, whereas females were equally responsive to VLNC cigarettes with and without the nicotine patch (Figure VIII.D-49). There was no CO boost (Figure VIII.D-50). Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the VLNC cigarettes; however, males

were more likely to quit smoking in the nicotine patch alone condition than females (Table VIII.D-45).

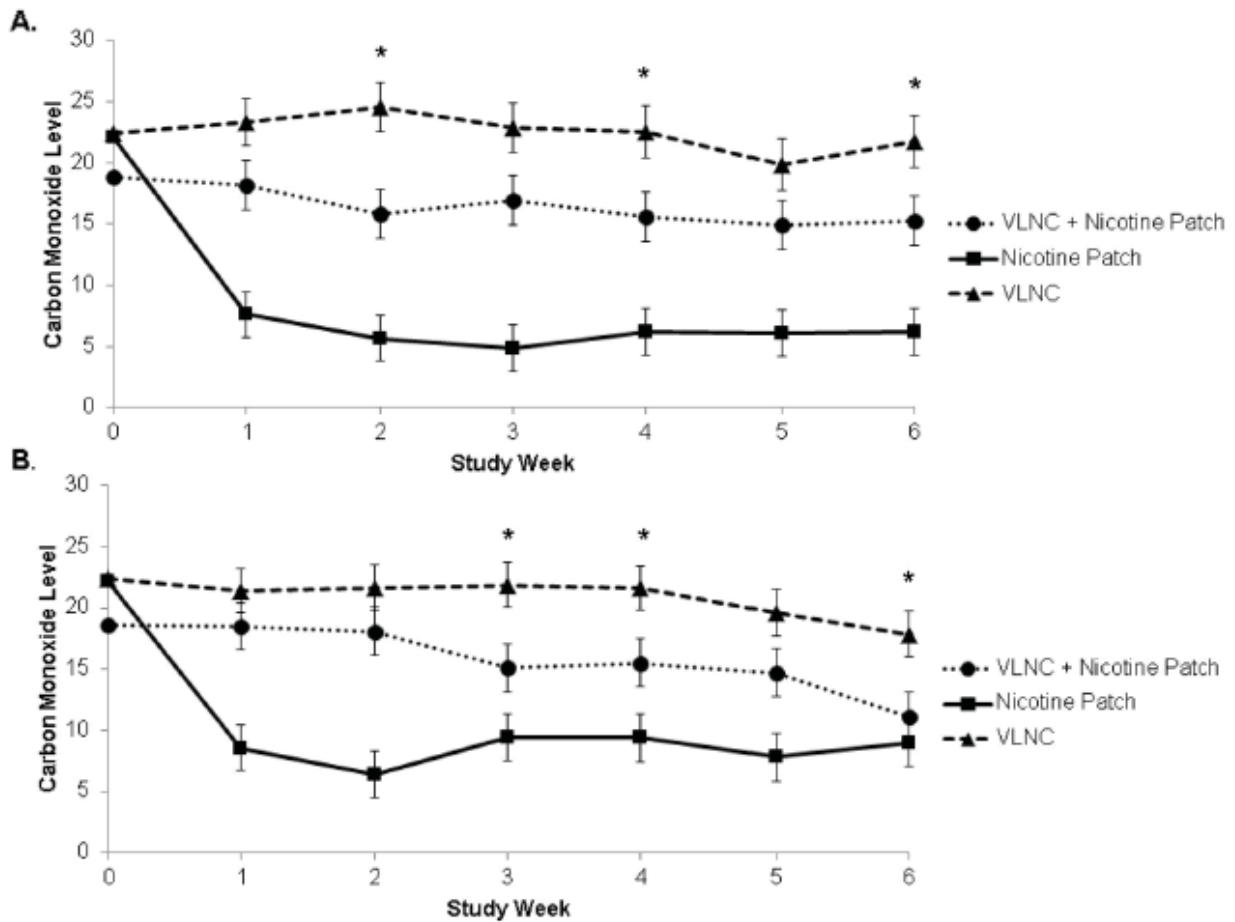
Conclusion: There appears to be a sex difference in response to VLNC cigarettes.

Figure VIII.D-49. CPD (From Vogel *et al.* 2014 [pg304])



Least squares mean (\pm SE) of number of study cigarettes smoked per day for males (Panel A) and females (Panel B). Visit 0 data represent usual brand cigarette use. Triangle represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

Figure VIII.D-50. CO (From Vogel *et al.* 2014 [pg304])



Least squares mean (\pm SE) of exhaled carbon monoxide for males (Panel A) and females (Panel B). Triangle represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

Table VIII.D-45. Abstinence (From Vogel *et al.* 2014 [pg304]).

| CO and Cotinine Verified Continuous Abstinence | | | | | | | | | | | | | |
|--|-------------|-----|-----------------------|------|--------------------|-----|-------------|------|-----------------------|-----|--------------------|------|-----------|
| Males | | | | | | | Females | | | | | | |
| | VLNC (n=32) | | Nicotine Patch (n=34) | | Combination (n=33) | | VLNC (n=47) | | Nicotine Patch (n=46) | | Combination (n=43) | | |
| Week | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | p-value * |
| 12 | 1 | 3.1 | 7 | 20.6 | 2 | 6.1 | 10 | 21.3 | 4 | 8.7 | 6 | 14.0 | 0.0288 |
| 24 | 1 | 3.1 | 6 | 17.7 | 1 | 3.0 | 8 | 17.0 | 4 | 8.7 | 5 | 11.6 | 0.0594 |
| 36 | 1 | 3.1 | 5 | 14.7 | 1 | 3.0 | 7 | 14.9 | 3 | 6.5 | 5 | 11.6 | 0.0782 |

* P-value for treatment by sex interaction.

xxxv. Complementing the standard multicomponent treatment for smokers with denicotinized cigarettes: A randomized trial.

McRobbie, *et al.* (2016) [pg301] hypothesized that Xodus cigarettes could help alleviate urges to smoke and tobacco withdrawal symptoms in subjects receiving standard therapy (ST) for cessation. Two hundred subjects seeking treatment received nine weekly behavioral support therapy and pharmacotherapy (100 used varenicline and 100 used NRT). They were randomized on the quit date to receive Xodus cigarettes for two weeks in conjunction with ST or ST alone. The subjects were evaluated using subjective questionnaires. Abstinence was measured at 1, 4, 6 and 12 weeks post quit.

Incorporation of Xodus cigarettes into the treatment program reduced the urge to smoke but not the strength in the first week of abstinence (Table VIII.D-46). There were no differences in the composite withdrawal scores between groups. Abstinence was significantly higher in the Xodus groups compared to ST alone at 1- and 4-weeks post quit but not at 12-weeks (Table VIII.D-47).

Conclusion: VLNC may assist smokers trying to quit.

Table VIII.D-46. Smoking urges (From McRobbie, *et al.*, 2016 [pg301])

| | | Frequency of urges to smoke ^a | | | Strength of urges to smoke ^a | | |
|-------------------|--------|--|-------------|---|---|-------------|--|
| | | <i>N</i> | Mean (SD) | Difference | <i>N</i> | Mean (SD) | Difference |
| Total sample | DNC+ST | 70 | 2.61 (0.80) | 0.35, <i>F</i> = 4.86, <i>P</i> = .033 | 68 | 2.85 (0.90) | 0.25, <i>F</i> = 1.67, <i>P</i> = .20 |
| | ST | 53 | 2.96 (0.98) | | 52 | 3.10 (1.16) | |
| Varenicline users | DNC+ST | 38 | 2.50 (0.76) | 0.33, <i>F</i> = 2.31, <i>P</i> = .13 | 38 | 2.68 (0.96) | 0.39, <i>F</i> = 1.93, <i>P</i> = .17 |
| | ST | 29 | 2.83 (1.00) | | 29 | 3.07 (1.31) | |
| NRT users | DNC+ST | 32 | 2.75 (0.84) | 0.38, <i>F</i> = 2.44, <i>P</i> = .12 | 30 | 3.07 (0.79) | 0.06, <i>F</i> = 0.07, <i>P</i> = .79 |
| | ST | 24 | 3.13 (0.95) | | 23 | 3.13 (0.97) | |

DNC = denicotinized cigarette; NRT = nicotine replacement therapy; ST = standard treatment.

^aMood and Physical Symptoms Scale: 6-point scale from 1 [not at all] to 6 [all of the time] for frequency of urges to smoke; and 1 [no urges] to 6 [extremely strong] for strength of urges to smoke, in the first week of abstinence.

Table VIII.D-47. Abstinence (From McRobbie, *et al.*, 2016 [pg301])

| Period after TQD | Total sample | | | | Varenicline users | | | | NRT users | |
|------------------------|---------------------|------------------|-------------------|------------------------------------|--------------------|-------------|-----------------------|--------------------|----------------|-----------------------|
| | DNC+ST (N = 100) | | P | Crude OR (95% CI) | DNC+ST (N = 50) | | Crude OR (95% CI) | DNC+ST (N = 50) | ST (N = 50) | Crude OR (95% CI) |
| | ST (N = 100) | ST (N = 100) | | | ST (N = 50) | ST (N = 50) | | | | |
| 1 week | 70% | 53% | .014 | 2.07 (1.16% to 3.70%) | 76% | 58% | 2.29 (0.97% to 5.41%) | 64% | 48% | 1.93 (0.87% to 4.29%) |
| 4 weeks ^{a,b} | 58% ^b | 43% ^b | .034 ^b | 1.83 (1.05% to 3.21%) ^b | 66% | 48% | 2.10 (0.94% to 4.71%) | 50% | 38% | 1.63 (0.74% to 3.62%) |
| 6 weeks ^a | 51% | 40% | .119 | 1.56 (0.89% to 2.73%) | 60% | 44% | 1.91 (0.86% to 4.23%) | 42% | 36% | 1.29 (0.58% to 2.88%) |
| 12 weeks ^a | 39% | 31% | .237 | 1.42 (0.79% to 2.55%) | 42% | 34% | 1.41 (0.63% to 3.16%) | 36% | 28% | 1.45 (0.62% to 3.37%) |

DNC = denicotinized cigarette; NRT = nicotine replacement therapy; ST = standard treatment; TQD = target quit day.

^aContinuous CO-validated abstinence from 2 weeks post-TQD.^bPrimary smoking cessation outcome.

xxxvi. Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls.

Nicotine has beneficial effects on cognitive function. AhnAllen, *et al.*, (2015) [[pg297](#)] investigated whether switching to VLNC cigarettes impairs cognitive function in smokers with and without schizophrenia, and whether nicotine replacement reverses these effects. Smokers with schizophrenia (SS;29) and control smokers (CS;28) smoked usual-brand cigarettes, VLNC cigarettes while wearing 2 placebo patches (PLA), or VLNC cigarettes while wearing 2 nicotine patches totaling 42 mg (NIC) for 5 hours, and then completed computerized assessments of visual sustained attention, motor speed, visual working memory, processing speed, inhibitory control, and response variability.

Across conditions, SS were slower than CS in tasks of motor speed and visual working memory and had poorer target detectability on a visual sustained attention task. Across groups, functioning in domains of visual sustained attention, inhibitory control, processing speed, and response variability was impaired in the VLNC + PLA condition relative to the usual-brand and VLNC + NIC conditions (Table VIII.D-48).

Conclusions: Reducing nicotine may impair cognitive function. Supplementing therapy with NRT may ameliorate impaired cognitive function.

Table VIII.D-48. Performance (From AhnAllen *et al.* 2015 [pg297])

| | Control smokers | | | Smokers with schizophrenia | | |
|---|--------------------------|--------------------------|---------------------------|----------------------------|--------------------------|---------------------------|
| | Usual brand | VLNC + PLA | VLNC + NIC | Usual brand | VLNC + PLA | VLNC + NIC |
| Motor speed | | | | | | |
| MOT latency** | 887 (271) | 919 (240) | 896 (264) | 1,162 (401) | 1,190 (394) | 1,096 (307) |
| Visual sustained attention [†] | | | | | | |
| CPT-II Omissions (%) | 1.40 (2.82) | 3.00 (5.71) | 1.19 (2.48) | 2.83 (5.33) | 3.89 (7.63) | 1.94 (2.52) |
| RVP A*** | 0.99 (0.02) | 0.98 (0.03) | 0.99 (0.02) | 0.95 (0.06) | 0.96 (0.04) | 0.97 (0.03) |
| Visual working memory | | | | | | |
| DMS 12s accuracy | 81.0 (20.5) | 82.9 (17.1) | 84.8 (17.8) | 82.2 (22.6) | 71.1 (27.6) | 75.6 (18.9) |
| DMS 12s latency** | 3,009 (635) | 3,144 (1,153) | 2,969 (1,030) | 3,917 (1,406) | 3,972 (1,293) | 4,130 (1,863) |
| Inhibitory control | | | | | | |
| CPT-II commissions (%)** | 32.6 (25.4) ^a | 38.1 (28.1) ^b | 37.8 (29.4) ^{ab} | 32.1 (20.4) ^a | 39.1 (22.1) ^b | 38.4 (17.1) ^{ab} |
| SRT commissions (%)*** | 1.13 (1.32) ^a | 2.00 (1.83) ^b | 1.09 (1.65) ^a | 0.67 (1.64) ^a | 2.94 (3.06) ^b | 1.22 (2.98) ^a |
| Processing speed | | | | | | |
| RVP latency** | 346 (72.8) ^a | 367 (62.6) ^b | 346 (71.0) ^a | 407 (122) ^a | 426 (112) ^b | 382 (109) ^a |
| CPT-II Hit RT** | 377 (70.1) ^a | 407 (94.3) ^b | 382 (77.9) ^a | 428 (79.9) ^a | 442 (87.3) ^b | 413 (78.9) ^a |
| Response variability | | | | | | |
| CPT-II Hit RT SE** | 6.9 (3.8) ^a | 9.0 (6.2) ^b | 7.4 (5.7) ^a | 8.5 (7.1) ^a | 11.4 (8.1) ^b | 8.4 (5.3) ^a |

Note. VLNC = very low nicotine content cigarette; PLA = placebo patch condition; NIC = 42mg nicotine patch condition; MOT = CANTAB motor screening test; CPT-II = Continuous performance test II; DMS = CANTAB delayed matching to sample test; RVP = CANTAB rapid visual information processing test; SRT = CANTAB simple reaction time test; RT = reaction time.

Asterisks indicate significant effects of group (**p* < .01). Plus signs indicate significant effects of condition (***p* < .01; ****p* < .001; conditions with different letters (a, b) are significantly different.

[†]MANOVA results indicated a significant effect of condition on this domain, but follow-up univariate ANOVAs examining effects on each task were not significant.

xxxvii. Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes.

Ding, *et al.*, (2014) [pg299] investigated the mouth level exposure to BaP after smoking Quest cigarettes. Seventy-two daily smokers were given progressively reduced nicotine content cigarettes (Quest 1, Quest 2 and Quest 3) to smoke over a 7-day period. Butts were collected for BaP analysis. CPD, urinary cotinine, and 1-hydroxypyrene were measured throughout the study.

The average cigarette per day was 14.8 ± 6.4 when participants smoked their usual brands. CPDs for Quest 1, 2 and 3 periods were 14.8 ± 6.7 , 15.8 ± 7.6 and 15.0 ± 9.4 , respectively. The median total mouth-level BaP intake decreased as participants switched to the reduced-nicotine Quest cigarettes (Figure VIII.D-51). There were statistically significant differences between each collection period. The same analyses was applied to the biomarkers (urinary cotinine (Figure VIII.D-52) and 1-HOP (Figure VIII.D-53) from the same group. Box plot results

indicated a similar decreasing trend of median urinary cotinine. Median 1-HOP did not change over the four periods when smokers switched to Quest cigarettes (Figure VIII.D-53).

Conclusion: Use of VLNC cigarettes can reduce mouth level exposure to BaP, but not urinary 1-hydroxypyrene.

Figure VIII.D-51. BaP BOE (From Ding *et al.* 2014 [pg299]).

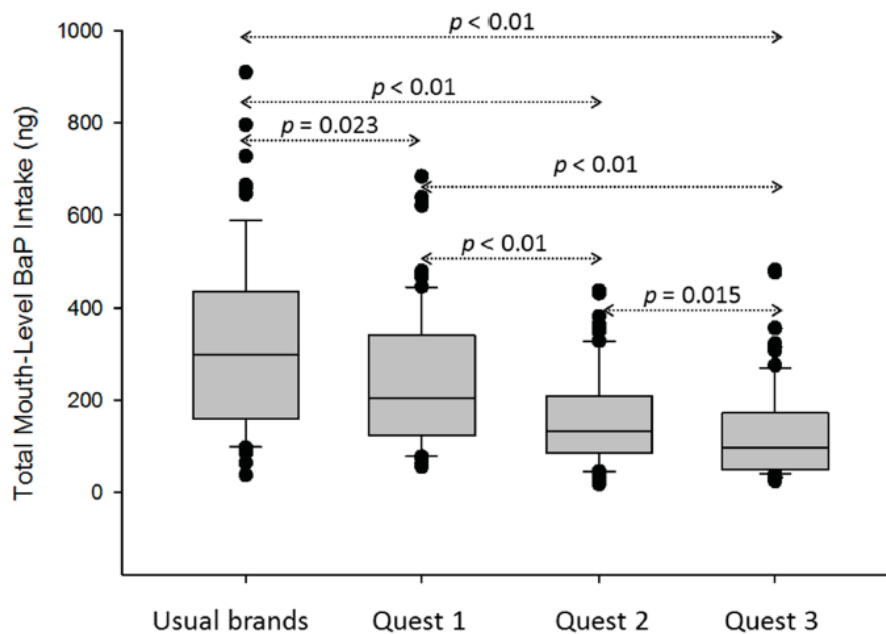


Figure VIII.D-52. Cotinine BOE (From Ding *et al.* 2014 [pg299])

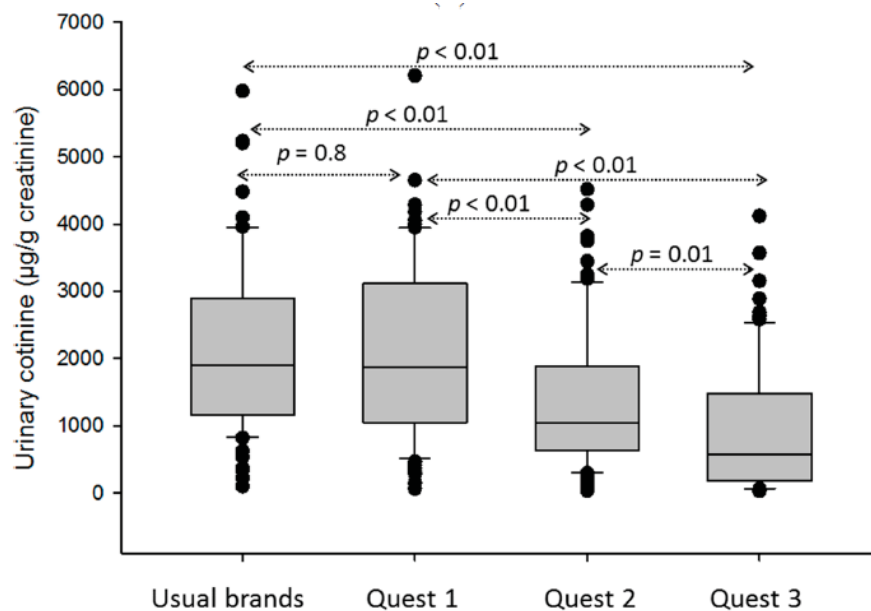
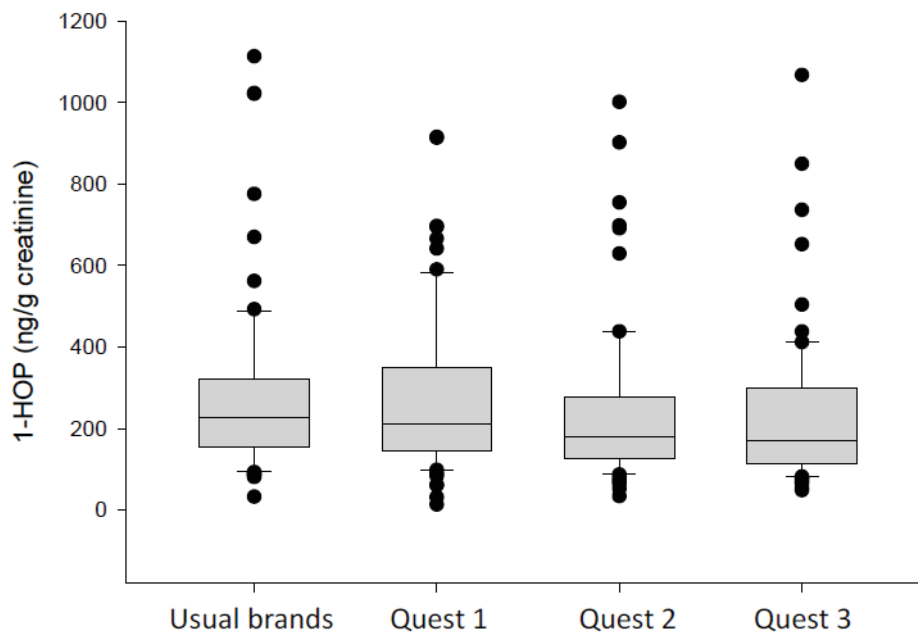


Figure VIII.D-53. 1-HOP (From Ding *et al.* 2014 [pg299])



xxxviii. Dose-Response Effects of Spectrum Research Cigarettes.

Hatsukami, *et al.*, (2013, Nicotine & Tobacco Research) [pg300] conducted two studies with SPECTRUM® cigarettes. In the first study, subjects first smoked their usual brand (4 puffs) and then randomly were assigned to smoke a low nicotine (LN;0.4 mg), intermediate nicotine

(LN;5.7mg) or high nicotine (HN;~12 mg). Each smoking was separated by 30 minutes. Subjects completed questionnaires and vital signs after each smoking. In the second study, subjects were assigned to smoke one of the three cigarettes for 1-week, and subjective evaluations and biomarkers were assessed.

In the first study, significant dose-response effects were observed, particularly between the LN and HN cigarette groups. The LN cigarettes were less satisfying and suppressed the urge to smoke less than the usual brand (Table VIII.D-49). In the one-week study there were decreases in CPD (Figure VIII.D-54) and BOE in the LN group (Table VIII.D-50). There was no increase in expired CO indicating no compensation.

Conclusions: VLNC reduced cigarette consumption and BOE. There was no compensation.

Table VIII.D-49. Craving (From Hatsukami *et al.* 2013, Nicotine & Tobacco Research [pg300])

| Measurement ^a (0–100 Scale) | Usual Brand Mean (SE) | Lower LS Means (SE) ^b | Intermediate LS Mean (SE) ^b | Higher LS Mean (SE) ^b | Lower vs. Intermediate t = 3.26* | Lower vs. Higher t = 4.65*** | Intermediate vs. Higher t = 1.38 |
|---|--------------------------|-------------------------------------|---|-------------------------------------|--|--------------------------------------|--|
| Satisfaction | 83.6 (1.4) | 36.8 (4.1) | 54.1 (4.1) | 61.4 (4.1) | t = 1.85 | t = 2.53 ⁺ | t = 0.68 |
| Psychological Reward | 53.7 (2.2) | 33.5 (3.1) | 40.9 (3.1) | 43.6 (3.1) | t = 0.73 | t = 0.40 | t = 1.14 |
| Aversion | 13.0 (1.7) | 16.7 (2.8) | 14.1 (2.8) | 18.2 (2.8) | t = 2.70* | t = 4.09** | t = 1.03 |
| Enjoyment of Sensation | 73.1 (2.4) | 32.7 (4.2) | 49.3 (4.2) | 54.8 (4.2) | t = 2.07 | t = 2.71 ⁺ | t = 0.64 |
| Craving Reduction | 62.8 (3.3) | 42.8 (4.5) | 54.9 (4.5) | 58.6 (4.5) | | | |

Notes. LS = least square; SE = standard error.

^aSubscale scores were averaged across the items.

^bAdjusted for baseline response (usual brand), gender, menthol use, study site, cigarette order, interactions between nicotine level and menthol and gender, and repeated measures across subjects.

* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$. **** $p \leq .0001$.

Figure VIII.D-54. CPD (From Hatsukami *et al.* 2013, Nicotine & Tobacco Research [pg300])

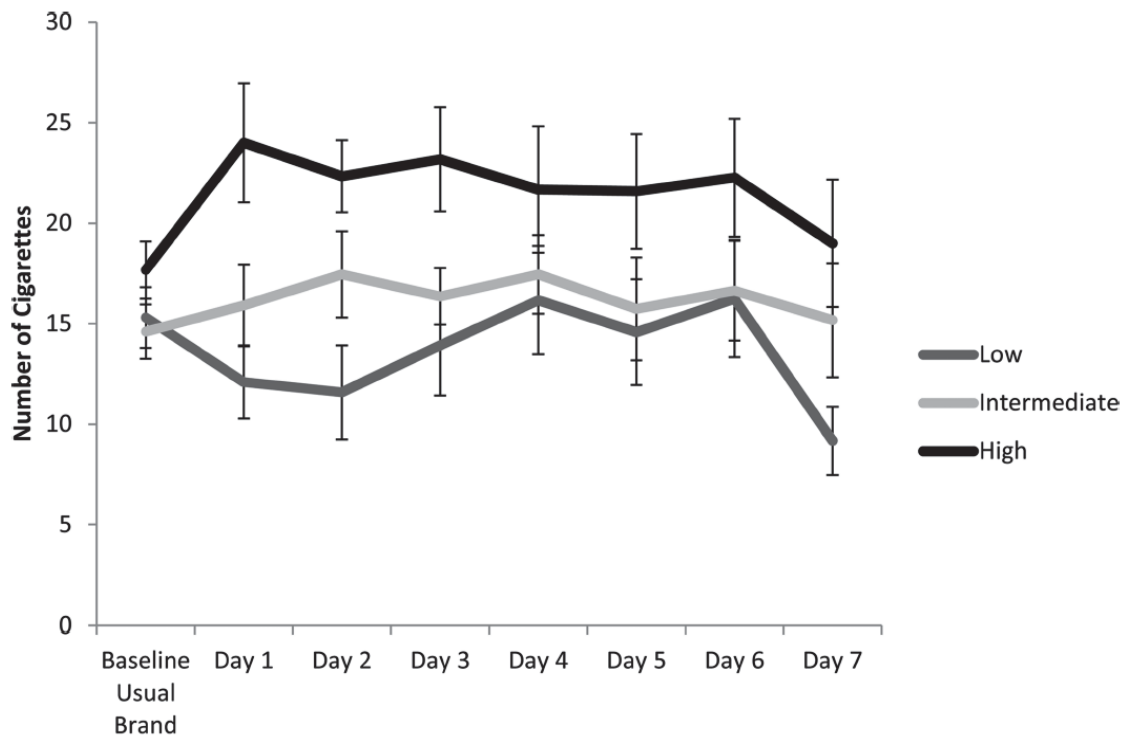


Table VIII.D-50. BOE (From Hatsukami *et al.* 2013, Nicotine & Tobacco Research [pg300])

| | Usual Brand | Lower LS | Intermediate LS | Higher LS | | | |
|--------------------------------|-------------|------------|-----------------|------------|--------------------------|----------------------------|--------------------------|
| Measurement | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) | Lower vs. Intermediate | Lower vs. Higher | Intermediate vs. Higher |
| Cotinine (nmol/ml) | 21.8 (2.3) | 5.0 (3.5) | 13.4 (3.2) | 20.3 (3.1) | <i>l</i> <i>t</i> = 1.77 | <i>l</i> <i>t</i> = 3.31* | <i>l</i> <i>t</i> = 1.55 |
| Nicotine equivalents (nmol/ml) | 81.6 (7.8) | 19.9 (8.1) | 40.1 (7.6) | 60.8 (7.1) | <i>l</i> <i>t</i> = 1.81 | <i>l</i> <i>t</i> = 3.79* | <i>l</i> <i>t</i> = 2.01 |
| Carbon monoxide | 17.1 (1.4) | 11.3 (2.3) | 18.9 (2.1) | 19.9 (1.9) | <i>l</i> <i>t</i> = 2.43 | <i>l</i> <i>t</i> = 2.91** | <i>l</i> <i>t</i> = 0.38 |

Notes. LS = least square; SE = standard error.

Excludes three subjects who smoked more than three usual-brand cigarettes during the study period.

p* ≤ .01. *p* ≤ .05.

xxxix. Effects of reduced nicotine content cigarettes on individual withdrawal symptoms over time and during abstinence (NCT01681875).

The data comes from a previously published seven-arm, double-blind, 10-site randomized trial that included a 2-week baseline and 6-week experimental period (Donny *et al.*, 2015 [pg299]). Dermody *et al.*, (2018) [pg298] hypothesized that individual withdrawal symptoms would be lower in the RNC conditions than the NNC cigarette group because RNC cigarette use

over the 6-week period would reduce nicotine dependence. To test these hypotheses, analyses included assessments of individual withdrawal symptoms at daily (i.e., during first week of switching to RNC cigarettes) and weekly (i.e., for 6 weeks) units of measurement, and also evaluated withdrawal during a period of overnight smoking abstinence at the end of 6 weeks of study cigarette use. During baseline, participants smoked their UB of cigarettes. Participants were then randomly assigned to smoke SPECTRUM® cigarettes varying in nicotine content: 0.4 mg/g, 0.4 mg/g-high tar (HT; defined a priori as exploratory), 1.3 mg/g, 2.4 mg/g, 5.2 mg/g, 15.8 mg/g (defined a priori as the primary control), and UB cigarettes. Following baseline, participants were provided a free 14-day supply of cigarettes at each weekly visit. Participants were instructed to not use other cigarettes, received brief weekly counseling aimed at increasing compliance, and completed weekly laboratory assessments (BOE) and subjective evaluations.

There were no effects on daily or weekly withdrawal symptoms in the 0.4 mg group. When withdrawal symptoms were compared after overnight abstinence, individuals in the 0.4 mg group reported significantly less anger/irritability/frustration and difficulty concentrating than the usual brand smoker (Table VIII.D-51).

Conclusions: Use of VLNC cigarettes can cause mild withdrawal symptoms. There was no evidence in nontreatment-seeking smokers that lowering the nicotine content in cigarettes to a less addictive level would result in severe or protracted nicotine withdrawal.

Table VIII.D-51. Craving (From Dermody *et al.* 2018 [pg298])

| Withdrawal symptom | .4 mg/g | .4 mg/g HT | 1.3 mg/g | 2.4 mg/g | 5.2 mg/g | Usual brand |
|--|-------------------------------|------------|--------------------|------------|------------|------------------------|
| Angry/irritable/frustrated | -.64 (.29)* | .09 (.27) | -.38 (.27) | -.20 (.28) | -.35 (.27) | .67 (.27)* |
| Anxious/nervous | -.54 (.30)[†] | .20 (.28) | -.41 (.28) | .19 (.28) | .04 (.28) | .76 (.27)** |
| Depressed mood/sad | -.47 (.36) | .02 (.32) | -.32 (.33) | -.26 (.33) | -.18 (.33) | .04 (.32) |
| Desire or craving to smoke | -.48 (.27)[†] | -.08 (.27) | -.65 (.27)* | -.24 (.27) | -.32 (.27) | .58 (.28)* |
| Difficulty concentrating | -.70 (.30)* | .11 (.28) | -.38 (.28) | -.20 (.28) | -.41 (.28) | .33 (.27) |
| Increased appetite/hungry/weight gain | -.23 (.29) | .16 (.29) | .18 (.27) | -.19 (.28) | -.40 (.29) | .05 (.27) |
| Insomnia/sleep problems/awakening at night | -.09 (.31) | .16 (.30) | -.07 (.31) | .12 (.30) | -.14 (.31) | .60 (.32) [†] |
| Restless | -.32 (.29) | -.01 (.28) | -.24 (.28) | -.28 (.28) | -.23 (.28) | .56 (.28)* |

Note. HT = high tar. Unstandardized coefficients (standard errors) are reported for the effect of each group relative to the normal nicotine content (NNC) control. Significant and positive effects indicate that the group of interest reported increased withdrawal relative to the NNC control during the abstinence period. Significant coefficients are bolded using a significance level of .05.

[†] $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

xl. Nicotine and non-nicotine smoking factors differentially modulate craving, withdrawal and cerebral blood flow as measured by arterial spin labeling.

Smoking cessation results in withdrawal symptoms. Addicott *et al.*, (2014) [pg297] investigated the impact of VLNC and NRT on cerebral blood flow in 29 adult smokers. The groups were: nicotine patch and Quest 3, nicotine patch and abstinence, placebo patch and Quest 3, and placebo patch and abstinence. Subjective evaluations and BOE were also measured.

Smokers reported more withdrawal symptoms in the abstinence condition than in the de-nicotine (Quest) group (Figure VIII.D-55). There were no changes in cerebral blood flow (CBF) across treatment groups. CBF was reduced in all smokers compared to non-smokers (Figure VIII.D-56).

Conclusion: Non-nicotine factors must be involved with withdrawal as indicated by CBF.

Figure VIII.D-55. Craving (From Addicott *et al.* 2014 [pg297]).

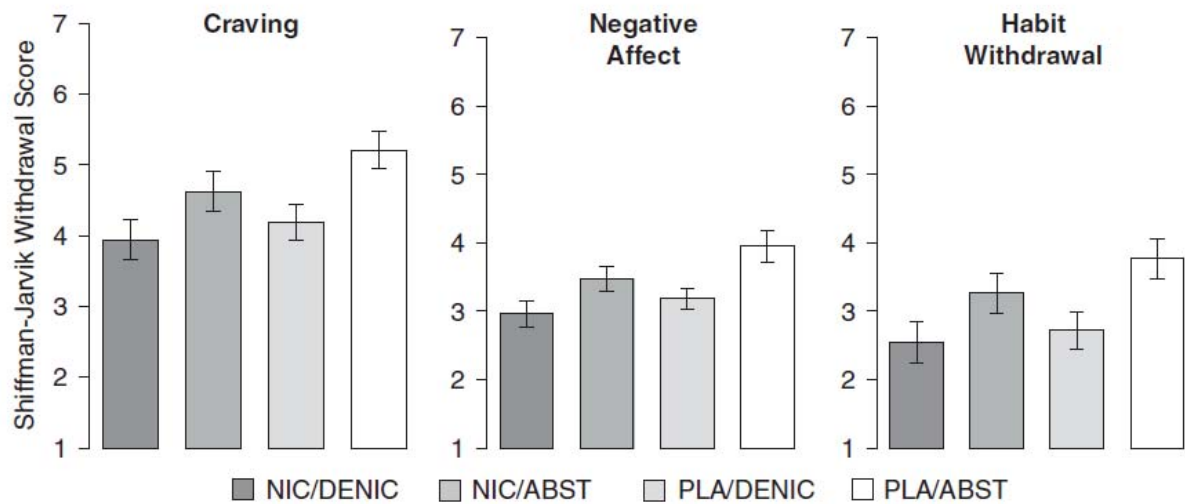
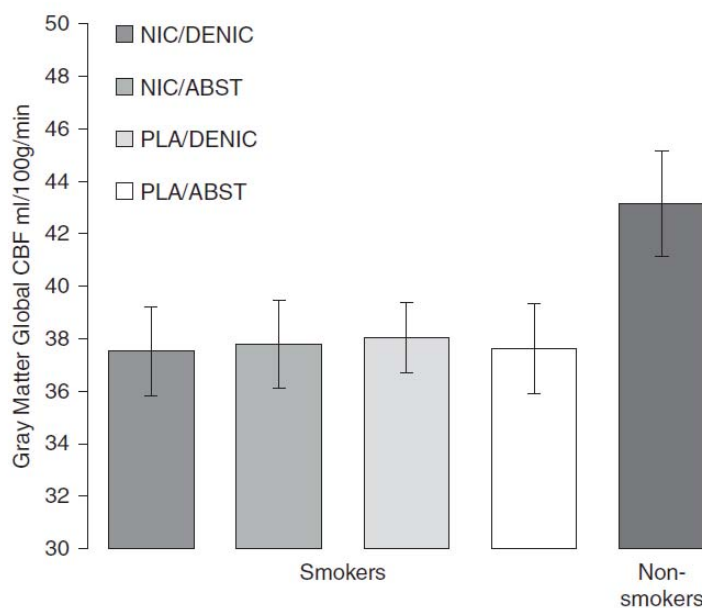


Figure VIII.D-56. Brain activity (From Addicott *et al.* 2014 [pg297]).



xli. Experimental evidence for a causal relationship between smoking lapse and relapse.

Juliano *et al.*, (2006) [pg301] evaluated the impact of a smoking lapse on relapse probability. Sixty smokers were randomly assigned to smoke either Ultratech low nicotine (0.07 mg) or high nicotine cigarettes (0.6 mg) after being abstinent for 4 days. Smoking behavior was tracked for 6 days.

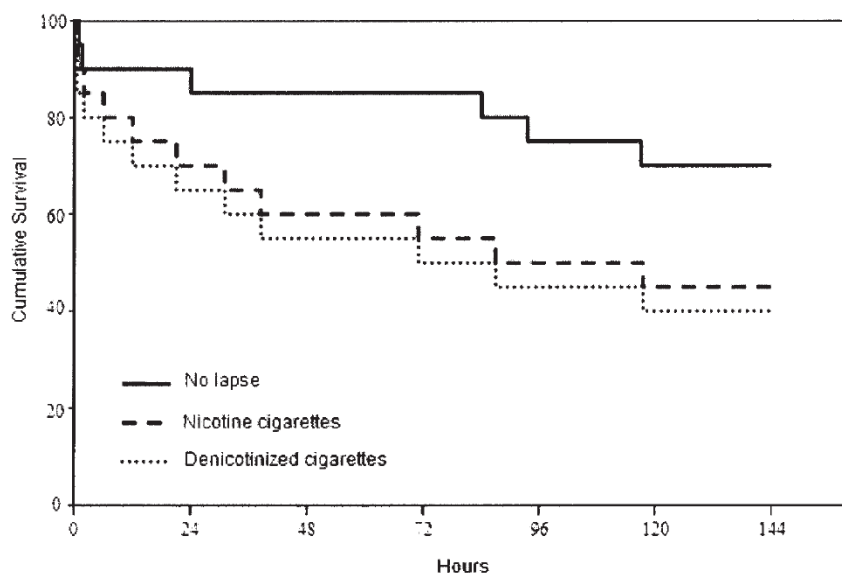
The subjects smoked 5 cigarettes. There was no CO boost, indicating no compensation. Heart rate boost was present for the high nicotine product compared to the low nicotine. Craving and withdrawal were increased in the denicotinized cigarette (Table VIII.D-52). The percentage of subjects that were abstinent at the end of the 6-day follow up period was 70% in the no lapse group compared to 45% and 40% in the smoker groups. There was no difference between the low and high nicotine groups (Figure VIII.D-57). Subjects in the smoking group were more than twice as likely to smoke during the 6-day follow up period.

Conclusion: Smoking a VLNC after trying to quit does not produce a different abstinence outcome than smoking a regular cigarette.

Table VIII.D-52. BOE (From Juliano *et al.*, 2006 [pg301])

| Variable | Nicotine | Denicotinized | No lapse | Significance |
|--|-----------------------------|-----------------------------|---------------------------|------------------------------|
| CO boost after first cigarette (ppm) | 4.45 (2.31) | 4.05 (2.67) | — | (2, 37) <i>ns</i> |
| CO boost after experimental manipulation (ppm) | 9.15 (6.67) _a | 7.20 (4.66) _a | -0.40 (1.35) _b | $F(2, 37) = 22.42, p < .001$ |
| Smoking time (s) | 408.65 (96.77) | 363.65 (93.31) | — | <i>ns</i> |
| Cigarette butt weights | | | | |
| First cigarette | 0.42 (0.11) | 0.44 (0.14) | — | <i>ns</i> |
| Four cigarettes | 1.75 (0.48) | 1.59 (0.80) | — | <i>ns</i> |
| Heart rate boost (beats per minute) | 9.05 (6.09) | 1.01 (5.86) | — | $F(1, 38) = 12.68, p < .001$ |
| Dizzy (0–100) | 54.26 (37.27) | 33.95 (31.44) | — | $F(1, 38) = 3.40, p = .073$ |
| Harsh (0–100) | 32.47 (35.80) | 59.10 (36.38) | — | $F(1, 38) = 5.30, p = .027$ |
| Tastes different than usual brand (0–100) | 68.16 (38.71) | 89.05 (21.46) | — | $F(1, 38) = 4.40, p = .043$ |
| Craving change | | | | |
| After first cigarette | -24.22 (32.77) | -8.20 (26.89) | — | $F(1, 38) = 2.77, p = .105$ |
| After all five cigarettes | -15.09 (13.28) _a | -15.20 (21.93) _a | .14 (11.23) _b | $F(2, 53) = 5.08, p = .010$ |
| Withdrawal ratings | | | | |
| After first cigarette | 3.55 (3.38) | 3.44 (3.11) | — | <i>ns</i> |
| After all five cigarettes | 3.40 (3.03) _a | 3.65 (2.91) _a | 6.70 (4.82) _b | $F(2, 59) = 4.95, p = .010$ |

Figure VIII.D-57. Abstinence (From Juliano *et al.*, 2006 [pg301])



xlii. Decreasing nicotine content reduces subjective and physiological effects of smoking.

Penetar *et al.*, (2014) [pg302] investigated the subjective and physiological effects of smoking Quest cigarettes. Eight volunteers rated the characteristics of Quest cigarettes with varying levels of nicotine. At 30-minute intervals, participants smoked one of three different Quest cigarettes in a counterbalanced order (reported machine-smoked nicotine yield: 0.6 mg, 0.3 mg, or 0.05 mg). Smoking satisfaction and sensations were measured on a cigarette evaluation questionnaire. A mood questionnaire measured self-reported subjective changes in 'happy,' 'stimulated,' 'anxious,' 'desire to smoke,' and 'desire not to smoke.' Heart rate and skin temperature were recorded continuously.

Subjective ratings of the cigarettes indicated that the Quest cigarettes were less like the own brand as the amount of nicotine declined. The subjects also reported being less awake. The 0.05 mg product was less satisfying (Figure VIII.D-58). There was an initial heart rate boost in the 0.6 and 0.3 mg nicotine groups but not in the 0.05 mg group (Figure VIII.D-59).

Conclusions: VLNC cigarettes are less satisfying. Low nicotine (0.05 mg) does not product heart rate boost.

Figure VIII.D-58. Craving (From Penetar *et al.*, 2014 [pg302])

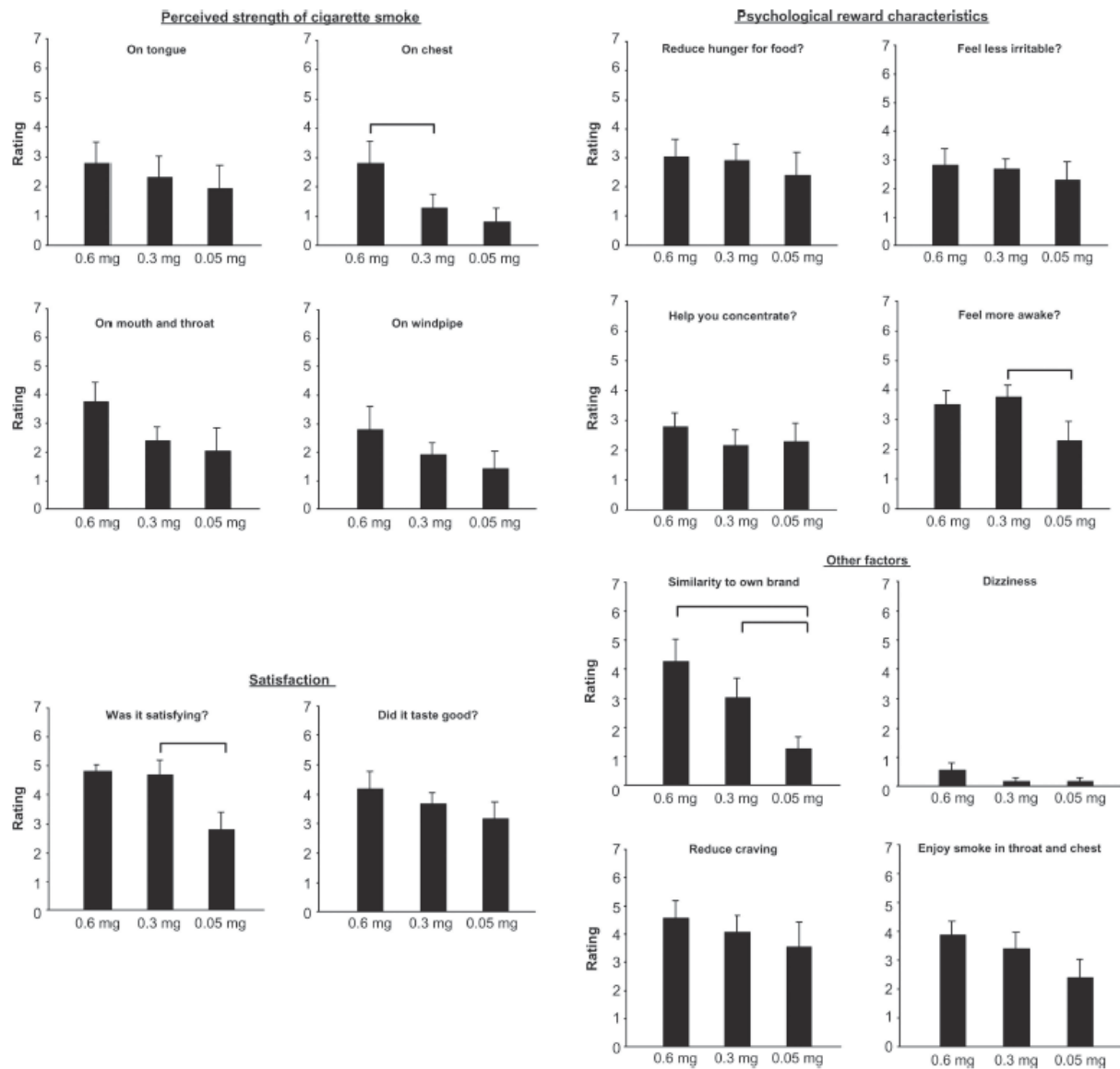
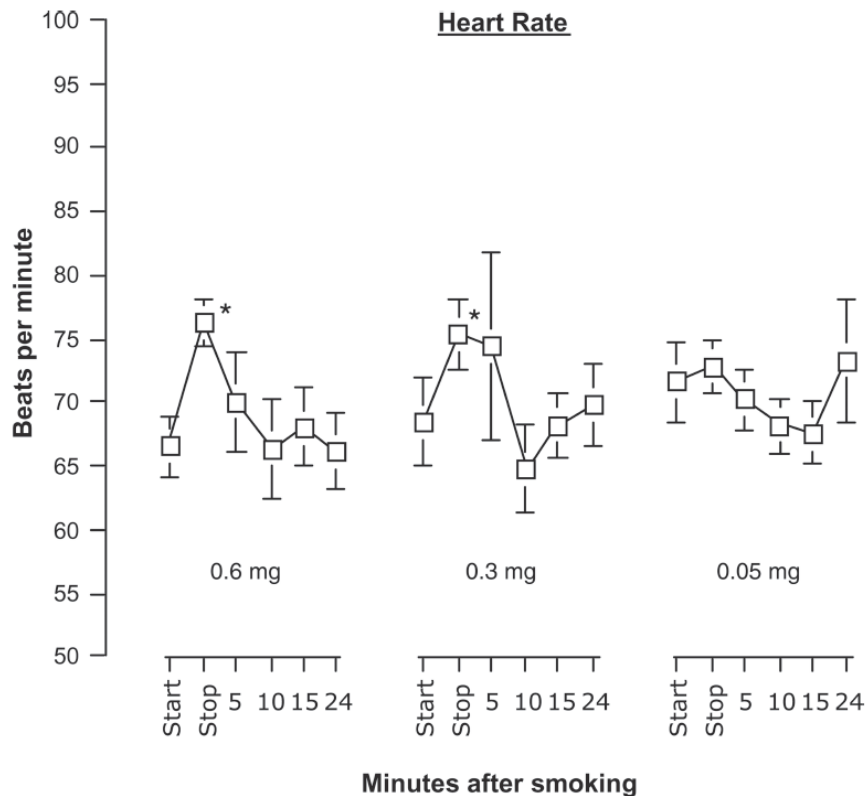


Figure VIII.D-59. Effect on heart rate (From Penetar *et al.*, 2014 [pg302])



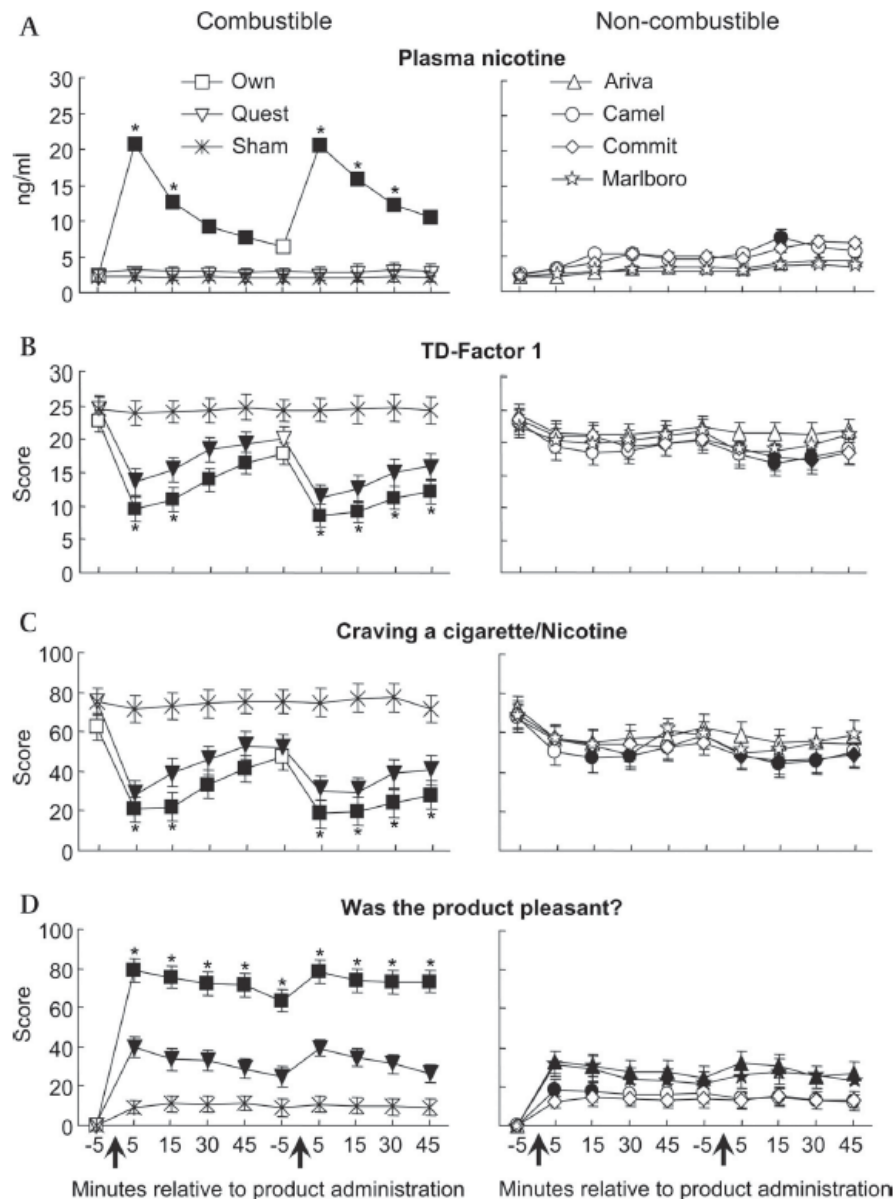
xlili. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers.

Cobb *et al.*, (2010) [pg298] compared the effects of oral products to own brand, Quest 3, and sham smoking in 28 overnight abstinent cigarette smokers. In each session the product was administered twice (separated by 60-minutes) and plasma nicotine, expired CO, and subjectives were evaluated.

Plasma nicotine was significantly reduced after smoking Quest 3. Urge to smoke (QSU Factor 1) was similar between own brand and Quest as was craving. Quest was less pleasant than own brand (Figure VIII.D-60).

Conclusion: VLNC results in lower nicotine exposure, reduces urge to smoke and craving.

Figure VIII.D-60. BOE and craving (From Cobb *et al.* 2010 [pg298])



VIII.

xliv. The airway sensory impact of nicotine contributes to the conditioned reinforcing effects of individual puffs from cigarettes.

Naqvi and Bechara (2005) [pg302] evaluated the sensory impact of nicotine from Quest cigarettes by assessing the strength of the smoke impact before the nicotine had the chance to reach the brain (<7 seconds). Subjects smoked a Quest 3, Quest 1 or dry puffed the cigarette.

The Quest 3 (denic) cigarettes were perceived as less pleasant and desirable and weaker than Quest 1 (nic) (Figure VIII.D-61). That is, nicotinized puffs were stronger and more rewarding. The extent to which nicotine elicited reward was directly correlated with the extent to which nicotine elicited airway sensations (Figure VIII.D-62).

Conclusion: Removing nicotine from the cigarette will reduce reward.

Figure VIII.D-61. Subjectives (From Naqvi and Bechara 2005 [pg302])

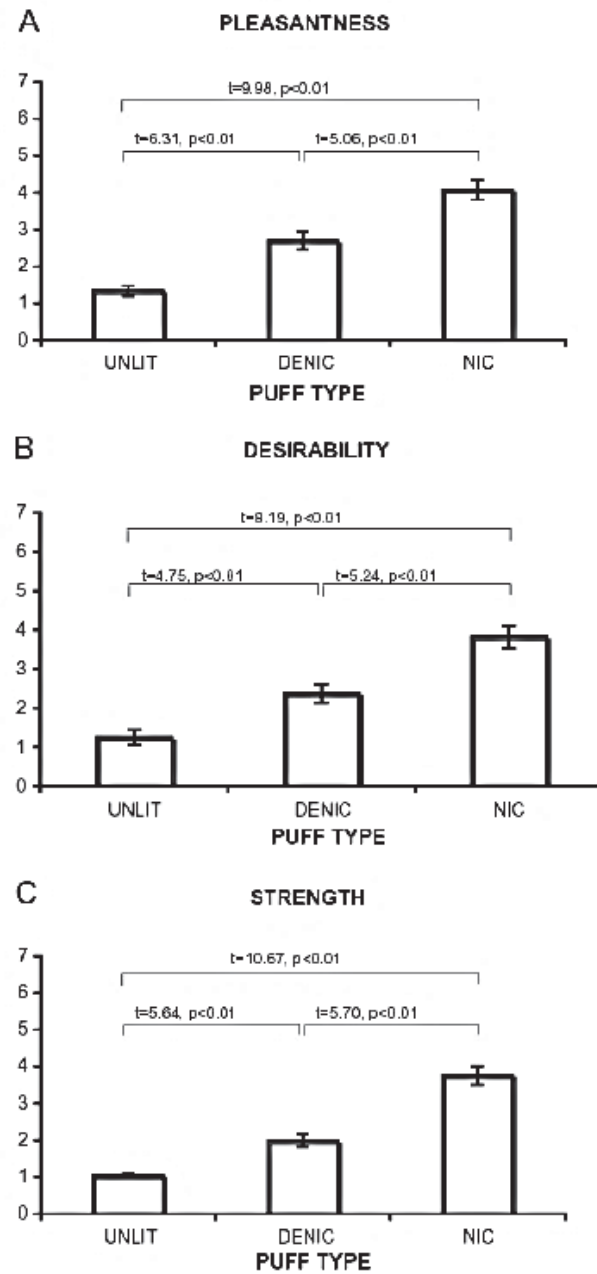
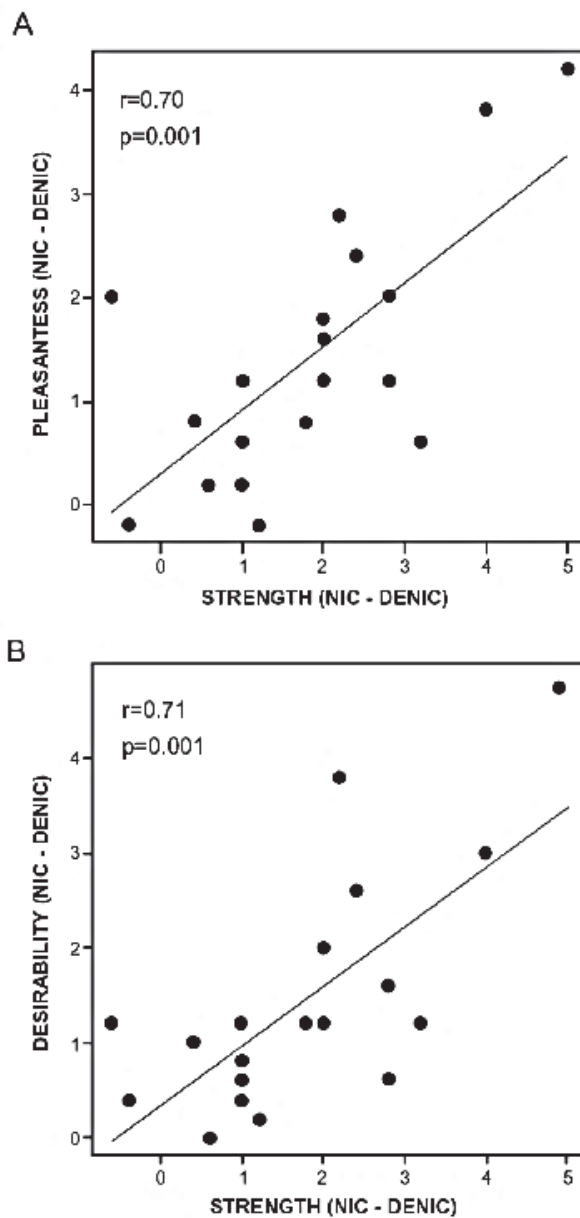


Figure VIII.D-62. Subjectives (From Naqvi and Bechara 2005 [pg302])



xliv. Placebo cigarettes in a spaced smoking paradigm.

Eid *et al.*, (2005) [pg299] investigated whether recentness of smoking was an important determinant in the ability of a placebo cigarette (Ultratech; 0.07 mg nicotine) to reduce tobacco craving. Eight subjects smoked either Ultratech or conventional cigarette (1.1 mg nicotine) in

intervals of 30, 60, or 240 minutes. Heart rate, exhaled CO and subjective measures of urges were measured.

Cigarette smoking increased heart rate and expired CO but there was no difference between placebo or nicotine cigarettes (i.e. no compensation) (Figure VIII.D-63). Craving was also not affected by nicotine content (i.e. the placebo was as effective as the nicotine cigarette in suppressing craving) (Figure VIII.D-64).

Conclusion: Craving can be reduced by VLNC cigarettes.

Figure VIII.D-63. BOE (From Eid *et al.*, 2005 [pg299])

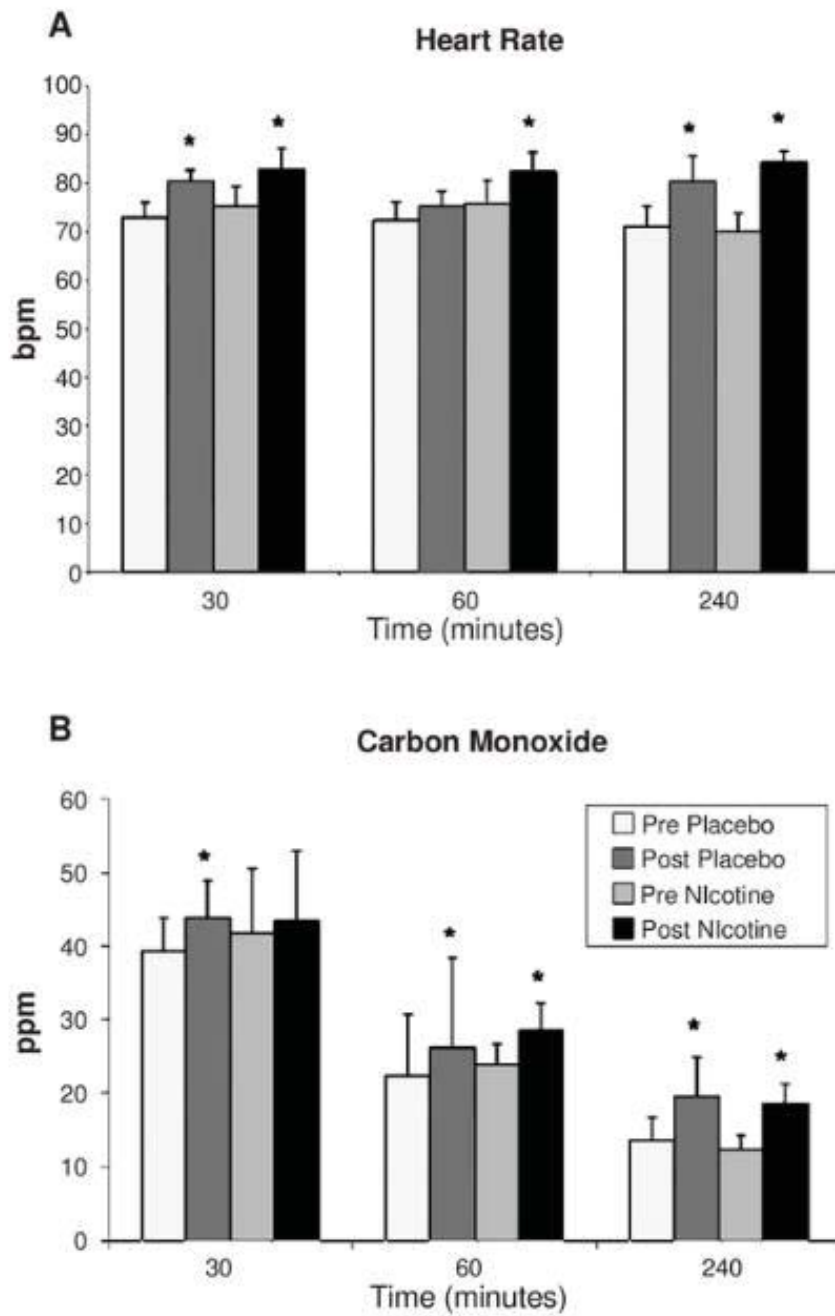
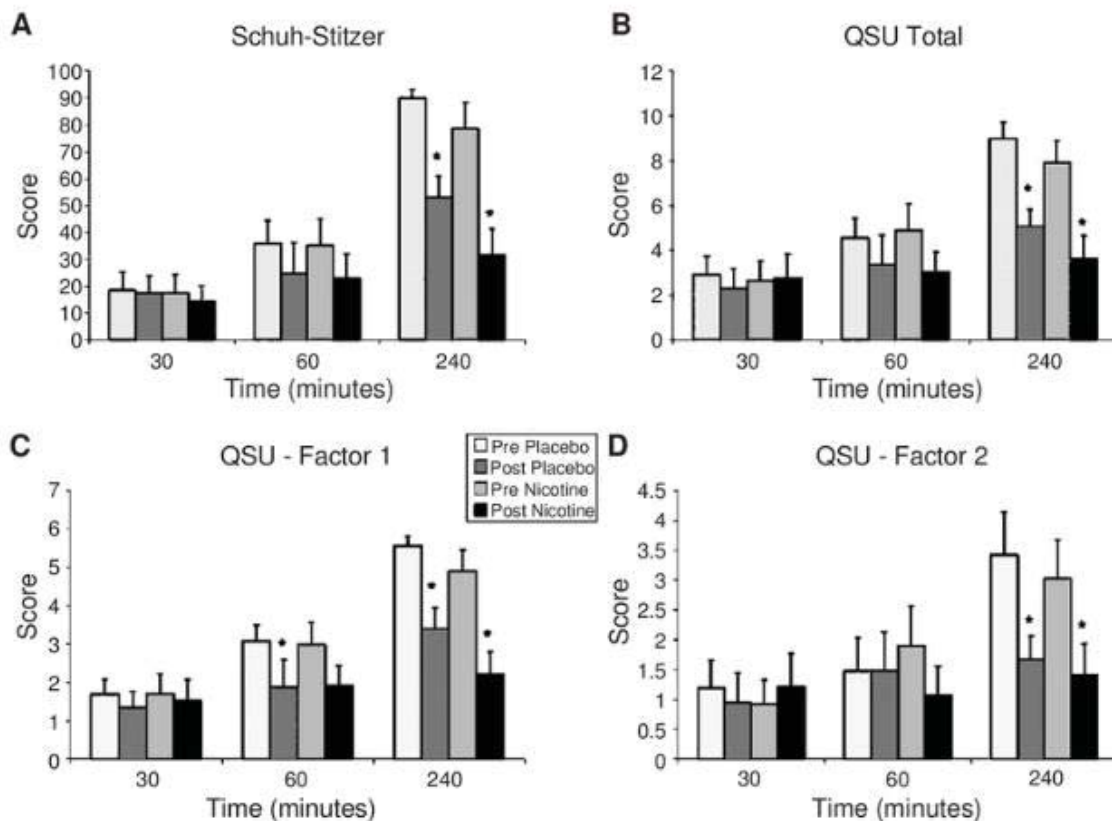


Figure VIII.D-64. Smoking urges (From Eid *et al.*, 2005 [pg299])



xlvi. Reducing nicotine exposure results in weight gain in smokers randomized to very low nicotine content cigarettes.

Cessation is associated with weight gain. Rupperecht *et al.*, (2017) [pg303] evaluated the effect of switching to various SPRECTUM cigarettes in a seven-group double blind 6-week usage period. There was a 2-week baseline period during which participants smoked their own usual brand cigarettes, and a 6-week investigational cigarette use period. During the 6-week experimental period, participants were provided with one of seven types of cigarettes varying in nicotine content (mg nicotine per g of tobacco): 0.4 mg/g; 0.4 mg/g high tar (HT); 1.3 mg/g; 2.4 mg/g; 5.2 mg/g; 15.8 mg/g, and usual brand (UB). Average tar yields were 8 to 10 mg; however, for the high tar cigarettes it was 13 mg. The 0.4 HT condition, which contained tobacco filler with the same nicotine content, but differed from 0.4 mg/g cigarettes in filter and ventilation resulting

in higher yield (ISO) of tar and nicotine, was added to the design to explore the impact of tar yield on the use and acceptability of VLNC cigarettes. A two-week supply of cigarettes was provided free of charge at each weekly session during the experimental period. During this time, participants were instructed to smoke only the provided investigational cigarettes and received counseling aimed to increase compliance, though there was no penalty for using other nicotine/tobacco products. During each visit to the laboratory, body weight was measured. Biomarkers of nicotine exposure were assessed from urine samples collected at randomization, week 2, and week 6. Urinary total nicotine equivalents (TNE) were analyzed by liquid chromatography tandem mass spectrometry. Saliva samples for the assessment of nicotine metabolite ratio (NMR), an indicator of CYP2A6 activity and the rate of nicotine metabolism, were collected during the second baseline session.

There were no significant differences in weight gain when comparing the reduced nicotine conditions with the 15.8 mg/g control group across all treatment groups and weeks (Table VIII.D-53). However, weight gain at Week 6 was negatively correlated with nicotine exposure in the two lowest nicotine content cigarette conditions (Figure VIII.D-65). Within the two lowest nicotine content cigarette conditions, both male and female smokers biochemically verified to be compliant on study product gained significantly more weight than non-compliant smokers and control groups (Figure VIII.D-66).

Conclusion: As with cessation, usage of VLNC cigarettes is likely to result in weight gain.

Table VIII.D-53. Weight gain (From Rupprechet *et al.*, 2017 [pg303])

Effect of smoking reduced nicotine content cigarette on weight gain (kg) over six weeks.

| Treatment Group | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| 15.8 mg group as reference group (primary analysis): | | | | | | |
| 5.2 mg/g | 0 (-0.48, 0.48) | 0.29 (-0.2, 0.77) | 0.01 (-0.47, 0.5) | 0.13 (-0.36, 0.62) | 0.14 (-0.36, 0.63) | 0.01 (-0.48, 0.49) |
| 2.4 mg/g | 0.01 (-0.47, 0.5) | 0.34 (-0.15, 0.83) | 0.08 (-0.41, 0.58) | 0.24 (-0.26, 0.73) | 0.37 (-0.13, 0.87) | 0.22 (-0.27, 0.71) |
| 1.3 mg/g | 0.2 (-0.28, 0.68) | 0.52 (0.03, 1) | 0.25 (-0.24, 0.73) | 0.16 (-0.34, 0.65) | 0.22 (-0.27, 0.71) | 0.18 (-0.3, 0.67) |
| 0.4 mg/g | 0.1 (-0.39, 0.59) | 0.36 (-0.13, 0.85) | 0.11 (-0.39, 0.6) | 0.28 (-0.22, 0.77) | 0.34 (-0.16, 0.83) | 0.18 (-0.32, 0.67) |
| 0.4 mg/g (HIT) | 0.11 (-0.38, 0.59) | 0.51 (0.03, 0.99) | 0.23 (-0.25, 0.72) | 0.65* (0.16, 1.14) | 0.33 (-0.16, 0.82) | 0.12 (-0.36, 0.6) |
| Usual Brand group as reference group (secondary analysis): | | | | | | |
| 15.8 mg/g | -0.06 (-0.55, 0.42) | -0.04 (-0.53, 0.45) | -0.14 (-0.63, 0.35) | -0.16 (-0.65, 0.33) | -0.43 (-0.92, 0.06) | -0.2 (-0.69, 0.29) |
| 5.2 mg/g | -0.07 (-0.55, 0.42) | 0.25 (-0.24, 0.73) | -0.13 (-0.62, 0.36) | -0.03 (-0.52, 0.46) | -0.3 (-0.79, 0.2) | -0.19 (-0.68, 0.29) |
| 2.4 mg/g | -0.05 (-0.53, 0.44) | 0.3 (-0.18, 0.79) | -0.06 (-0.55, 0.44) | 0.08 (-0.42, 0.57) | -0.06 (-0.56, 0.44) | 0.02 (-0.47, 0.51) |
| 1.3 mg/g | 0.14 (-0.34, 0.62) | 0.48 (0, 0.96) | 0.1 (-0.38, 0.59) | 0 (-0.49, 0.49) | -0.21 (-0.7, 0.28) | -0.02 (-0.5, 0.47) |
| 0.4 mg/g | 0.04 (-0.45, 0.52) | 0.32 (-0.17, 0.81) | -0.04 (-0.53, 0.46) | 0.12 (-0.38, 0.61) | -0.09 (-0.59, 0.4) | -0.02 (-0.52, 0.47) |
| 0.4 mg/g (HIT) | 0.04 (-0.44, 0.52) | 0.47 (-0.01, 0.95) | 0.09 (-0.39, 0.57) | 0.49 (0.01, 0.97) | -0.1 (-0.59, 0.38) | -0.08 (-0.56, 0.4) |

* indicates $p < 0.01$.

Mean differences (95% confidence interval) are reported.

Figure VIII.D-65. Weight gain (From Rupprechet *et al.*, 2017 [\[pg303\]](#))

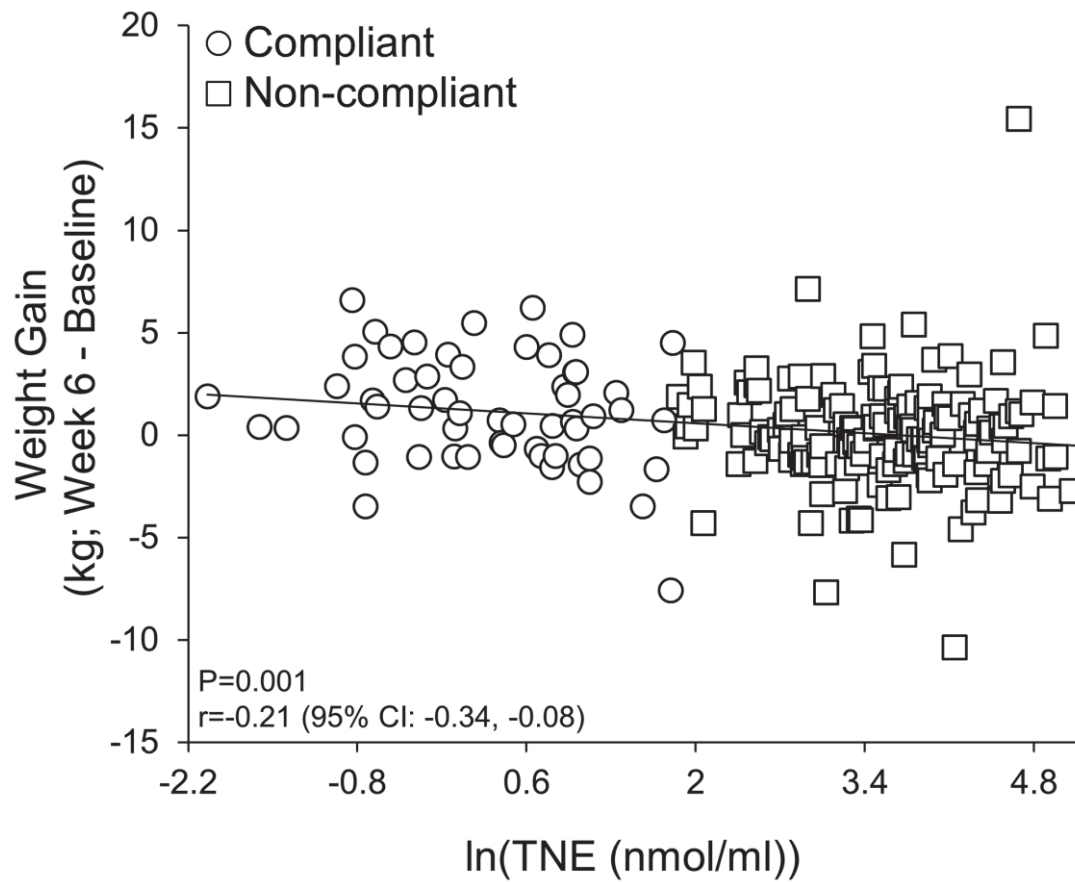
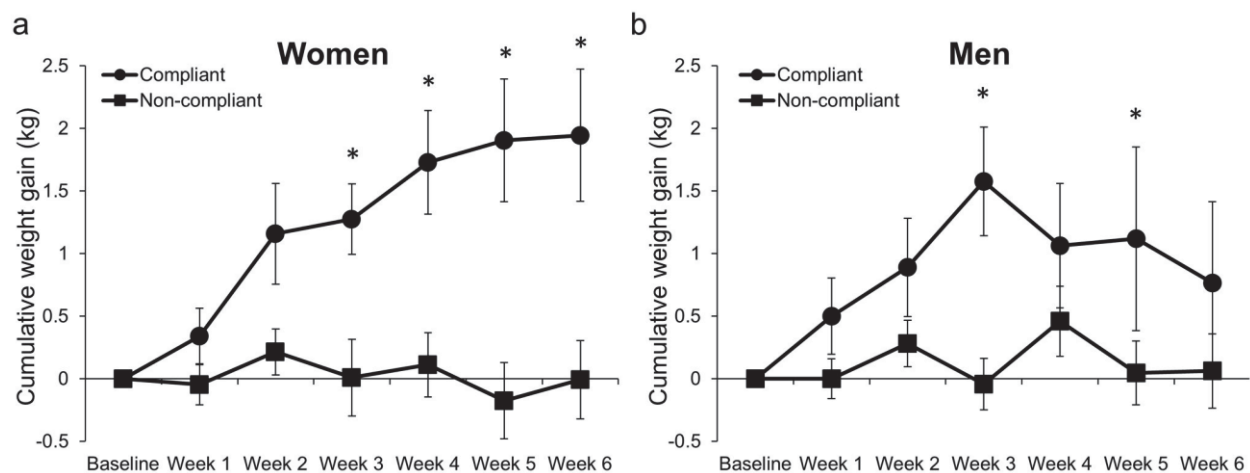


Figure VIII.D-66. Cumulative weight gain (From Rupprechet *et al.*, 2017 [\[pg303\]](#))



xlvi. Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls.

This study by Tidey *et al.*, (2013) [pg304] used a within-subjects design to investigate the separate and combined effects of sensorimotor replacement for smoking (very low nicotine content Quest 3 [VLNC] cigarettes vs. no cigarettes) and transdermal nicotine replacement (42 mg nicotine [NIC] vs. placebo [PLA] patches) in smokers with schizophrenia (SS; n = 30) and control smokers without psychiatric illness (CS; n = 26). Each session contained a 5-hr controlled administration period in which participants underwent the following conditions, in counterbalanced order: VLNC + NIC, VLNC + PLA, no cigarettes + NIC, no cigarettes + PLA, usual-brand cigarettes + no patches. Next, participants completed measures of cigarette craving, nicotine withdrawal, smoking habit withdrawal, and cigarette subjective effects, followed by a 90-min period of ad libitum usual-brand smoking.

There was no CO boost in the VLNC group with placebo nicotine patch when compared to usual brand. There was an increase in total puff volume in SS compared to CS (data not shown). Nicotine withdrawal was higher in the SS group than the CS group. Nicotine withdrawal was not different between the VLNC with placebo patch and usual brand (i.e. VLNC suppressed withdrawal symptoms). Urge to smoke was not different between SS and CS groups. VLNC had the same urge to smoke rating as usual brand (Figure VIII.D-67). Comparison between VLNC cigarettes with and without NRT and usual brand cigarettes on the Cigarette Effect Scale (CES) indicated that VLNC cigarettes were less rewarding and satisfying than usual brand. Craving and enjoyment were not affected by VLNC in SS but appeared to be reduced in the CS group (Figure VIII.D-68).

Conclusion: VLNC can suppress withdrawal and urge to smoke. Schizophrenics appear to respond differently to withdrawal than conventional smokers.

Figure VIII.D-67. CO and smoking urge (From Tidey *et al.* 2013 [\[pg304\]](#))

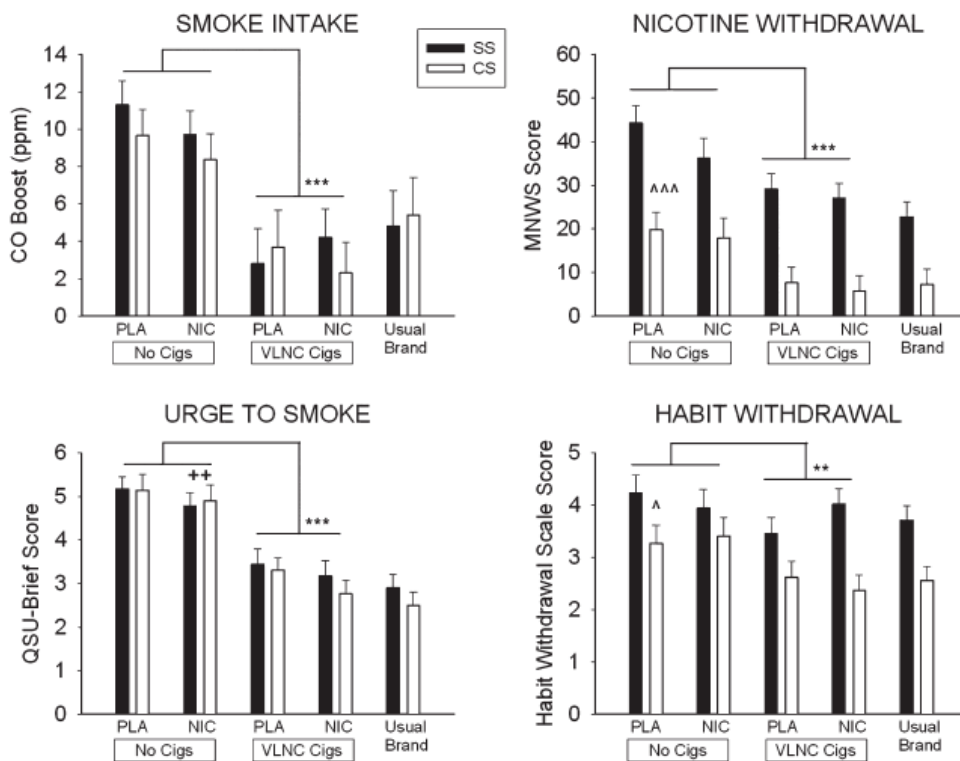
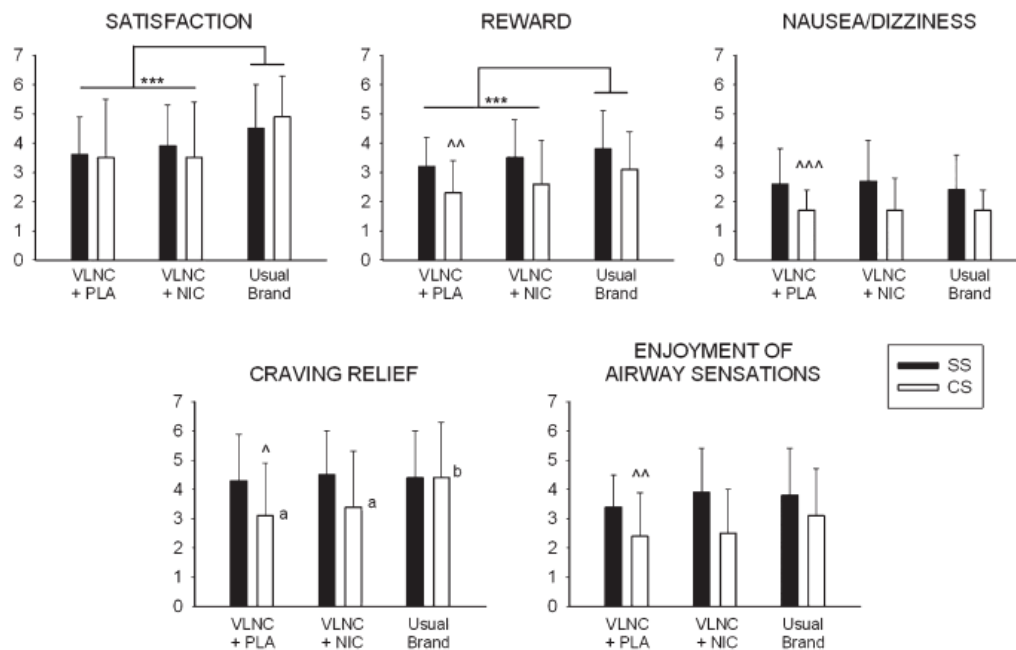


Figure VIII.D-68. Craving (From Tidey *et al.* 2013 [pg304])



xlvi. Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations.

Cassidy *et al.*, (2018, Drug and Alcohol Dependence) [pg298] evaluated the effect of smoking SPECTRUM reduced nicotine cigarettes in adolescent daily smokers (ages 15 - 19). Following overnight abstinence, the subjects reported on their craving, withdrawal, and positive and negative affect pre- and post- ad libitum smoking of one cigarette containing varying nicotine content (15.8, 5.2, 1.3 and 0.4 mg/g of tobacco) in the laboratory and reported their subjective evaluations of each cigarette. Carbon monoxide (CO) boost from pre- to post-cigarette was calculated to determine if lower-nicotine cigarettes led to differential acute changes in toxicant exposure.

All four nicotine cigarette types significantly reduced abstinence-induced craving, withdrawal, and negative affect (Figure VIII.D-69). Mixed models evaluating the effect of nicotine

content, with nicotine dependence level and gender included as covariates, revealed a significant effect of nicotine content on craving and subjective evaluations: higher nicotine content resulted in greater reductions in craving and increases in both positive and negative subjective evaluations (Figure VIII.D-70). There were no significant effects of nicotine dose on withdrawal symptoms, negative affect, or CO boost (Table VIII.D-54).

Conclusion: These results suggest that lower nicotine cigarettes may be less addictive due to reduced positive subjective effects.

Figure VIII.D-69. Smoking urge (From Cassidy *et al.*, 2018, Drug and Alcohol Dependence [pg298])

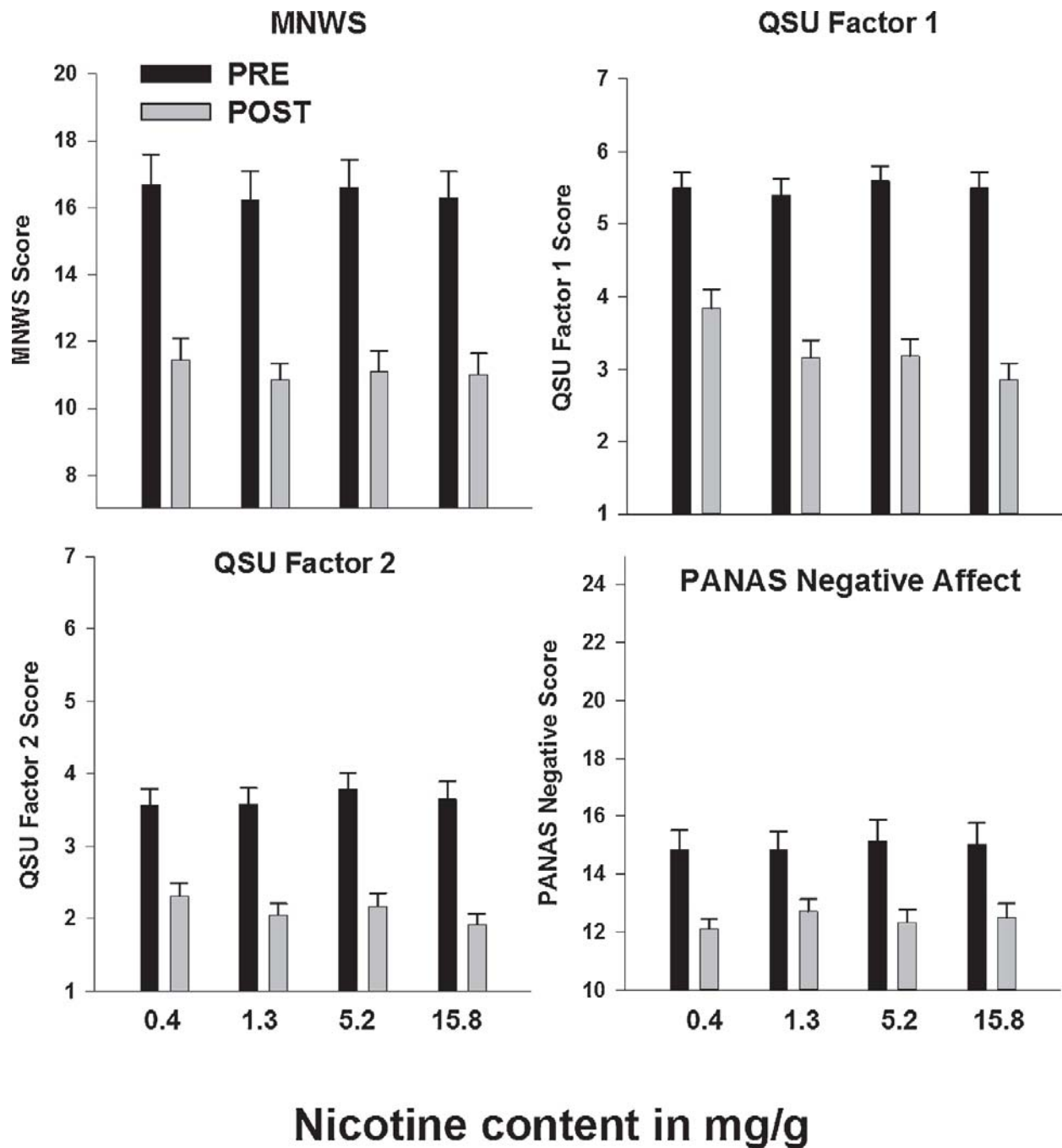


Figure VIII.D-70. Craving (From Cassidy *et al.*, 2018, Drug and Alcohol Dependence [pg298])

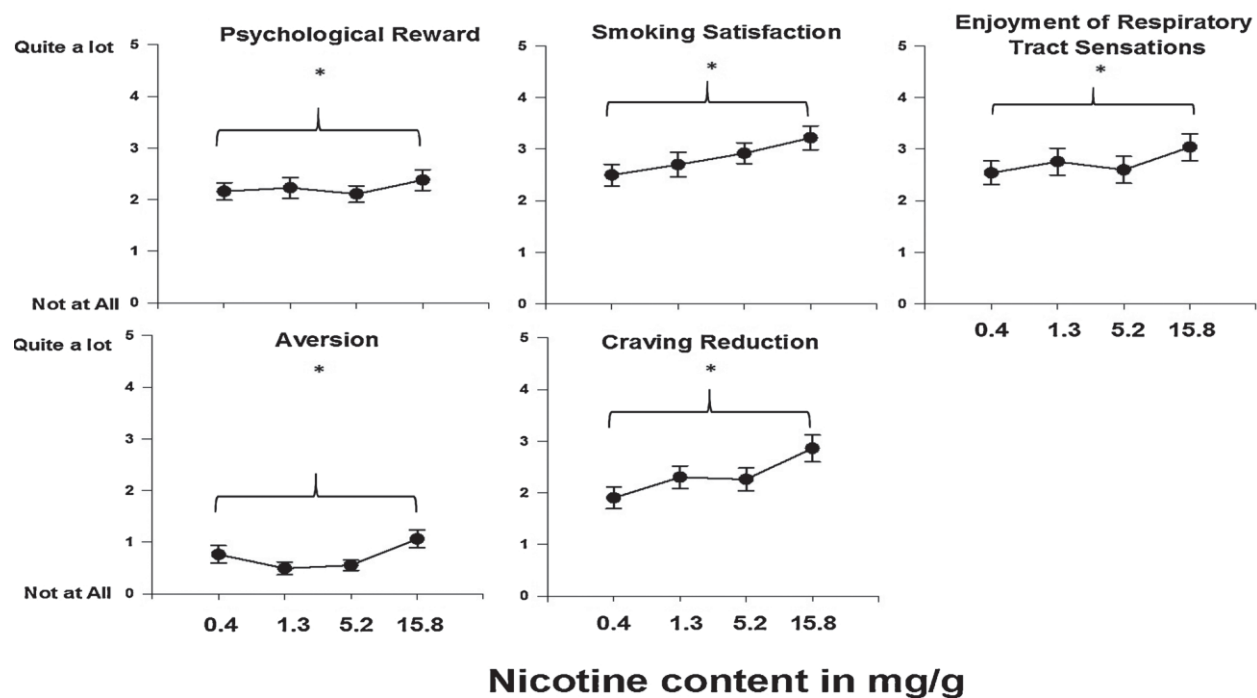


Table VIII.D-54. Craving (From Cassidy *et al.*, 2018, Drug and Alcohol Dependence [pg298])

| Predictor | Withdrawal MNWS | | Craving QSU F1 | | Craving QSU F2 | | Negative Affect PANAS | | CO Boost ppm | |
|----------------------------------|-----------------|------|----------------|------|----------------|------|-----------------------|------|--------------|------|
| | B | SE | B | SE | B | SE | B | SE | B | SE |
| Intercept | -4.41** | 0.52 | -1.95** | 0.26 | -1.2** | 0.16 | -1.78** | 0.44 | 4.26** | 0.49 |
| Baseline Dependence ¹ | -0.52 | 0.38 | -0.03 | 0.10 | -0.04 | 0.08 | -0.11 | 0.24 | 0.13 | 0.26 |
| Sex ² | -1.75 | 1.09 | -0.10 | 0.36 | -0.27 | 0.28 | -1.90 | 0.83 | -0.29 | 0.78 |
| Slope | | | | | | | | | | |
| Dose ³ | -0.98 | 1.23 | -1.3** | 0.42 | -0.59** | 0.25 | -1.6 | 1.24 | -0.13 | 0.62 |
| Dependence x Dose | -0.38 | 0.45 | -0.31 | 0.17 | -0.42** | 0.11 | -0.46 | 0.51 | -0.04 | 0.51 |
| Gender x Dose | 2.14 | 1.68 | 0.82 | 0.59 | 0.29 | 0.34 | 2.39 | 1.71 | 1.60 | 1.01 |

Note. All outcomes except CO boost are expressed as difference scores (post-pre smoking score); negative values indicate a decrease from pre- to post-smoking. MNWS refers to the Minnesota Nicotine Withdrawal Scale. QSU F1 and QSU F2 refer to the Questionnaire on Smoking Urges Factor 1 and 2, respectively. PANAS refers to the Positive and Negative Affect Scale. CO boost is presented in parts per million (ppm) from pre- to post-smoking, positive values represent an increase in CO. Statistical significance is denoted by bold text.

¹ Baseline Dependence was mean-centered across participants.

² Sex was entered with males as the referent category.

³ Dose was entered in to the model as nicotine yield per cigarette dose level.

** p < .01.

xlx. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days.

Donny *et al.*, (2007) [pg299] evaluated Quest cigarettes in thirty adult regular smokers. After assessing preferred brand smoking characteristics, participants were assigned randomly to one

of three groups corresponding to subsequent smoking conditions: nicotine-containing cigarettes (Quest 1), de-nicotinized Quest 3 cigarettes or no smoking. The subjects were allowed to smoke ad libitum and also observations were made under confined smoking conditions. Measures of smoking reinforcement, subjective effects, physiological effects, withdrawal/craving and puff topography were taken repeatedly during both periods of free access and controlled assessments during abstinence.

Daily Quest 3 (Denic) cigarette consumption declined over the 11 days. There were no effects on smoking topography. There was no CO boost (Figure VIII.D-71). Heart rate was increased in the Quest 1 group more so than the Quest 3 group. Subjective ratings of smoking were largely negative for Quest 3 throughout the study. The subjects found the Quest 3 cigarette to be unpleasant and not enjoyable after the first cigarette (Figure VIII.D-72). There was no difference between Quest 1 and Quest 3 for acute craving suppression (QSU Factor 1) (Figure VIII.D-73).

Conclusions: VLNC reduced cigarette consumption. There was no compensation. Quest 3 suppressed craving and withdrawal in the same manner as Quest 1.

Figure VIII.D-71. CPD (From Donny *et al.* 2007 [pg299])

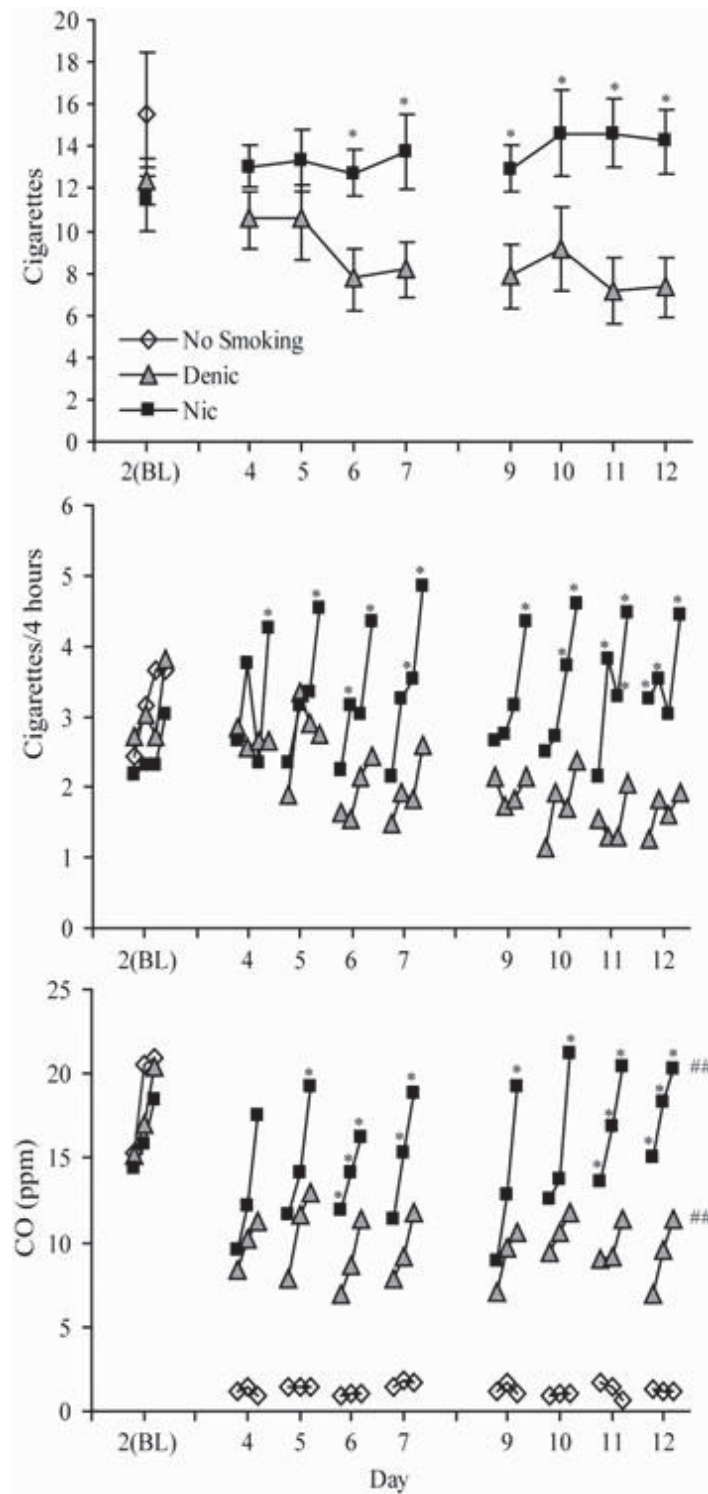


Figure VIII.D-72. Subjectives (From Donny *et al.* 2007 [pg299])

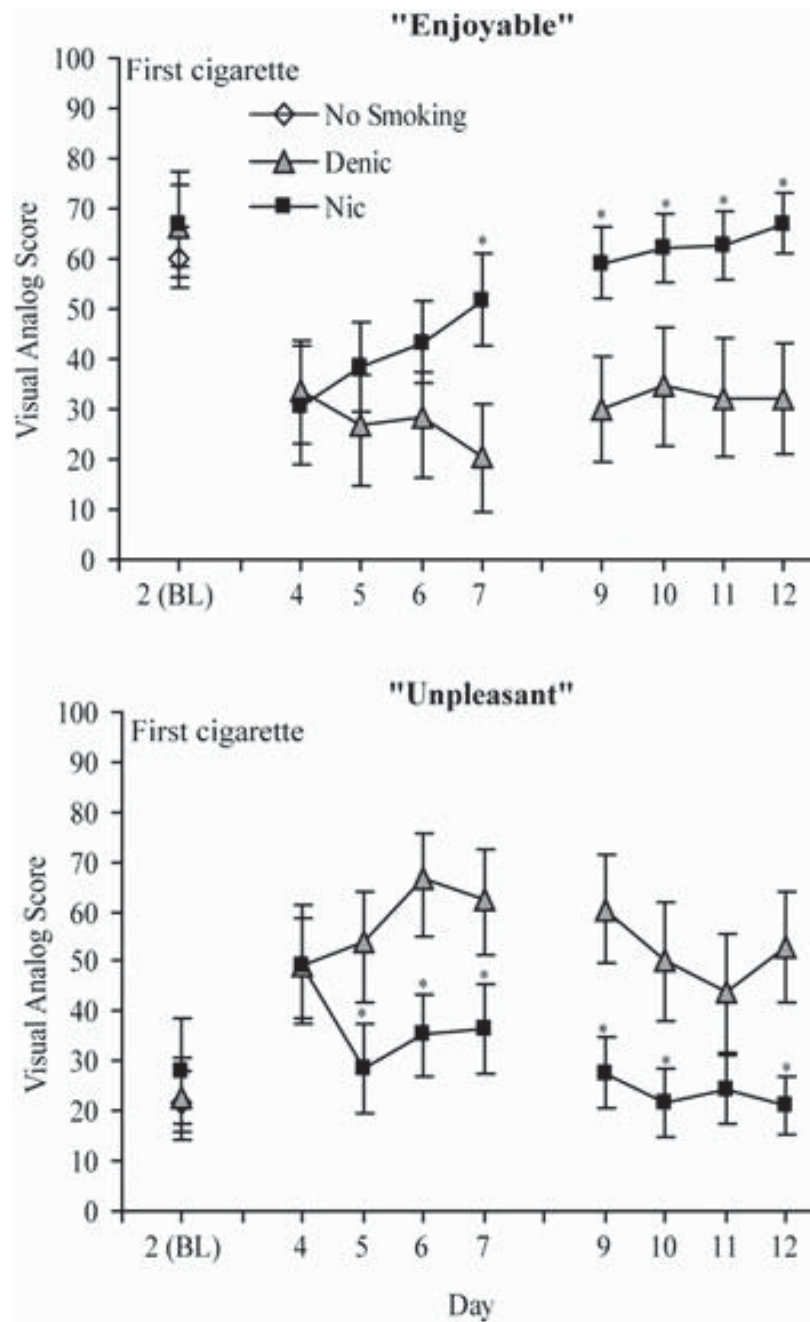
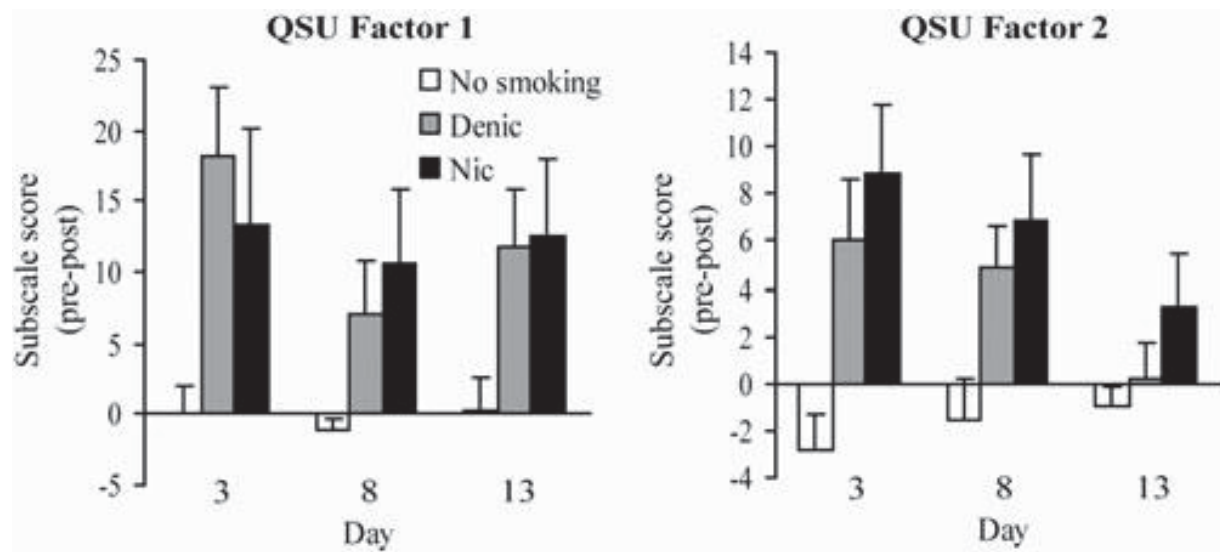


Figure VIII.D-73. Smoking urges (From Donny *et al.* 2007 [pg299])



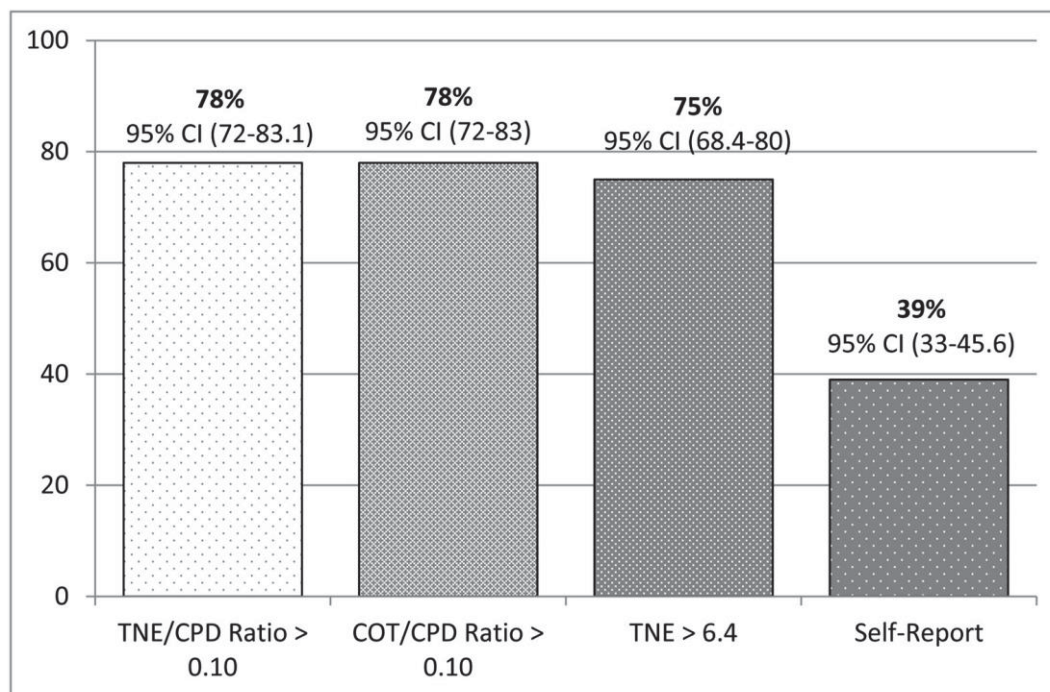
1. Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes.

This is a secondary analysis of the multi-site study conducted by Donny *et al.*, (2015) [pg299]. Nardone *et al.*, (2016) [pg302] were interested in non-compliance in their study. They measured smoking as determined by urine cotinine (COT) and total nicotine equivalents (TNE) and compared the results with self-reported consumption. Data from 242 subjects was used in the analysis. The primary outcome was biochemically verified non-compliance as indicated by COT/CPD and TNE/CPD ratios considering changes in nicotine levels in the VLNC cigarettes as well as the week-6 TNE.

The COT/CPD and TNE/CPD ratios indicated 78% of the subjects had some level of non-compliance. There was high concordance between the two ratios (98%). Absolute TNE values were also highly correlated with non-compliance. Non-compliance was self-reported by 39% of the subjects at week 6 (Figure VIII.D-74).

Conclusions: Biochemical assessment can detect non-compliance. Even though there was significant non-compliance in the studies, nicotine intake was reduced by an average 60%.

Figure VIII.D-74. Compliance (From Nardone *et al.* 2016 [pg302]).



li. Preliminary test of cigarette nicotine discrimination threshold in non-dependent versus dependent smokers.

Perkins *et al.*, (2017) [pg302] used Spectrum research cigarettes to compare non-dependent with dependent smokers on the lowest content of nicotine they could discriminate (i.e., “threshold”). Dependent (n=21) or non-dependent (n=7) smokers were tested on ability to discriminate between cigarettes with nicotine contents of 17, 11, 5, 2, and 1 mg/g, one per session, from an “ultra-low” cigarette with 0.4 mg/g (all had 9–10 mg “tar”). All abstained from smoking overnight prior to sessions, and number of sessions was determined by the lowest nicotine content they could reliably discriminate from the ultra-low on >80% of trials (i.e., ≥5 of

6). Subjective perceptions and cigarette choice behavior were also assessed and related to discrimination behavior.

Dependent smokers took larger puffs than non-dependent smokers. Discrimination thresholds did not differ between dependent and non-dependent smokers with a median nicotine content threshold of 11 mg for both groups. “Liking” (Figure VIII.D-75) and puff choice for threshold cigarettes (Figure VIII.D-76) were greater in dependent but not non-dependent smokers.

Conclusion: Threshold for detection of nicotine level may not vary by dependence level.

Figure VIII.D-75. Liking (From Perkins *et al.*, 2017 [[pg302](#)])

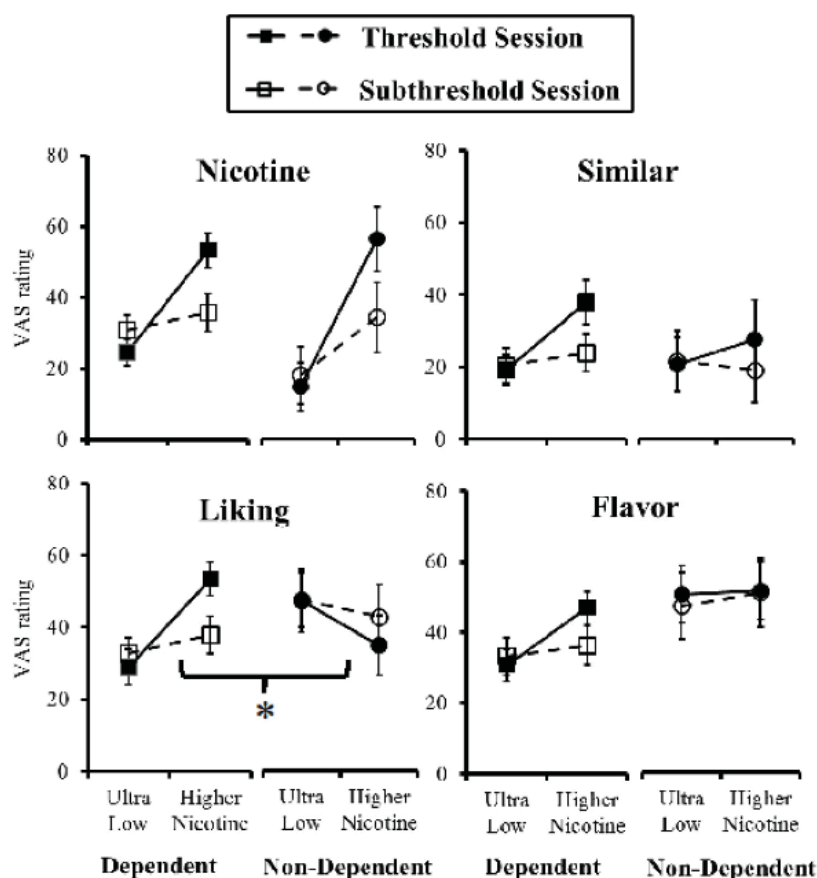
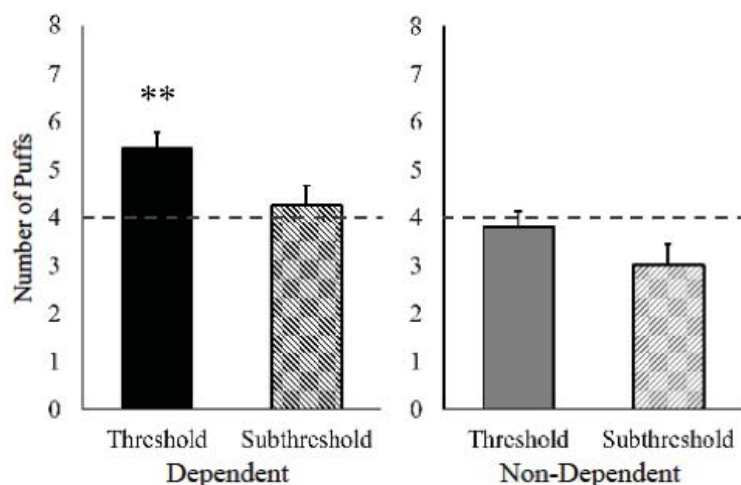


Figure VIII.D-76. Topography (From Perkins *et al.*, 2017 [pg302])



lii. Effects of low nicotine content cigarettes on smoke intake.

Rose and Behm (2004) [pg303] compared the effects of smoking Quest 3 to an ultra-light cigarette (Now). Sixteen subjects smoked either Now or Quest for 8-hours ad libitum after overnight abstinence. Plasma samples were collected every hour for nicotine and cotinine analysis. Expired CO was also measured hourly, as was heart rate and blood pressure. Smoking topography was measured 15 minutes before the end of the session. Subjective measures were also collected. Smokers smoked more Now cigarettes than Quest (11.9 vs. 10.4). The smokers of Now (highly ventilated) compensated as indicated by the compensation index. Quest (low nicotine content) smokers did not compensate when compared to own brand. Puff volume was also increased (Figure VIII.D-77). Plasma nicotine levels were significantly higher in the Now cigarette group (Figure VIII.D-78). The highly ventilated cigarettes were liked more and were more satisfying. There was no difference in craving (Figure VIII.D-79). There was no statistically significant effect on heart rate or blood pressure.

Conclusions: There was no compensation with Quest. Nicotine intake was reduced.

Figure VIII.D-77. CO and topography (From Rose and Behm, 2004 [pg303])

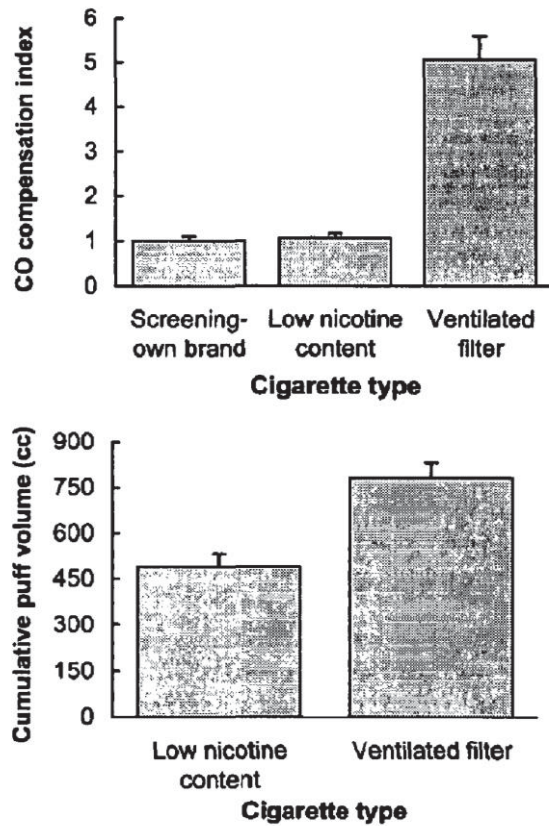


Figure VIII.D-78. Plasma nicotine (From Rose and Behm, 2004 [pg303])

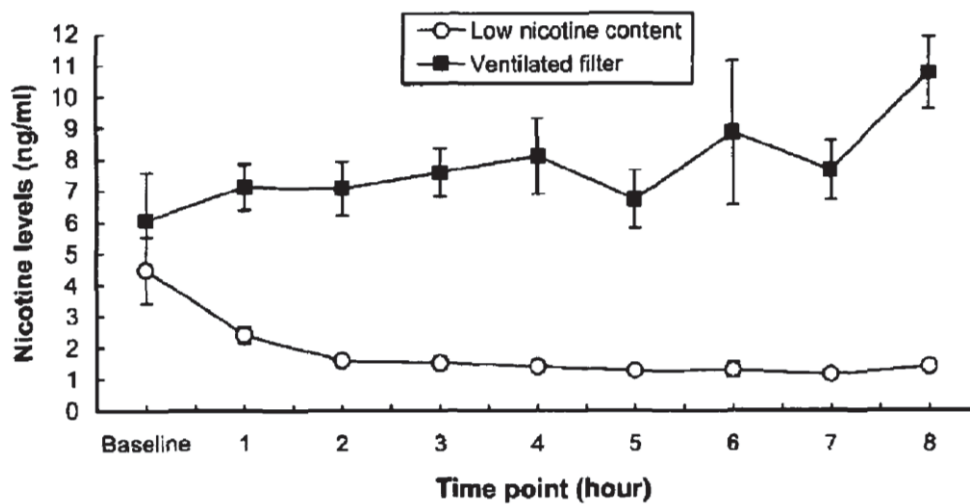
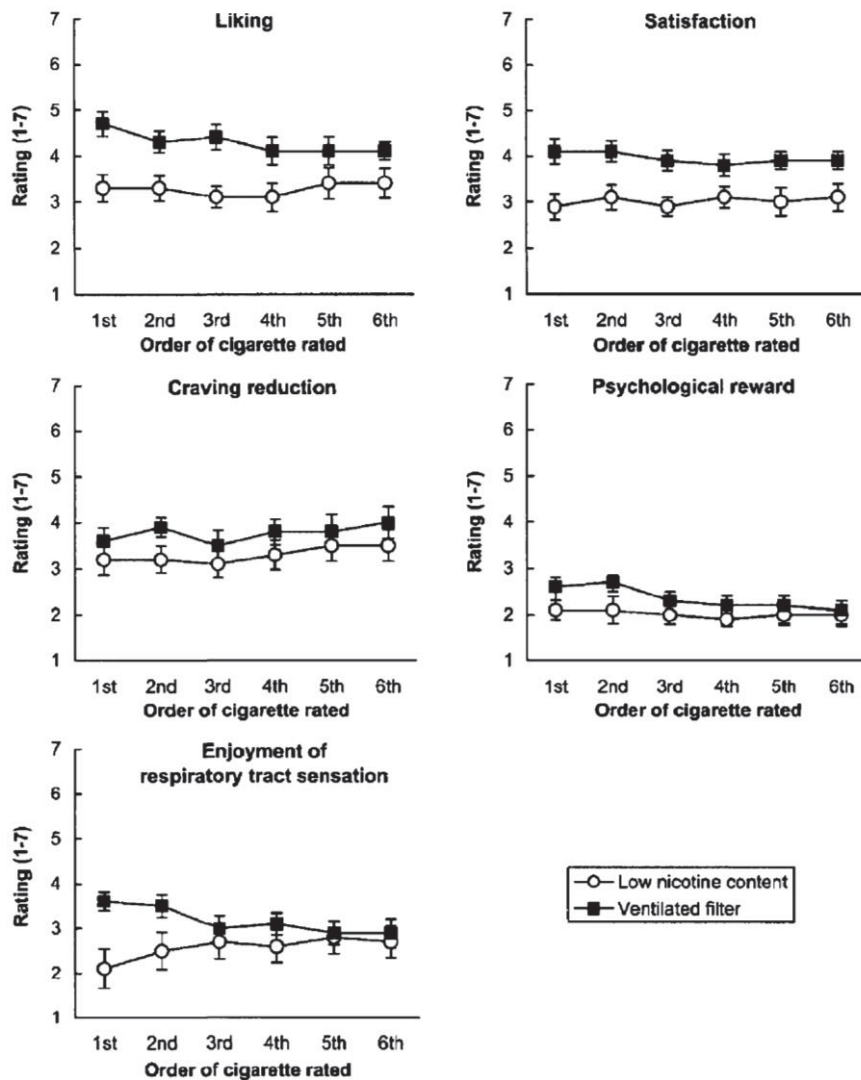


Figure VIII.D-79. Craving (From Rose and Behm, 2004 [pg303])



liii. Age moderates smokers' subjective response to very-low nicotine content cigarettes: Evidence from a randomized controlled trial.

This is a secondary analysis of the Donny *et al.*, multi-site study. Cassidy *et al.*, (2018, Nicotine & Tobacco Research) [pg298] investigated if age affected smoking behavior and subjective measures. The age categories were 18-24 and equal to or greater than 25. The results of cigarettes containing 0.4 to 2.4 mg nicotine were combined. Other groups were usual brand, 15.8 mg nicotine and 5.2 mg nicotine. Only the low nicotine group will be discussed. The low

nicotine group was less rewarding, and less satisfying in the young vs. old group (Figure VIII.D-80).

There was no age effect on total cigarettes per day, puff volume, or total nicotine equivalents after 6-weeks (Table VIII.D-55).

Conclusion: There were reduced positive affects in young smokers.

Figure VIII.D-80. Satisfaction (From Cassidy *et al.* 2018, Nicotine & Tobacco Research [pg298])

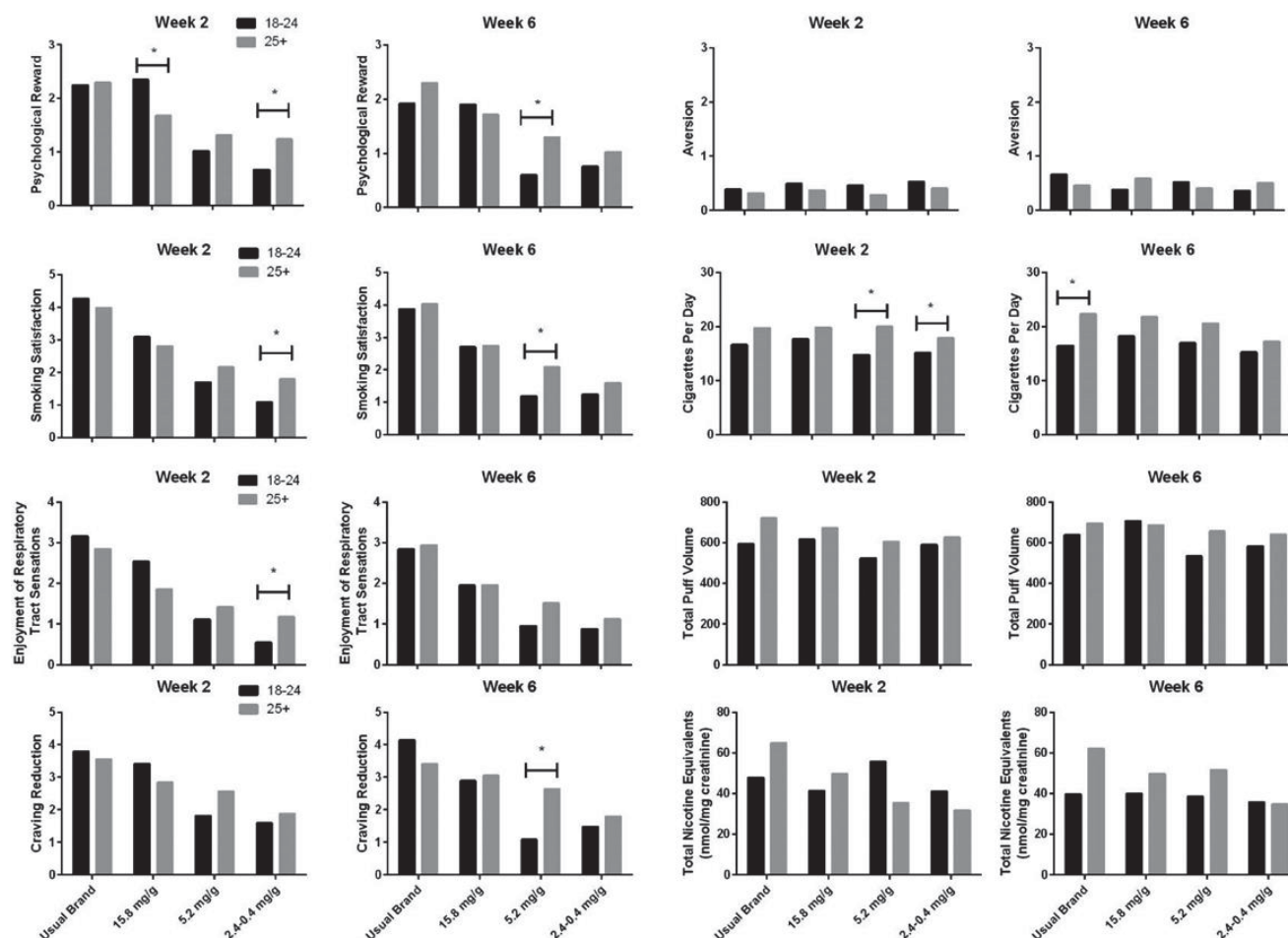


Table VIII.D-55. CPD ((From Cassidy *et al.* 2018, Nicotine & Tobacco Research [pg298])

| Outcome | Interaction test <i>p</i> value | Usual brand | | 15.8 mg/g | | 5.2 mg/g | | 2.4–0.4 mg/g | |
|--------------------------------|------------------------------------|-----------------|----------------|-----------------|----------------|-----------------|----------------|-----------------|----------------|
| | | Mean difference | <i>p</i> value | Mean difference | <i>p</i> value | Mean difference | <i>p</i> value | Mean difference | <i>p</i> value |
| Total CPD ^a | 0.54 | –5.94 (2.50) | 0.02 | –3.62 (2.52) | 0.09 | –3.65 (2.47) | 0.14 | –2.01 (1.31) | 0.13 |
| Total puff volume ^a | 0.64 | –57 (74) | 0.44 | 20.79 (68) | 0.76 | –123 (99) | 0.22 | –59 (44) | 0.17 |
| Log TNEs ^a | 0.53 | 0.31 (0.32) | 0.33 | –0.16 (0.29) | 0.58 | 0.10 (0.34) | 0.77 | 0.31 (0.17) | 0.08 |

liv. Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine cigarettes in young smokers.

Faulkner *et al.*, (2018) [pg299] were interested if sex differences in response to using very low nicotine cigarettes existed in young smokers. Overnight abstinent young smokers (23 men, 23 women, mean age 22.18) provided self-reports of craving, withdrawal, and affect before and after smoking SPECTRUM cigarettes with yields of 0.027, 0.110, 0.231, or 0.763 mg nicotine, and evaluated characteristics of each cigarette.

Men, but not women reported greater craving reduction, perceived nicotine content, and cigarette liking with increasing nicotine dose (Figure VIII.D-81). Women reported greater psychological withdrawal, greater sedation, and a trend toward greater craving than men during abstinence. Women also reported greater reductions in psychological withdrawal and sedation than men due to smoking, with no effect of nicotine dose. Men reported greater reductions in craving after smoking cigarettes delivering ≥ 0.231 mg nicotine than after smoking cigarettes delivering ≤ 0.231 mg nicotine. Cigarette liking, cigarette disliking, and perceived nicotine content in women and men is shown in Figure VIII.D-82. *Liking* (From Faulkner *et al.* 2018 [pg299]).. Women reported no effect of nicotine dose on all three cigarette ratings, whereas men reported greater liking, less disliking, and greater perceived nicotine content as the nicotine content of the cigarette increased.

Conclusion: There appears to be a sex difference in response to very low nicotine cigarettes.

Figure VIII.D-81. Craving (From Faulkner *et al.* 2018 [pg299]).

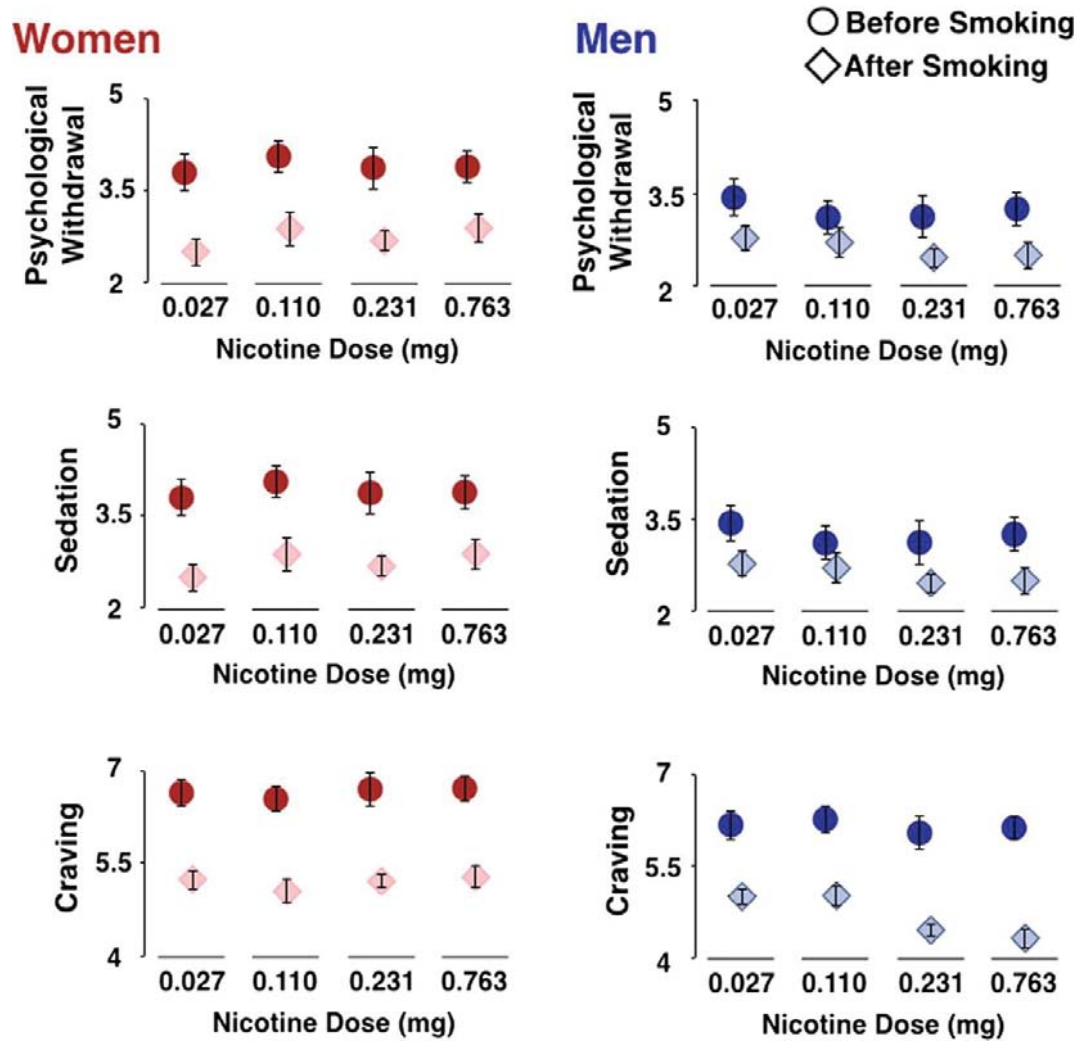
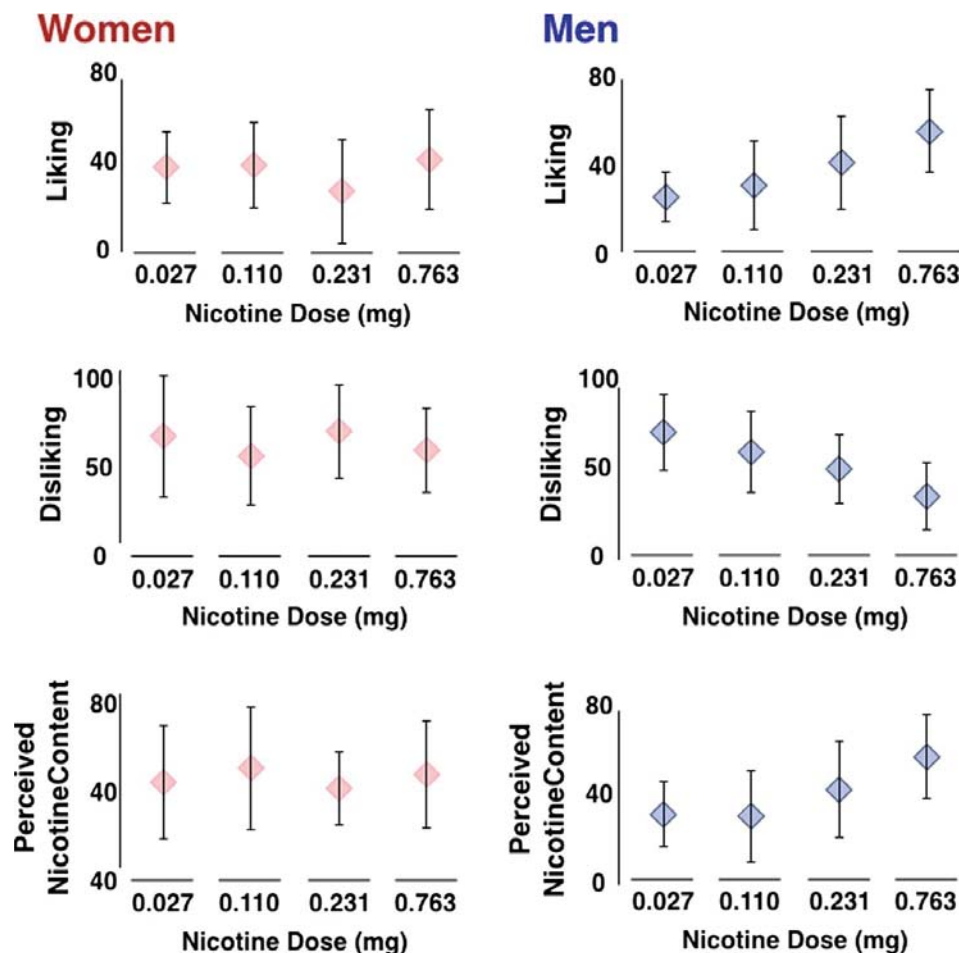


Figure VIII.D-82. Liking (From Faulkner *et al.* 2018 [pg299]).



iv. Response to reduced nicotine content cigarette among smokers differing in tobacco dependence severity.

Higgins *et al.*, (2018) [pg301] investigated how the level of dependence affects the acute effects of smoking SPECTRUM® cigarettes. Participants (N=169) were daily smokers with mild, moderate, or high tobacco-dependence severity using the Heaviness of Smoking Index (HSI). Following brief abstinence, participants smoked research cigarettes varying in nicotine content (0.4, 2.4, 5.2, 15.8 mg nicotine/g tobacco) in a within-subject design. Participants completed fourteen 2–4 h sessions in a within-subjects design. Participants abstained from smoking for 6–8 h prior to sessions. Sessions were organized into three phases. In Phase 1 (Sessions 1–5), participants sampled the research cigarettes under double-blind conditions with cigarettes

identified by arbitrary letter codes. Participants were oriented to the research protocol in Session 1 using their usual-brand cigarette. In Sessions 2–5 participants smoked one research cigarette per session ad libitum using a topography device. After smoking the assigned cigarette each session, participants completed the Cigarette Purchase Task (CPT), a behavioral economic simulation task that has participants estimate the number of cigarettes they would anticipate smoking in a 24-hour period across a wide range of cigarette prices; those estimates are used to model (1) participant cigarette smoking rate when unconstrained by cost (Intensity), (2) maximal amount of money one is willing to spend on daily smoking (Omax), (3) the price at which smoking rate begins decreasing proportionate to increasing price (Pmax), (4) the price at which one would quit smoking rather than incur the cost (Breakpoint), and (5) overall sensitivity of demand to price (Alpha). Participants also completed the modified Cigarette Evaluation Questionnaire (mCEQ) once prior to and immediately after smoking, and the Minnesota Tobacco Withdrawal Scale (MTWS) and Questionnaire of Smoking Urges-brief scale (QSU-brief) administered prior to and every 15 min for 60 min after smoking. Phase 2 (Sessions 6–11) directly tested the relative reinforcing effects of the different dose cigarettes by allowing participants to choose which cigarette they preferred to smoke in two-choice concurrent test sessions. Each of the six possible cigarette dose-pair combinations was tested once in separate sessions. In these 3-hour sessions, a participant sat alone in a comfortable, ventilated room. When they wished to smoke, they used a computer mouse to click on one of two icons on a screen representing the two cigarettes available that session. After ten clicks on the icon they could take two puffs of the associated cigarette. Participants were free to choose either option as often as they wished or abstain. Lastly, Phase 3 (Sessions 12–14) used the same arrangement as Phase 2 but compared only the

0.4 and 15.8 g/mg doses. This phase assessed whether preference could be reliably shifted away from the high dose. Puffs from the low dose remained available by clicking that option 10 times while the number of clicks necessary to earn puffs from the highest dose started at 10 and increased each time it was chosen to 160, 320, 640, 1280, 2400, 3600, 4800, 6000, 7200, and 8400 clicks.

Dependence severity did not affect smoking topography (Table VIII.D-56). The effects of nicotine dose were in the direction of larger, more intense, and greater number of puffs as a function of increasing nicotine dose, opposite of what is expected with compensatory smoking. There were no main effects of dependence severity or interactions with nicotine dose in relative reinforcing effects in concurrent choice testing or subjective effects on the modified Cigarette Evaluation Questionnaire (Table VIII.D-57). Demand for smoking in the Cigarette Purchase Task was greater among more dependent smokers but reducing nicotine content decreased demand independent of dependence severity (Figure VIII.D-83). Dependence severity did not significantly alter response to reduced nicotine content cigarettes on the Minnesota Tobacco Withdrawal Scale nor Questionnaire of Smoking Urges-brief (QSU) Factor-2 scale; dependence severity and dose interacted significantly on the QSU-brief Factor-1 scale, with reductions dependent on dose among highly, but not mildly or moderately, dependent smokers

Conclusion: Dependence severity has no effect on the effects of reduced nicotine content cigarettes to lower the addiction potential of smoking, and minimal effects on relief from craving/withdrawal or smoking topography.

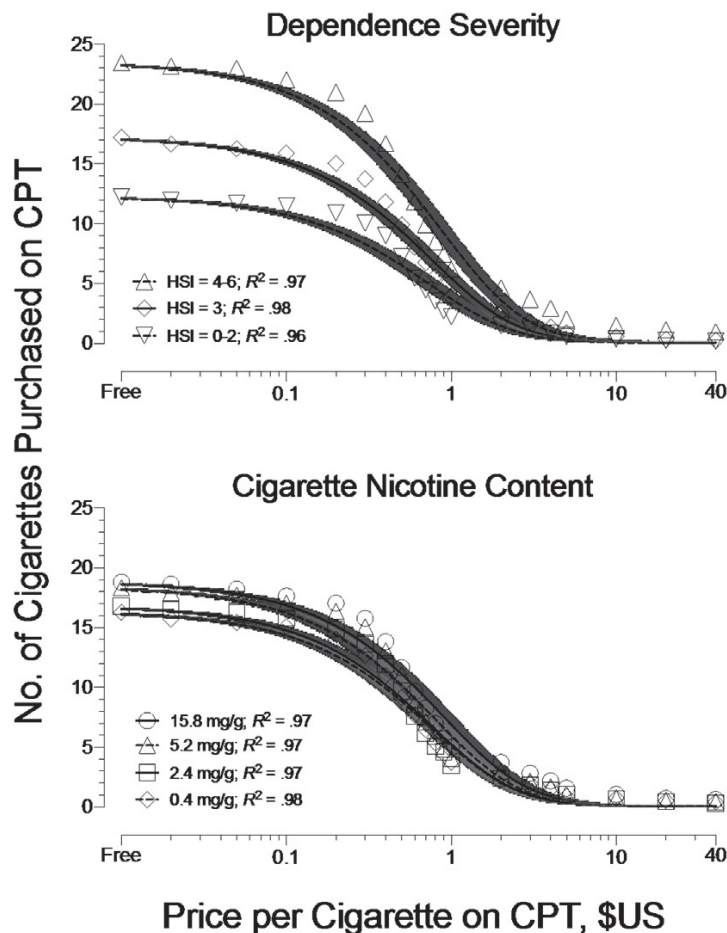
Table VIII.D-56. Topography (From Higgins *et al.* 2018 [pg301])

| | Total puff volume | Mean puff volume | Mean puff duration | Mean inter-puff interval | Mean maximum flow rate | Puff number |
|-------------------------------------|---------------------------------|------------------|--------------------|--------------------------|--------------------------------|-------------------------------|
| Dependence severity, mean \pm SEM | | | | | | |
| HSI mild | 653.85 \pm 65.43 | 53.24 \pm 3.08 | 1.58 \pm 0.09 | 23.44 \pm 1.77 | 38.62 \pm 6.55 | 12.33 \pm 0.90 |
| HSI moderate | 593.99 \pm 67.38 | 49.75 \pm 3.26 | 1.56 \pm 0.10 | 23.33 \pm 1.84 | 37.78 \pm 6.57 | 12.06 \pm 0.94 |
| HSI high | 649.24 \pm 68.72 | 52.59 \pm 3.29 | 1.53 \pm 0.10 | 23.45 \pm 1.90 | 42.38 \pm 6.56 | 12.20 \pm 0.96 |
| Nicotine dose, mean \pm SEM | | | | | | |
| 0.4 mg/g | 591.79 \pm 61.33 ^a | 50.33 \pm 2.75 | 1.56 \pm 0.09 | 23.21 \pm 1.63 | 37.86 \pm 6.44 ^a | 11.51 \pm 0.82 ^a |
| 2.4 mg/g | 613.03 \pm 61.40 ^a | 51.60 \pm 2.76 | 1.54 \pm 0.09 | 22.99 \pm 1.63 | 39.29 \pm 6.44 ^{ab} | 11.87 \pm 0.82 ^a |
| 5.2 mg/g | 616.33 \pm 61.41 ^a | 52.89 \pm 2.76 | 1.58 \pm 0.09 | 23.49 \pm 1.63 | 40.35 \pm 6.44 ^{ab} | 11.79 \pm 0.82 ^a |
| 15.8 mg/g | 708.29 \pm 61.43 ^b | 52.62 \pm 2.76 | 1.54 \pm 0.09 | 23.94 \pm 1.63 | 40.89 \pm 6.44 ^b | 13.62 \pm 0.82 ^b |

Table VIII.D-57. Craving (From Higgins *et al.* 2018 [pg301])

Modified cigarette evaluation questionnaire subscale scores by dependence severity and cigarette nicotine dose.

| | Smoking satisfaction | Psychological reward | Aversion | Enjoyment of respiratory tract sensations | Craving reduction | Taste |
|-------------------------------------|------------------------------|-------------------------------|------------------------------|---|-------------------------------|------------------------------|
| Dependence severity, mean \pm SEM | | | | | | |
| HSI mild | 3.84 \pm 0.22 | 2.92 \pm 0.21 | 1.43 \pm 0.13 | 3.36 \pm 0.23 | 4.03 \pm 0.25 | 3.35 \pm 0.21 |
| HSI moderate | 3.70 \pm 0.23 | 3.12 \pm 0.22 | 1.54 \pm 0.14 | 3.19 \pm 0.25 | 4.12 \pm 0.27 | 3.30 \pm 0.22 |
| HSI high | 3.87 \pm 0.23 | 3.02 \pm 0.22 | 1.52 \pm 0.14 | 3.37 \pm 0.25 | 4.33 \pm 0.27 | 3.25 \pm 0.23 |
| Nicotine dose, mean \pm SEM | | | | | | |
| 0.4 mg/g | 3.16 \pm 0.19 ^a | 2.69 \pm 0.18 ^a | 1.41 \pm 0.11 ^a | 2.77 \pm 0.21 ^a | 3.65 \pm 0.23 ^a | 2.67 \pm 0.19 ^a |
| 2.4 mg/g | 3.59 \pm 0.19 ^b | 2.85 \pm 0.18 ^{ab} | 1.45 \pm 0.11 ^a | 3.02 \pm 0.21 ^a | 3.95 \pm 0.23 ^{ab} | 3.07 \pm 0.19 ^b |
| 5.2 mg/g | 3.84 \pm 0.19 ^b | 3.08 \pm 0.18 ^b | 1.45 \pm 0.11 ^a | 3.42 \pm 0.21 ^b | 4.24 \pm 0.23 ^b | 3.31 \pm 0.19 ^b |
| 15.8 mg/g | 4.61 \pm 0.19 ^c | 3.46 \pm 0.18 ^c | 1.69 \pm 0.11 ^b | 4.00 \pm 0.21 ^c | 4.82 \pm 0.23 ^c | 4.16 \pm 0.19 ^c |

Figure VIII.D-83. Cigarette purchase task (From Higgins *et al.* 2018 [pg301]).

lvi. Cigarette nicotine content as a moderator of the relationship between negative affect and smoking (NCT01681875).

Robinson *et al.*, (2017) [pg303] investigated the effects of SPECTRUM® cigarettes and nicotine content on Negative Affect (NA) and smoking in this secondary analysis of the Donny *et al.*, (2015) [pg299] multi-site study. Seven hundred and seventeen participants, 237 in the normal nicotine content (NNC; 15.8 mg/g and usual brand) cigarette group and 480 in the very low nicotine content (VLNC; 2.4 mg/g nicotine or less) cigarette group, participated in a randomized trial that examined the effects of cigarette nicotine content on smoking behavior over 6 weeks. Usual brand was smoked for 2 weeks prior to the test cigarettes. Positive and negative affect were measured with the PANAS scale. Nicotine exposure was assessed by urinary cotinine and total nicotine equivalents. Latent growth curve modeling was used to estimate the relationship between changes in NA and changes in the numbers of cigarettes smoked per day, from baseline to 6 weeks, as a function of cigarette nicotine content. The results of smokers using VLNC cigarettes with less than 2.4 mg nicotine were combined.

VLNC cigarette consumption was reduced (Table VIII.D-58). The relationship between NA and CPD reduced over time for the VLNC group but not for the NNC group. There was no significant relationship between Positive Affect and CPD over time for either cigarette group.

Conclusion. Results suggest that VLNC cigarettes can disrupt the relationship between smoking and NA.

Table VIII.D-58. CPD (From Robinson *et al.* 2017 [pg303]).

| | Baseline | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|----------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| NNC | | | | | | | |
| CPD | | 18.7 (10.41) | 19.5 (10.41) | 20.1 (11.52) | 20.9 (11.93) | 20.6 (11.80) | 21.4 (12.68) |
| NA | 15.4 (5.75) | | | 15.1 (5.60) | | | 15.7 (5.85) |
| Cotinine | 15.8 (11.13) | | | 15.1 (11.33) | | | 14.7 (11.73) |
| VLNC | | | | | | | |
| CPD | | 15.1 (10.02) | 14.7 (10.04) | 14.5 (10.01) | 14.1 (9.81) | 14.2 (9.71) | 14.2 (10.21) |
| NA | 16.1 (5.62) | | | 15.9 (5.81) | | | 15.9 (6.33) |
| Cotinine | 15.6 (11.57) | | | 8.9 (9.29) | | | 9.6 (9.13) |

CPD = investigational cigarettes per day; NA = PANAS Negative Affect scale; NNC = normal nicotine content cigarette group; VLNC = very low nicotine content cigarette group. Cotinine = Total cotinine expressed as geometric mean adjusted for creatinine (nmols/mg creatinine).

lvii. Effects of acute abstinence and nicotine administration on taste perception in cigarette smokers.

Mullings (Mullings *et al.* 2010 [pg302]) investigated the effect of abstinence and nicotine levels on taste. Forty-eight male and female daily smokers attended a single testing session. Prior to testing, participants were randomized to either abstain from smoking for 12 hours or smoke as usual on the morning of testing. At the testing session, participants completed subjective ratings of mood and ratings of intensity and pleasantness of supra-threshold salt and sucrose solutions, followed by measurement of the threshold at which these solutions could be detected. Participants were then randomized to smoke either a nicotine-containing Quest 1 or denicotinized Quest 3 cigarette, after which they completed the same measures as previously.

Following cigarette smoking, lower taste thresholds are obtained after smoking a denicotinized cigarette compared with a nicotinized cigarette, but among females only (Table VIII.D-59). This effect was not observed among males and did not differ as a function of abstinence condition. In addition, among non-abstinent smokers, females demonstrated higher taste thresholds (i.e. reduced sensitivity) for salt than males, but this sex difference was not observed among abstinent smokers.

Conclusion: Use of a VLNC cigarette may affect taste thresholds, but only in women.

Table VIII.D-59. Taste thresholds (From Mullings *et al.* 2010 [pg302]).

| | | | Intensity | | | | Pleasantness | | | |
|--------|---------------|---------------|-----------|----------------|----------|----------------|--------------|----------------|----------|----------------|
| | | | Salt | | Sucrose | | Salt | | Sucrose | |
| | | | Baseline | Post-cigarette | Baseline | Post-cigarette | Baseline | Post-cigarette | Baseline | Post-cigarette |
| Male | Abstinent | Nicotinised | 44 (28) | 58 (29) | 36 (44) | 48 (20) | -14 (11) | 8 (17) | -24 (18) | 0 (27) |
| | | Denicotinised | 50 (25) | 59 (22) | 39 (18) | 51 (29) | -9 (24) | -1 (17) | -8 (30) | -2 (25) |
| | Non-abstinent | Nicotinised | 39 (18) | 58 (11) | 31 (15) | 37 (17) | -4 (5) | 10 (12) | -15 (13) | 18 (15) |
| | | Denicotinised | 43 (22) | 73 (18) | 34 (22) | 33 (18) | 0 (19) | 8 (10) | -1 (34) | 5 (11) |
| Female | Abstinent | Nicotinised | 48 (29) | 72 (19) | 43 (18) | 42 (21) | -22 (16) | 18 (15) | -25 (8) | 16 (16) |
| | | Denicotinised | 46 (30) | 43 (18) | 49 (42) | 59 (35) | -21 (18) | -4 (31) | -21 (14) | -3 (33) |
| | Non-abstinent | Nicotinised | 47 (30) | 71 (13) | 45 (15) | 60 (29) | -13 (21) | 16 (17) | -16 (19) | 10 (14) |
| | | Denicotinised | 40 (25) | 61 (25) | 43 (28) | 48 (30) | -14 (17) | 14 (20) | -14 (18) | 14 (19) |

lviii. Threshold dose for discrimination of nicotine via cigarette smoking.

Perkins *et al.*, (2016) [pg302] investigated the ability of smokers to detect different levels of nicotine in SPECTRUM® cigarettes. Eighteen dependent smokers were tested on their ability to discriminate cigarettes with nicotine contents of 11, 5, 2.4, and 1.3 mg/g, one per session, from the “ultra-low” cigarette with 0.4 mg/g, after having learned to discriminate 16 mg/g from 0.4 mg/. Exposure to each cigarette was limited to 4 puffs/trial. All subjects were abstinent from smoking overnight prior to each session, and the number of sessions was determined by the participant’s success in discrimination behavior on >80% of trials. Subjective perceptions and behavioral choice between cigarettes were also assessed and related to discrimination behavior.

The median threshold for discrimination was 11 mg/g (range 2.4- 16). None of the subjects could discriminate between 0.4 mg and 1.3 mg nicotine.

Conclusion: Subjects can tell the difference between normal cigarettes and 0.4 mg nicotine cigarettes but cannot tell the difference between 0.4 and 1.3 mg nicotine.

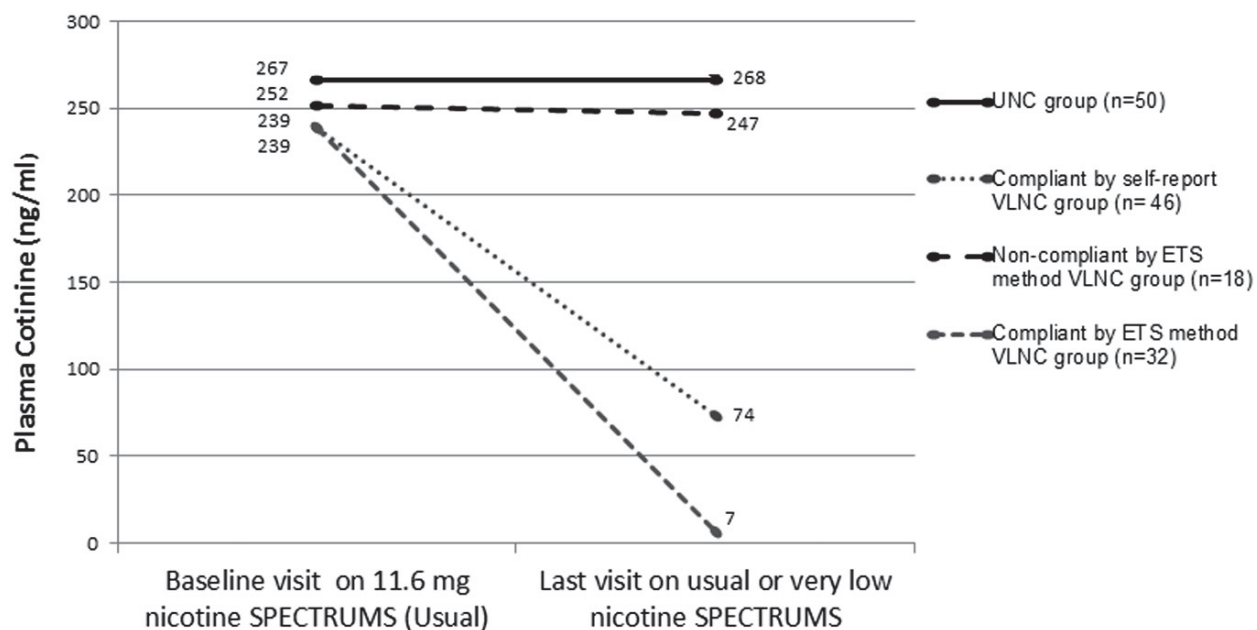
lix. Estimation of compliance with exclusive smoking of very low nicotine content cigarettes using plasma cotinine.

Methods have been developed to use nicotine biomarkers to estimate compliance with use of very low nicotine content cigarettes (VLNCs). Foulds *et al.*, (2018) [pg299] were interested in the impact of nicotine absorption from environmental tobacco smoke (ETS) among research participants on measures of compliance. This study used data from 100 randomly selected study completers in ongoing clinical trials of VLNCs (50 randomized to Usual Nicotine Content Cigarettes (UNCs) and 50 to SPECTRUM®) to assess the use of plasma cotinine to estimate compliance. Plasma cotinine and smoking behavior were recorded at baseline after 2 weeks smoking UNC cigarettes, and then after 18 weeks of either continuing smoking UNCs or reducing the nicotine content such that the last 6 weeks comprised smoking VLNC SPRECTRUM®.

Plasma cotinine remained stable in the UNC group but reduced in the VLNC group (Figure VIII.D-84). Compliance with smoking VLNCs was first estimated by comparing the cotinine per cigarette on VLNCs with UNCs after allowing for potential compensatory smoking. The authors found that 29 (58%) of the VLNC group were compliant. Adjusting for potential ETS exposure they estimated 32 (64%) to be compliant.

Conclusion: ETS can slightly impact apparent compliance calculations.

Figure VIII.D-84. BOE (From Foulds *et al.* 2018 [pg299]).



ix. Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction.

Higgins *et al.*, (2017, JAMA Psychiatry) [pg300] conducted a multisite, double-blind, within-participant assessment of acute response to SPECTRUM® cigarettes with nicotine content ranging from levels below a hypothesized addiction threshold (0.7 mg nicotine) to those representative of commercial cigarettes (0.4, 2.3, 5.2, and 15.8 mg/g of tobacco) at 3 academic sites including 169 daily smokers from 3 vulnerable populations: individuals with affective disorders (n = 56) or opioid dependence (n = 60) and socioeconomically disadvantaged women (n = 53). It was hypothesized that vulnerable populations are more addicted and would be less likely to quit. After a brief smoking abstinence, participants smoked cigarettes with varying nicotine doses across fourteen 2- to 4-hour outpatient sessions. Addiction potential of the

cigarettes was assessed using concurrent choice testing, the Cigarette Purchase Task (CPT), and measures of subjective effects.

Among the 169 daily smokers included in the analysis (120 women and 49 men), reducing the nicotine content of cigarettes decreased the relative reinforcing effects of smoking in all 3 populations. In concurrent choice testing with the cigarettes available at an equal response effort, participants chose those with higher compared with lower nicotine content across each of the 6 dose pairs, a finding consistent with cigarettes with reduced nicotine content having lower addiction potential. Across populations, the 0.4-mg/g dose was chosen significantly less than the 15.8-mg/g dose in concurrent choice testing and generated lower demand in the CPT (Figure VIII.D-85). Preference for higher over lower nicotine content cigarettes could be reversed by increasing the response cost necessary to obtain the higher dose (Figure VIII.D-86). All doses reduced Minnesota Nicotine Withdrawal Scale total scores, although duration of withdrawal symptoms was greater at higher doses (Table VIII.D-60). No significant changes were noted across doses in smoking topography or breath CO exposure levels indicative of compensatory smoking. The results suggest that participants may smoke the reduced nicotine content cigarettes less intensely. These effects were consistent across populations.

Conclusion: Reducing the nicotine content of cigarettes reduces the relative reinforcing effects of smoking and thus addiction potential in populations with psychiatric conditions and other vulnerabilities to tobacco withdrawal. Reductions in reinforcing effects were achieved without causing untoward withdrawal, craving, or compensatory smoking.

Figure VIII.D-85. Concurrent choice testing (From Higgins *et al.*, 2017, JAMA Psychiatry [pg300])

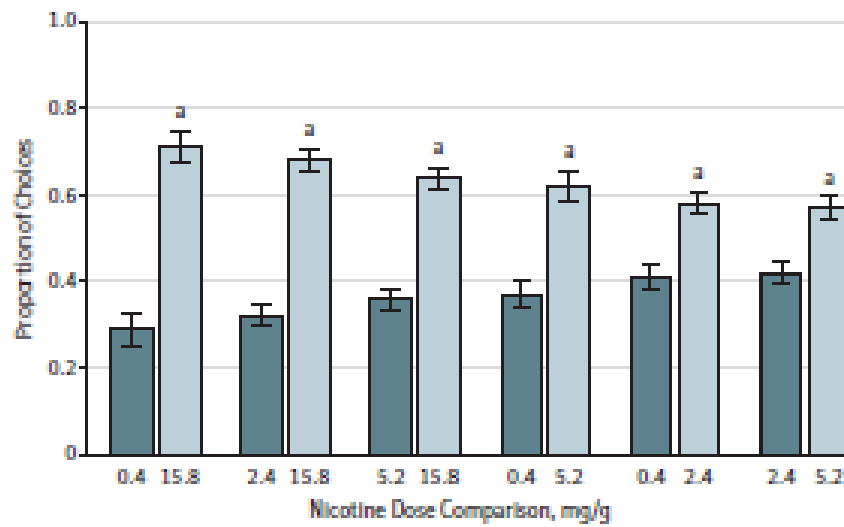


Figure VIII.D-86. Proportional choices (From Higgins *et al.*, 2017, JAMA Psychiatry [pg300])

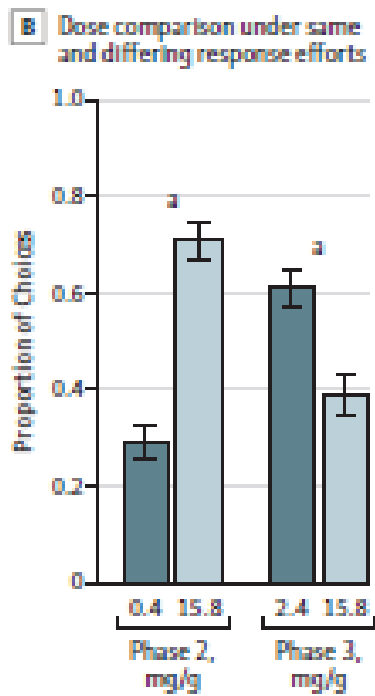


Table 3. Time Course of Effects of the Varying Dose Research Cigarettes on MINWS Desire to Smoke and Total Scores

| MINWS Score | Nicotine Level of Research Cigarettes by Score, Mean (SEM) ² | | | |
|------------------------|---|---------------------------|---------------------------|-------------------------|
| | 0.4 mg/g | 2.4 mg/g | 5.2 mg/g | 15.8 mg/g |
| Desire to smoke | | | | |
| Presmoking baseline | 3.0 (0.1)* ¹ | 3.0 (0.1)* ¹ | 3.0 (0.1)* ¹ | 3.1 (0.1)* ¹ |
| At 15 min | 2.2 (0.1)* ² | 2.1 (0.1)* ² | 1.9 (0.1)* ² | 1.5 (0.1)* ² |
| At 30 min | 2.4 (0.1)* ^{2,3} | 2.4 (0.1)* ² | 2.3 (0.1)* ² | 2.0 (0.1)* ² |
| At 45 min | 2.6 (0.1)* ² | 2.7 (0.1)* ⁴ | 2.7 (0.1)* ⁴ | 2.4 (0.1)* ⁴ |
| At 60 min | 2.9 (0.1)* ¹ | 2.9 (0.1)* ^{1,4} | 2.8 (0.1)* ^{1,4} | 2.7 (0.1)* ⁴ |
| Total | | | | |
| Presmoking baseline | 1.1 (0.1)* ¹ | 1.0 (0.0)* ¹ | 1.1 (0.1)* ¹ | 1.1 (0.1)* ¹ |
| At 15 min | 0.7 (0.1)* ² | 0.7 (0.1)* ² | 0.7 (0.1)* ² | 0.6 (0.1)* ² |
| At 30 min | 0.8 (0.1)* ² | 0.8 (0.1)* ² | 0.9 (0.1)* ² | 0.7 (0.1)* ² |
| At 45 min | 1.0 (0.1)* ¹ | 0.9 (0.1)* ¹ | 1.0 (0.1)* ⁴ | 0.8 (0.1)* ⁴ |
| At 60 min | 1.1 (0.1)* ¹ | 1.0 (0.1)* ¹ | 1.1 (0.1)* ^{1,4} | 0.9 (0.1)* ⁴ |

ixi. The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking.

This study by Juliano *et al.*, (2011) [pg301] investigated the independent and interactive effects of nicotine dose and nicotine dose expectancy on smoking outcomes using a 2 (given nicotine vs. placebo) × 2 (told nicotine vs. placebo) balanced placebo design. Smokers (N = 148) completed the Rapid Visual Information Processing Task (RVIP) and measures of smoking urge, mood, and cigarette ratings (e.g., satisfying) after smoking a nicotine (Quest 1) or placebo cigarette (Quest 3) crossed with instructions that the cigarette contained either nicotine or no nicotine. Smoking topography was measured also.

Smoking duration and number of puffs were reduced in the Quest 3 cigarettes (placebo) compared to Quest 1 cigarettes (nicotine). There was no effect on CO boost (Table VIII.D-61). There was a nicotine dose effect on urge to smoke with the placebo (Quest 3) partially suppressing the

urge. Dose expectancy altered the perception of the placebo on urge to smoke (Figure VIII.D-87). Quest 1 cigarettes (0.6 mg nicotine) produced better sustained attention performance than Quest 3 as indicated by RVIP reaction time, hits, and sensitivity (A') (Figure VIII.D-88). Quest 1 cigarettes also produced better mood and greater rewarding subjective effects of the cigarettes on 11 of 11 dimensions compared to Quest 3 (data not shown). Nicotine instructions resulted in fewer RVIP false alarms, better mood, and greater rewarding subjective effects of the cigarettes on 9 of 11 dimensions compared to placebo instructions. Nicotine dose by nicotine dose expectancy interactions were also observed for urge and tension-anxiety, such that the dose expectancy manipulation produced differential effects only among those who smoked placebo cigarettes. In contrast a significant interaction for self-reported vigor-activity demonstrated that the dose expectancy manipulation produced effects only among those who smoked nicotine cigarettes.

Conclusion: This study provides additional evidence that nicotine improves cognitive performance and provides initial evidence that denicotinized cigarettes smoked under the guise that they contain nicotine influence cognitive performance, albeit with less robust effects than nicotine.

Table VIII.D-61. Smoking exposure (From Juliano *et al*, 2011 [pg301])

Measures of Smoking Exposure

| | Condition (Given/Told) | | | | Effect | | |
|----------------------|-------------------------|------------------|------------------|-----------------|-----------------------|-----------------------------|----------------------------|
| | Nicotine/Nicotine | Nicotine/Placebo | Placebo/Nicotine | Placebo/Placebo | Main effect nicotine | Main effect dose expectancy | Nicotine X dose expectancy |
| | Mean ^a (SEM) | Mean (SEM) | Mean (SEM) | Mean (SEM) | $F \eta^2$ | $F \eta^2$ | $F \eta^2$ |
| Smoking duration (s) | 214.81 (9.69) | 217.93 (9.32) | 182.44 (9.83) | 179.09 (10.11) | $F=13.36^{***}, 0.09$ | <i>ns</i> | <i>ns</i> |
| Number of puffs | 13.76 (0.56) | 11.24 (0.54) | 9.94 (0.57) | 11.56 (0.58) | $F=9.90^{**}, 0.07$ | <i>ns</i> | $F=13.34^{**}, 0.09$ |
| CO boost | 3.43 (0.40) | 3.22 (0.40) | 3.41 (0.42) | 4.08 (0.42) | <i>ns</i> | <i>ns</i> | <i>ns</i> |
| Cigarette weight (g) | 0.48 (0.01) | 0.48 (0.01) | 0.50 (0.01) | 0.49 (0.01) | <i>ns</i> | <i>ns</i> | <i>ns</i> |

Note: CO = Carbon Monoxide.

[†] $p < .08$.

^{*} $p < .05$.

^{**} $p < .01$.

^{***} $p < .001$.

Figure VIII.D-87. Smoking urge (From Juliano *et al*, 2011 [pg301])

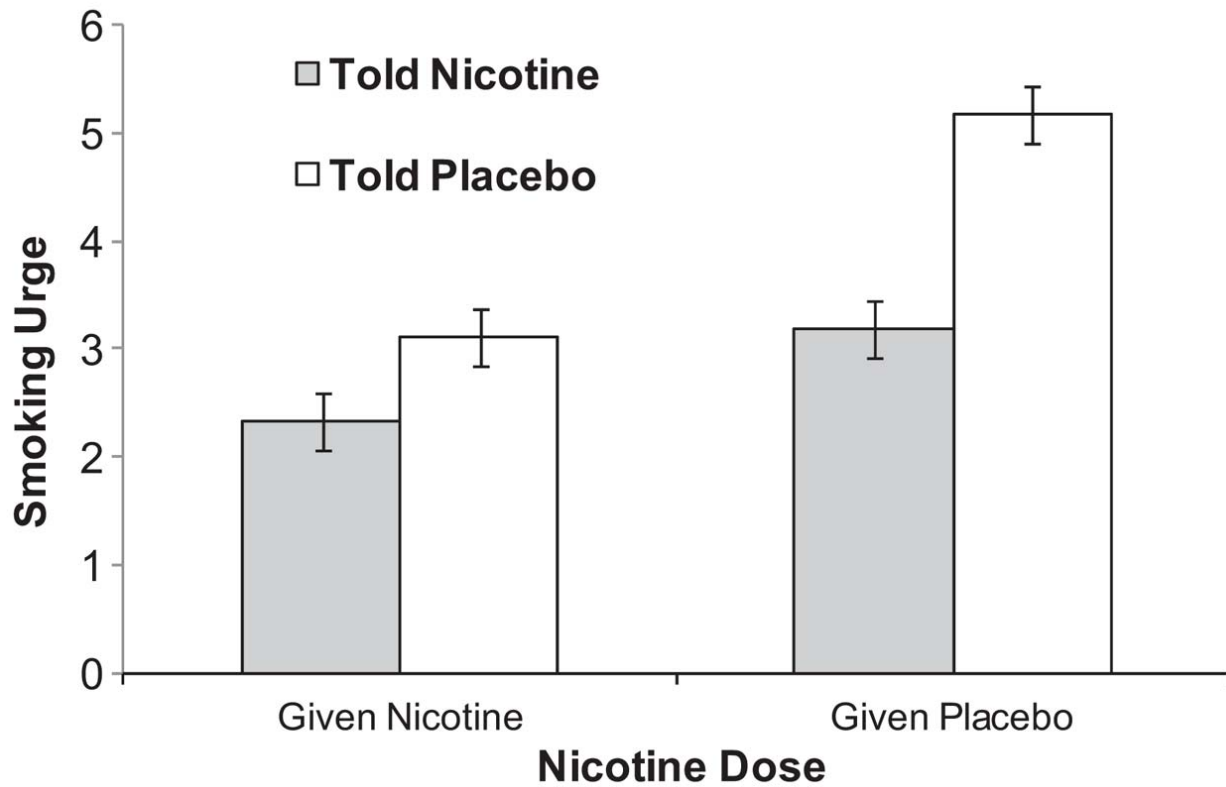
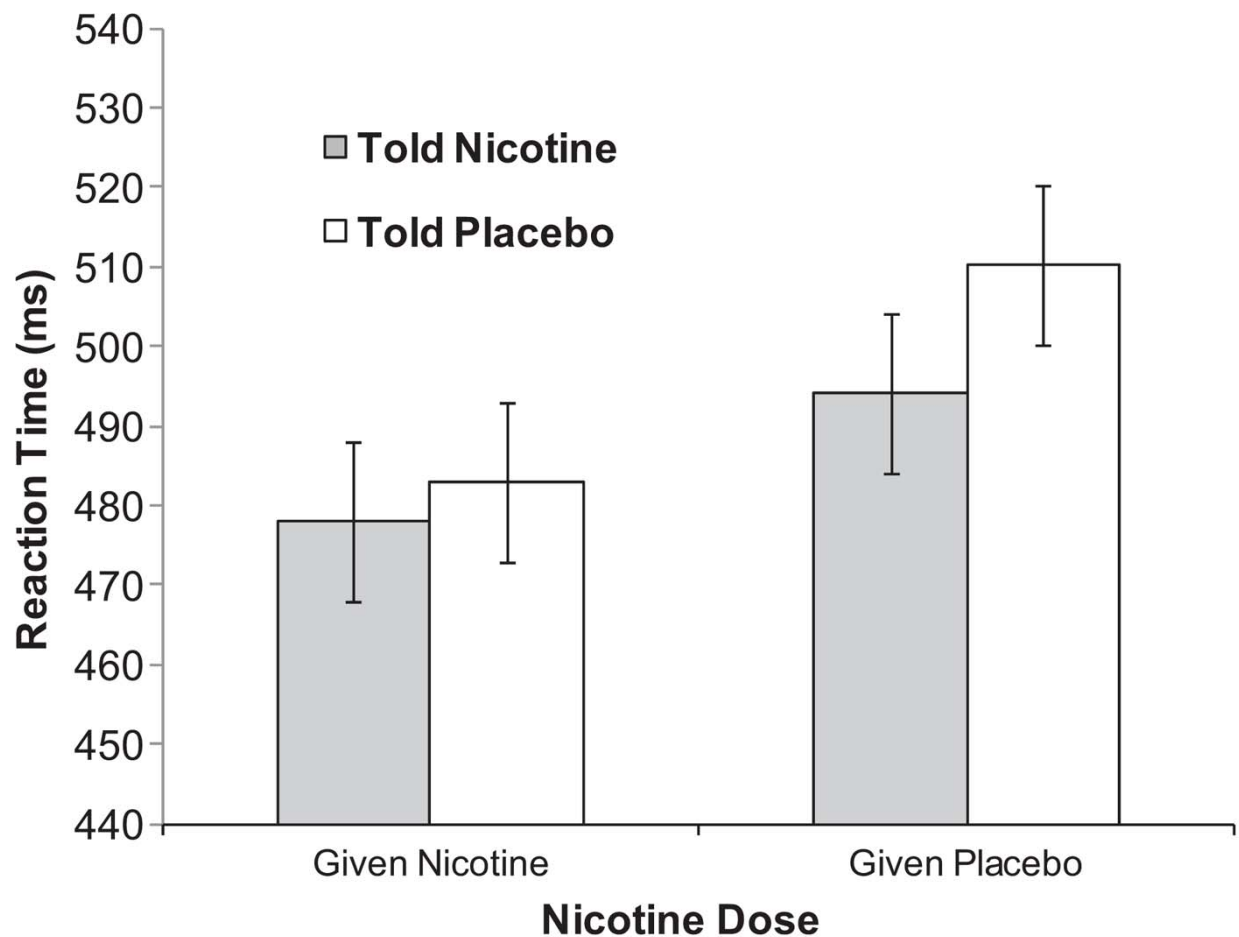


Figure VIII.D-88. Reaction time (From Juliano *et al*, 2011 [pg301])



Ixii. Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure: A Randomized Clinical Trial.

This study (Hatsukami *et al*. 2018 [pg300]) 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 different classes of smoke exposure included expired CO; urinary phenanthrene tetraol (PheT), an indicator of exposure to polycyclic aromatic hydrocarbons; and a urinary mercapturic acid, 3-HPMA, a metabolite of the volatile organic compound acrolein, which is a cardiopulmonary toxicant. Secondary end points included biomarkers of nicotine exposure, cotinine (not reported), and urinary total nicotine equivalents (TNE); mercapturic acid metabolites of acrylonitrile (CEMA), benzene (SPMA), propylene oxide (2-HPMA), and crotonaldehyde (HMPMA); and metabolites of a tobacco specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK; total NNAL). Effect biomarkers included 8-epi PGF2 α , prostaglandin E2 metabolite, white blood cell count, and C-reactive protein level (not reported). Other secondary end points included CPD, levels of cigarette dependence assessed by the Fagerstrom Test for Nicotine Dependence (FTND) and the Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM). Only the immediate reduction group will be discussed since this represents the likely scenario for VLN™ products.

This study was primarily focused on biomarkers of exposure. The biomarkers and cigarette per day data are shown in Table VIII.D-62. 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-89. *BOE* (From Hatsukami *et al.* 2018 [pg300]) shows the time course for the development of the reductions. Total nicotine equivalents and total NNAL were also reduced. Figure VIII.D-90. *QSU* (From shows the exposure biomarkers, Minnesota Nicotine Withdrawal Scale

(MNWS) and the Questionnaire on Smoking Urges (QSU) results. During week 1 withdrawal symptoms were more intense in the immediate group. Most relevant to smoking urges are the results of the QSU Factor 1 (strong desire and intention to smoke, with smoking perceived as pleasurable; scales range from 5-35). Scores were significantly lower, 9.00 vs. 14.2 at 20 weeks. At week 20, significantly lower Fagerström Test for Nicotine dependence scores were observed in the immediate group: 4.27 (low dependence) vs 5.48 (moderate dependence).

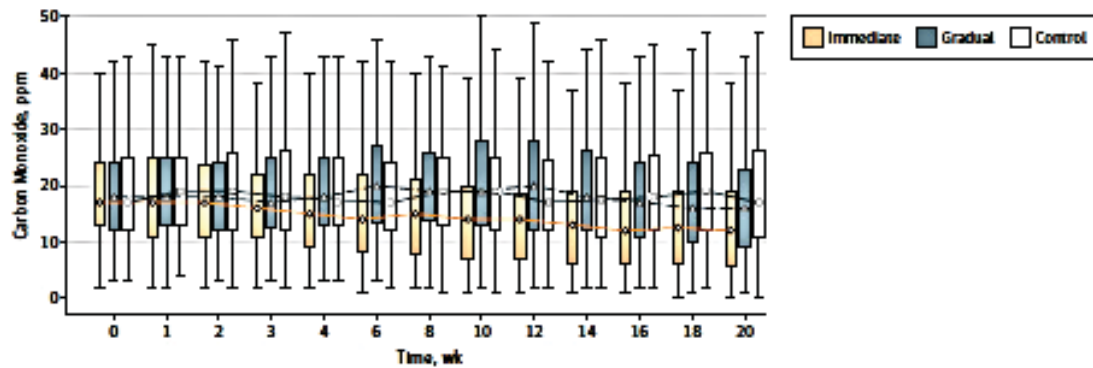
Conclusions: VLNC cigarettes reduce CPD, biomarkers of exposure, cigarette dependency and urge to smoke after 20-weeks of use.

Table VIII.D-62. BOE (From Hatsukami *et al.* 2018 [pg300]) (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 (pmol/mg) | 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-89. BOE (From Hatsukami *et al.* 2018 [pg300])

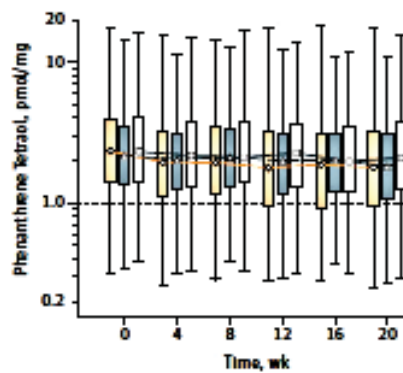
A Carbon monoxide



No. of participants

| | | | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Immediate | 503 | 459 | 428 | 405 | 416 | 394 | 380 | 357 | 359 | 341 | 348 | 335 | 342 |
| Gradual | 498 | 480 | 473 | 465 | 468 | 450 | 445 | 424 | 424 | 410 | 410 | 402 | 403 |
| Control | 249 | 240 | 233 | 227 | 234 | 221 | 222 | 212 | 218 | 213 | 214 | 210 | 213 |

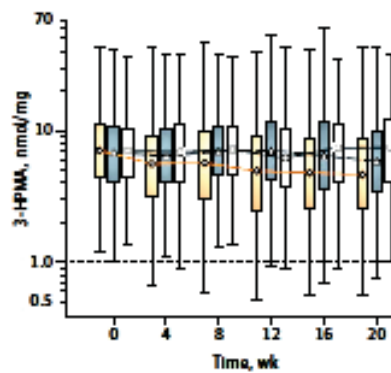
B Phenanthrene tetraol



No. of participants

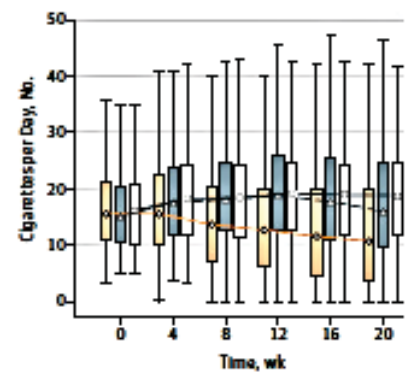
| | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|
| Immediate | 502 | 417 | 381 | 360 | 348 | 342 |
| Gradual | 496 | 466 | 445 | 423 | 410 | 403 |
| Control | 248 | 233 | 223 | 218 | 213 | 210 |

C 3-HPMA



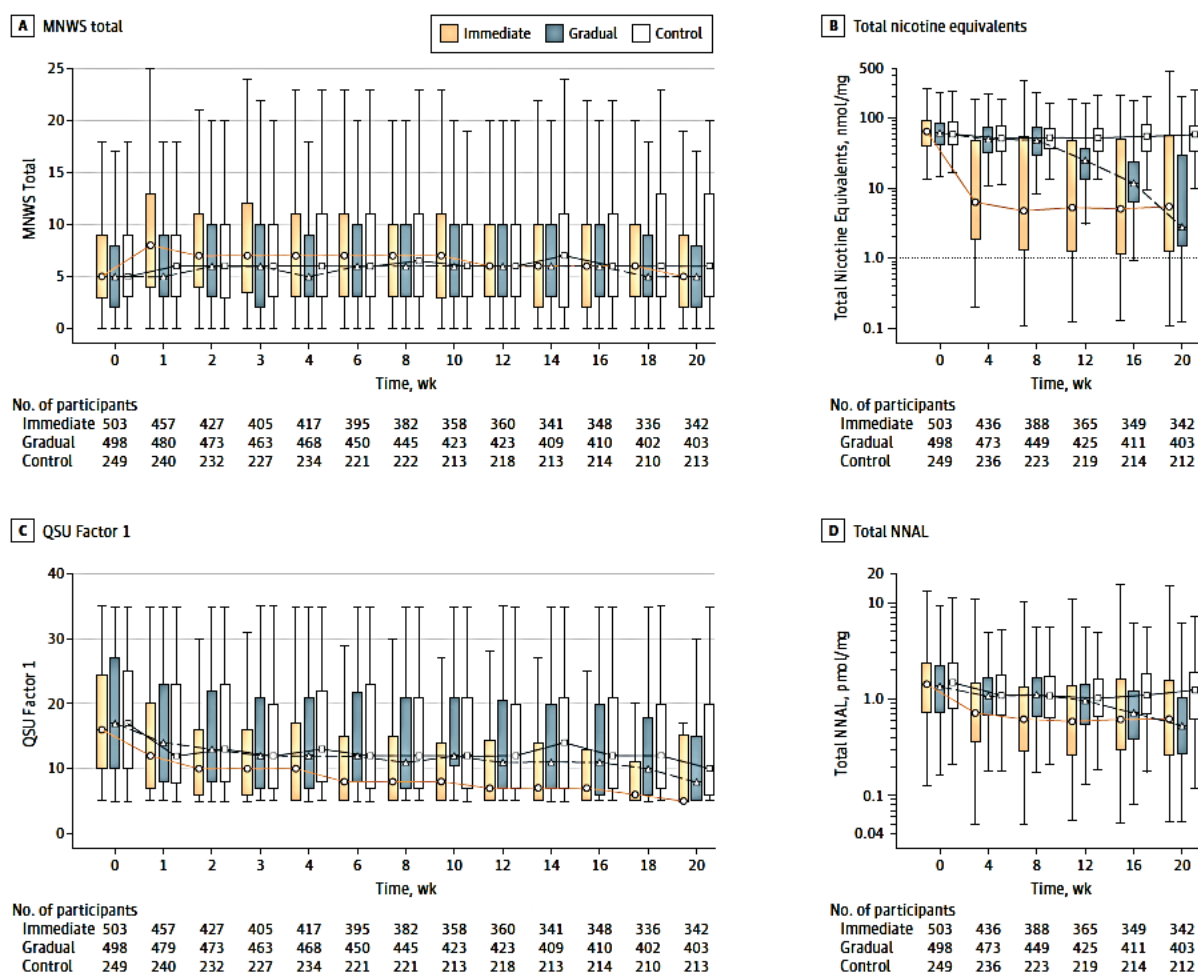
| | | | | | |
|-----|-----|-----|-----|-----|-----|
| 503 | 417 | 379 | 356 | 341 | 332 |
| 498 | 467 | 441 | 418 | 406 | 396 |
| 249 | 233 | 220 | 215 | 210 | 210 |

D Total cigarettes per day



| | | | | | |
|-----|-----|-----|-----|-----|-----|
| 503 | 498 | 422 | 387 | 367 | 358 |
| 497 | 498 | 473 | 444 | 428 | 408 |
| 249 | 249 | 235 | 225 | 218 | 215 |

Figure VIII.D-90. QSU (From Hatsukami *et al.* 2018 [pg300])



lxiii. Preliminary Validity of the Modified Cigarette Evaluation Questionnaire in predicting the reinforcing effects of cigarettes that vary in nicotine content.

This study (Arger *et al.* 2017 [pg297]) examined the relationship between subjective and behavioral measures across a range of nicotine doses. This was a secondary analysis of a double-blind study (Higgins *et al.* 2018 [pg301]) evaluating the subjective and reinforcing effects of Spectrum cigarettes under acute smoking abstinence. Current smokers were recruited from three vulnerable smoking populations (economically disadvantaged women of reproductive age, opioid-maintained individuals, individuals with affective disorders). In Phase 1 (five sessions), the mCEQ (Satisfaction, Psychological Reward, Enjoyment of Respiratory Tract Sensations, Craving

Reduction, Aversion subscales) was administered following ad lib smoking of Spectrum cigarettes and subscale difference scores were calculated by subtracting ratings of the 15.8 mg/g cigarette from ratings of the reduced nicotine content cigarettes. In Phase 2 (six sessions), participants completed six 2-dose concurrent choice tests. The relationship between mCEQ subscale difference scores from Phase 1 and nicotine dose choice from Phase 2 was examined using mixed-model repeated-measures analyses of variance.

Figure VIII.D-91 shows the results of the analysis. Only higher satisfaction and lower aversion subscale difference scores were associated with choosing the 15.8 mg/g cigarette more than the 5.2, 2.4, and 0.4 mg/g cigarettes. Scores on the other mCEQ subscales were not associated with nicotine choice. These results provide support for validity of the mCEQ Satisfaction and Aversion subscales predicting the relative reinforcing effects and abuse liability of varying nicotine content cigarettes.

Figure VIII.D-91. (From Arger *et al.* 2017 [pg297])

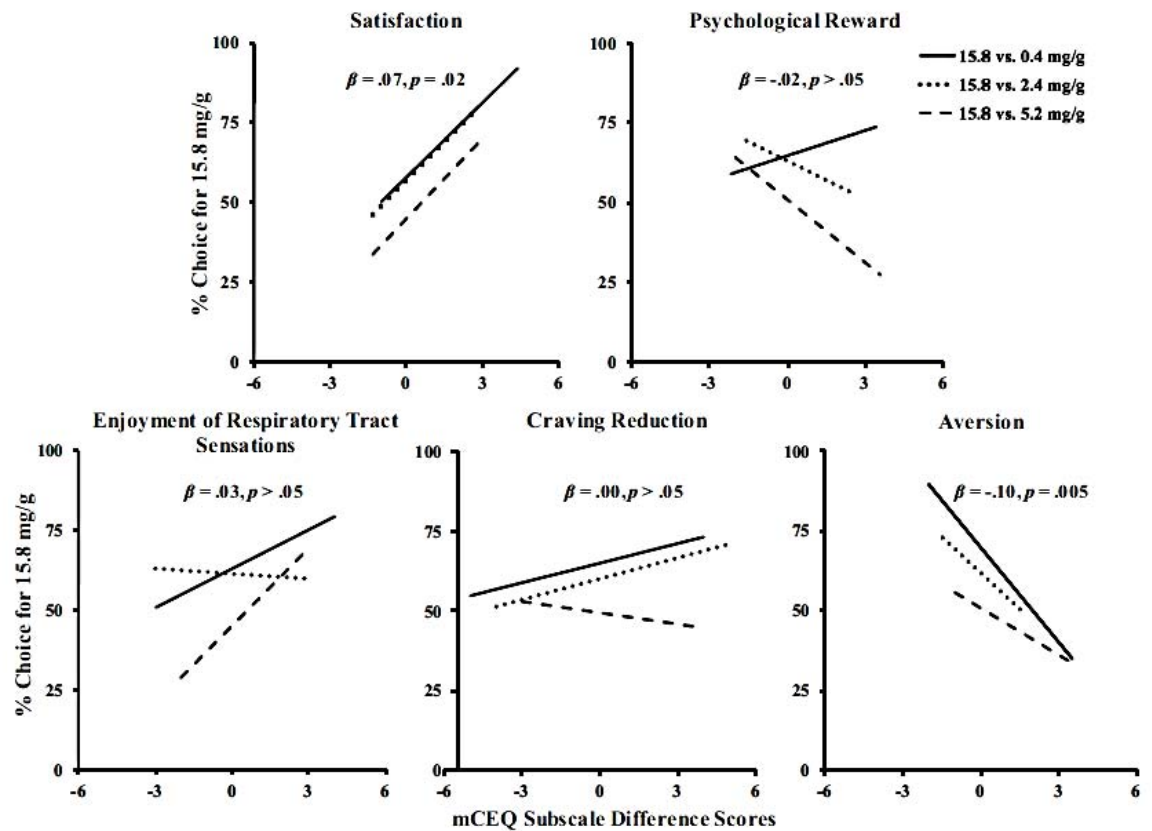
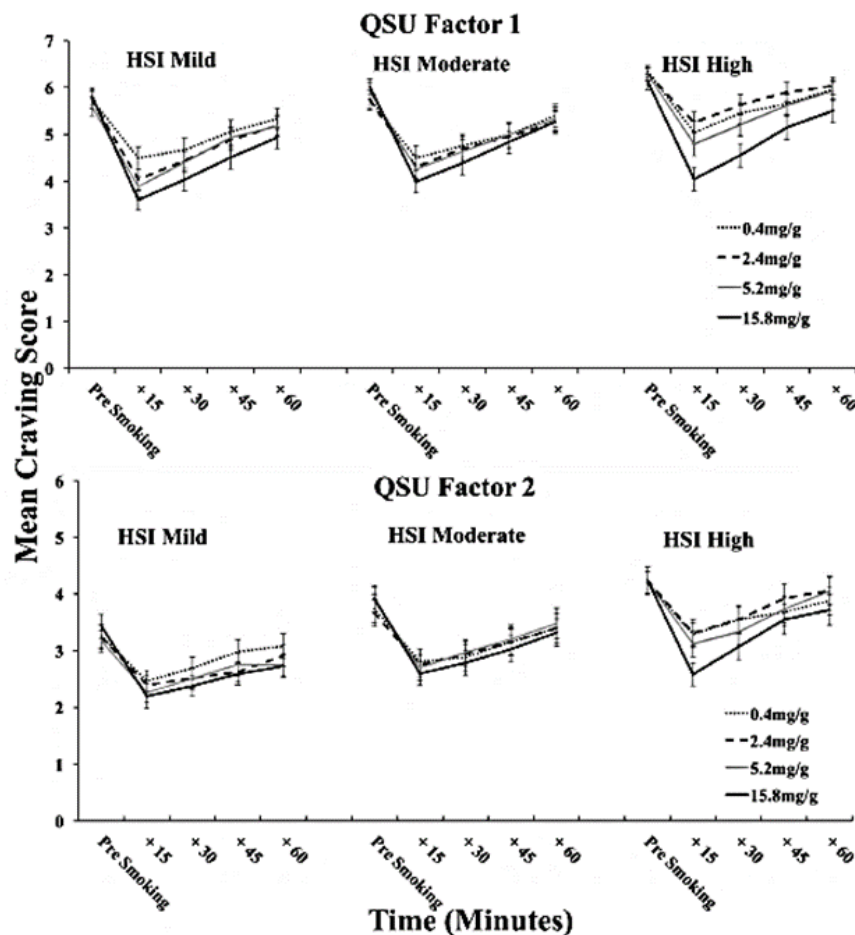


Figure VIII.D-92. QSU (From Higgins *et al.* 2018 [pg301])



Ixiv. Reduced-nicotine cigarettes increase platelet activation in smokers in vivo: A dilemma in harm reduction.

Cardiovascular disease due to cigarette smoking manifests itself in the form of venous thrombosis, stroke and myocardial infarction. Platelets play a major role in clot formation. Ramachandran *et al.*, 2004 [pg303] found that cigarette smoke increases platelet activation and that the activation is inhibited by nicotine in vitro. In this study (Girdhar *et al.* 2008, Nicotine & Tobacco Research [pg300]) subjects smoked Quest 3 cigarettes and the platelet activation score was measured and compared to that of Quest 1 smokers. Plasma nicotine was measured in select smokers to make sure that the smokers were getting nicotine.

Figure VIII.D-93 shows that PAS increased 94% in the medium nicotine group compared to the Quest 1 group (zero nicotine) while nicotine was reduced in select individuals. The authors concluded that reduced nicotine cigarettes may increase harm.

Figure VIII.D-93. PAS (From Girdhar *et al.* 2008, Nicotine & Tobacco Research [pg300])

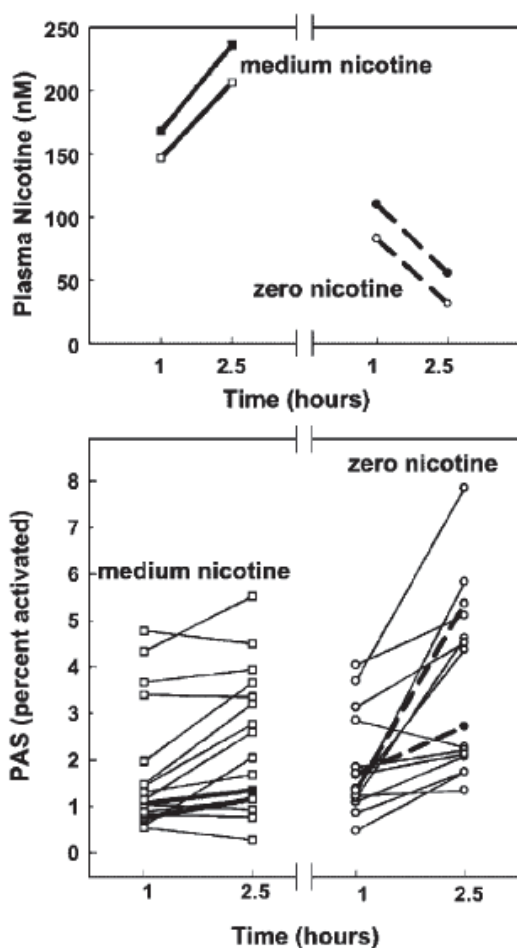


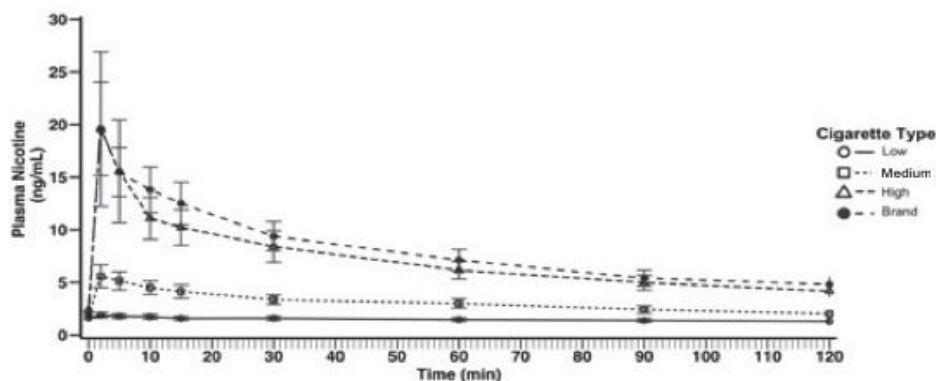
Figure 2. Plasma nicotine levels and platelet activation state in smokers. All subjects smoked three medium-nicotine cigarettes from 0 to 1 h. From 1 to 2.5 h, half the subjects continued to smoke five medium-nicotine cigarettes, and the others smoked five zero-nicotine cigarettes. (A) Plasma nicotine, measured in two randomly selected subjects in each group (top panel). (B) Platelet activation state (P-selectin expression) for all subjects individually (bottom panel). The bold lines in Figure 2B (solid and dashed) show the platelet-activation data for the four individuals who were selected for nicotine analysis, shown in Figure 2A.

lxv. Pharmacokinetic Profile of Spectrum Reduced Nicotine Cigarettes.

Kamens *et al.* 2019 investigated the pharmacokinetic profile and subjective effects of Spectrum research cigarettes comparing them to usual brand. 12 daily smokers attended 4 sessions and had blood nicotine, exhaled carbon monoxide (CO) and subjective effects measured before and after smoking either a single cigarette of their preferred brand or high (10.9 mg/cig), medium (3.2 mg/cig) or very low (0.2 mg/cig) nicotine content SPECTRUM research cigarettes, in a double-blind design with order counter-balanced. The 0.2 mg/cig SPECTRUM (NRC 102) cigarette is the same as VLN™ Kings. This study evaluated different nicotine yield SPECTRUM cigarettes. Only the results from the 0.2 mg/cigarette products will be discussed as compared to usual brand.

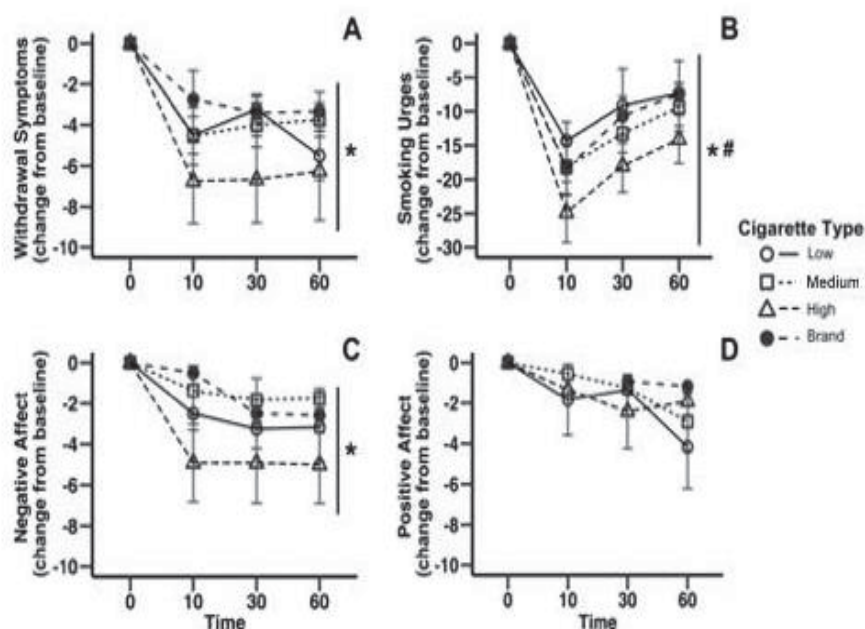
Results: The subjects (mean age: 29 years; range: 18-55 years) smoked an average of 13.9 cigarettes per day (range: 10-20) for 9.8 years (range: 1.5-40). The average score on the Fagerström Test for Nicotine Dependence was 4.6 ± 1.6 (Range 2 – 7). Participants smoked the 0.2 mg/cigarette SPECTRUM cigarette (VLN™ King) significantly faster than their usual brand (3.8 vs. 2.7 minutes). This difference in time to smoke the cigarette was not attributed to number of puffs (non-significant decrease from 14.9 for usual brand to 11.7), but the average puff duration was significantly longer (2.6 vs. 2.1 seconds). Plasma nicotine levels were reduced from 812 ng/ml (area under curve) to 46.2 ng/ml. This represents a 94% reduction in nicotine levels. Figure VIII.D-94 shows the plasma nicotine levels. The nicotine content of cigarette had no influence on CO parameters. There were no significant effects of cigarette type on baseline CO level, CO boost, or AUC_{CO}.

Figure VIII.D-94. Plasma Nicotine Levels; Low is VLN™ (from Kamens *et al* 2019)



The participants reported no difference in enjoyment of the cigarettes. The type of cigarette had no significant effect on satisfaction, reward, aversion, enjoyment of respiratory track sensations, or craving reduction subscales of the mCEQ. Withdrawal symptoms and smoking urges were suppressed by VLN™ but not to the extent produced by usual brand (Figure VIII.D-95). Negative affect was decreased but not to the extent caused by usual brand. There was no difference in positive affect.

Figure VIII.D-95. Subjective Effects of Test Cigarettes; Low = VLN™ (From Kamens *et al.* 2019)



Implications: These are essentially the same results that were obtained in the Company's non-menthol abuse liability study (Altasciences 2018 [pg297]). In that study using 55 subjects, nicotine plasma levels were reduced 97%. There was no change in puff duration, but the number of puffs and smoking duration were reduced. Similar reductions in withdrawal symptoms and urges to smoke were observed.

lxvi. Response to reduced Nicotine Content in Vulnerable Populations: Effect of Menthol Status (NCT02250534).

Davis *et al.* (2019 [pg298]) investigated the potential effects of being a menthol smoker on response to reduced nicotine content cigarettes in smokers especially vulnerable to smoking. 169 smokers

(61 menthol and 108 non-menthol smokers) with comorbid mental illness, substance use disorder, or socioeconomic disadvantage completed a double-blind study assessing addiction potential, withdrawal/craving, and compensatory smoking across 4 research cigarettes varying in nicotine content from very low levels to commercial levels (0.4, 2.4, 5.2, 15.8(NNC) mg/g of tobacco). The 0.4 mg/g cigarette is VLN™ King. Only the effects of VLN™ cigarettes compared to the normal nicotine content cigarettes (NNC) will be discussed.

Results: Menthol smokers made up 36% of the participants and were more likely to be non-white, have lower education, and female than the non-menthol smokers. There was no difference in cigarette consumption or level of dependence. There were no effects of menthol status on total puff volume, puff duration, interpuff interval or puff number. There was no effect of menthol status on change in breath CO. Withdrawal and craving were reduced by VLN™ but not to the extent of NNC. Menthol had no effect. The authors concluded that the benefits of VLN™ should extend to menthol smokers.

Conclusions: These results are the same as those observed in the menthol (Altasciences 2018 [pg297]) and non-menthol (Altasciences 2019 [pg297]) abuse liability studies. There is no indication that menthol smokers will respond differently to VLN™ cigarettes than non-menthol smokers.

Ixvii. Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content.

Perkins *et al.* (Kenneth A. Perkins, *et al.* 2018 [pg302]) evaluated the acute responses to each of two menthol or non-menthol SPECTRUM research cigarettes, moderate (16–17 mg/g) versus very low (0.4 mg/g) in nicotine contents following brief abstinence (overnight) in adult smokers preferring menthol (n=44) or non-menthol (n=29) brands. The 0.4 mg /g tobacco SPECTRUM cigarette is the VLN™ cigarette. The “moderate” and “very low” nicotine cigarettes were intermittently presented, one per trial in random order across 10 trials (five per cigarette), for rating of subjective perceptions of each cigarette (Acute Cigarette Perceptions; ACP). Participants were instructed that two different cigarettes would be evaluated

but kept blind as to the nicotine content of each one administered, both of which had no identifying labels on the paper and were thus identical in appearance. All trials consisted of four puffs (about one-third of a full cigarette), separated by 15 min, and so total exposure over the three-hour session was intentionally no more than that from ad lib smoking in the morning after overnight abstinence. After the four puffs in each of these 10 trials, participants completed the brief ACP measure on their subjective perceptions of that cigarette.

Results: All perceptions and choices were greater for moderate vs very low nicotine, as expected, and the magnitude of difference in four of six perceptions was associated with subsequently greater choice of the moderate nicotine cigarette (Table VIII.D-63). Virtually no differences were found between menthol and non-menthol, as nearly all perceptions, cigarette choices, and the association between perceptions and choice were not moderated by menthol or the interaction of nicotine by menthol (Figure VIII.D-96. Acute Cigarette Perceptions (ACP) (From Perkins *et al* 2018 [pg302])). These results indicate perceptions and reinforcement from cigarettes do not differ due to menthol when nicotine content and smoking topography are carefully controlled.

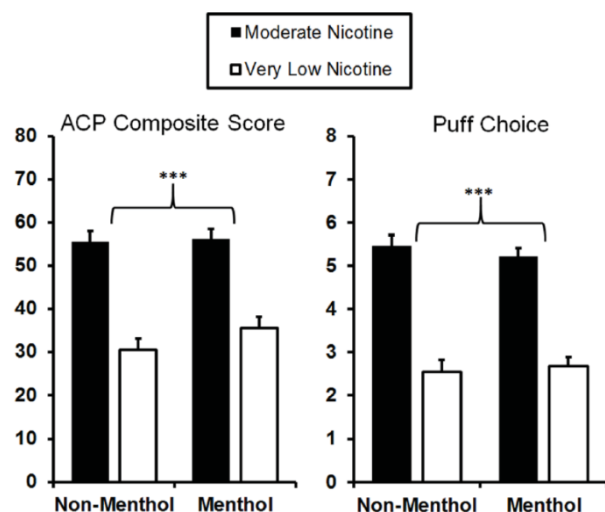
Table VIII.D-63 Acute cigarette perceptions (From Perkins *et al.* 2018 [pg302])

Table 1. Mean (standard error of the mean (SEM)) acute cigarette perceptions by nicotine content and menthol (non-menthol $n=29$, menthol $n=44$). The first five comprise the Acute Cigarette Perceptions (ACP) scale.

| | Moderate nicotine (Mod) | | Very low nicotine (VLN) | | Difference (Mod-VLN) |
|----------------------|-------------------------|------------|-------------------------|------------|-------------------------|
| | Non-menthol | Menthol | Non-menthol | Menthol | |
| Liking | 56.3 (3.6) | 55.6 (3.0) | 31.6 (3.9) | 33.3 (3.1) | 23.3 (2.7) ^a |
| Satisfying | 57.7 (3.5) | 55.8 (2.8) | 30.8 (3.7) | 32.9 (3.0) | 24.5 (2.7) ^a |
| How much nicotine | 60.1 (3.2) | 58.3 (2.6) | 32.5 (3.2) | 34.6 (2.6) | 25.2 (2.7) ^a |
| Strong ^b | 52.2 (3.4) | 56.4 (2.5) | 25.9 (3.3) | 38.7 (2.7) | 21.1 (2.8) ^a |
| Flavor | 52.4 (3.1) | 53.6 (2.5) | 33.5 (3.8) | 37.8 (3.1) | 17.0 (2.5) ^a |
| Similar to own brand | 45.3 (4.2) | 39.1 (3.5) | 19.8 (2.7) | 19.1 (2.8) | 22.2 (2.9) ^a |

Note. ^a $p<0.001$ for main effect of nicotine content; ^b $p<0.01$ for main effect of menthol.

Figure VIII.D-96. Acute Cigarette Perceptions (ACP) (From Perkins *et al* 2018 [pg302]).



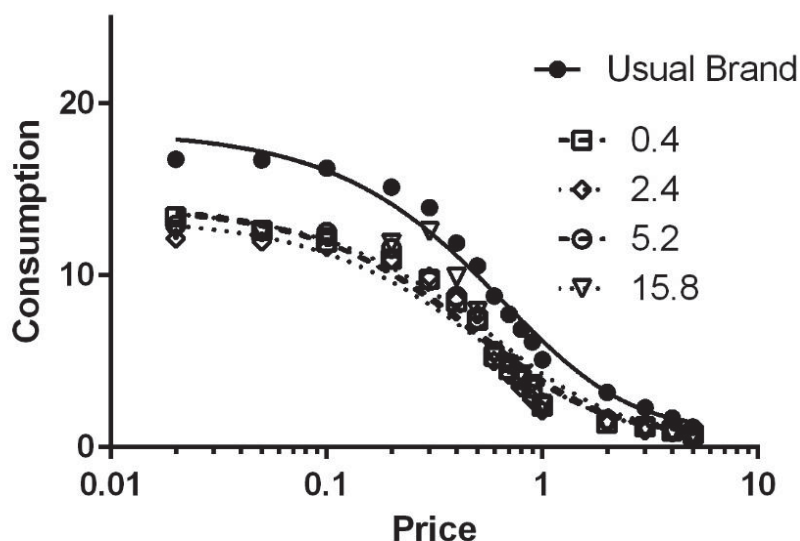
Implication: Menthol had no effect on subject's perceptions of VLN™ cigarettes.

lxviii. *The Impact of Nicotine Dose on the Reinforcing Value of Cigarettes in Adolescents.*

Cassidy *et al.* (2019 [pg298]) evaluated the effect of nicotine dose on a cigarette purchase task (CPT) in adolescent daily smokers (ages: 15-19). Subjects completed a CPT for their usual brand and for each dose of SPECTRUM cigarettes (15.8, 5.2, 1.3, 0.4 mg nicotine /g tobacco) during 4 laboratory sessions. The effect of nicotine dose on 5 demand indices were derived from the CPT. The 0.4 mg SPECTRUM cigarette is the same as the VLN™ cigarette. Previous studies in adults have indicated that cigarette demand decreases with decreased nicotine content in adults (Donny *et al.* 2015 [pg299]) and also in several vulnerable adult populations (Higgins, *et al.* 2017 [pg300]).

Results: In adolescents, there was a significantly higher demand for usual brand cigarettes than the research cigarettes (Figure VIII.D-97. Cigarette demand curve for various SPECTRUM cigarettes and usual brand vs. nicotine dose (From Cassidy *et al.* 2019 [pg298])).

Figure VIII.D-97. Cigarette demand curve for various SPECTRUM cigarettes and usual brand vs. nicotine dose (From Cassidy *et al.* 2019 [pg298])



Conclusion: These results are essentially the same as was observed with adults. This suggests that adolescents will respond similarly to the reduced levels of nicotine in VLN™ cigarettes.

4. Adverse Events

Availability of detailed adverse event information is limited for published reports. There have been no reports of serious adverse events attributed to VLN™ cigarettes. Based on the design of the cigarettes, it would be expected that the adverse event profile of VLN™ cigarettes would be the same as conventional or usual brand cigarettes.

i. Evaluation of the Abuse Liability of Very Low Nicotine Cigarettes

In an acute study (Altasciences 2018 [pg297]) designed to evaluate the abuse liability of VLN™ regular cigarettes, subjects used VLN™ (Product A), their usual brand (Product B) and nicotine gum (Product C) under controlled and *ad libitum* smoking conditions over 6 days. This was a randomized, two-part, 3-way crossover design to evaluate the abuse liability, PK, and

product use behavior associated in healthy adult male and female exclusive smokers. Subjects participated in a standard Screening visit and one 7-day Confined Assessment Phase, which included a product trial session (Day -1), and two study parts (Part A and Part B). Spontaneous AE reporting was continuous throughout the study, beginning with the time the subject gave informed consent; however, at regular intervals, AE checks were performed using a non-leading question.

With respect to safety, all 3 products were well-tolerated. There were no deaths or SAEs in the study and the majority of AEs were mild in severity. One subject was discontinued due to a mild AE of nephrolithiasis that was not related to product use (onset prior to any product use). The overall incidence of AEs was similar for nicotine gum and own-brand cigarette (~31-32%) and lower for VLN™ cigarettes (15%). The majority of AEs following use of VLN™ cigarettes were considered unrelated to study product, while most AEs following use of own-brand cigarette and nicotine gum were considered related to study product. The only AE reported in more than one subject following use of VLN™ cigarettes was headache. The most common AEs following use of own brand cigarettes were headache and presyncope, followed by dizziness. The most common AE following nicotine gum administration was hiccups. The majority of mean laboratory, vital signs, and ECG values were within normal ranges at all assessments and none of the subjects had clinically significant findings for laboratory, vital signs, or ECG assessments. Three subjects had clinically significant findings on physical examination that were associated with mild AEs, but none of the AEs were considered related to product use.

(a) *Adverse Events*

Table VIII.D-64 summarizes the AEs. One subject was discontinued due to an AE of nephrolithiasis that began prior to the use of any of the study products; the subject was subsequently withdrawn from the study on Day 5 of Part B. The majority of AEs were mild in severity and the incidence of AEs was lower for VLN™ compared with the other 2 products. The majority of AEs following use of VLN™ cigarettes were considered unrelated to study product. The majority of AEs following use of own-brand cigarette and nicotine gum were considered related to study product.

The most common individual AE (defined 2 or more subjects for any study product) following use of VLN™ cigarettes was headache. The most common AEs following use of own-brand cigarettes were headache and presyncope, followed by dizziness. The most common AE following nicotine gum administration was hiccups. All other AEs occurred in only 1 or 2 subjects.

The majority of mean laboratory, vital signs, and ECG values were within normal ranges at all assessments. In addition, no subjects had CS findings for laboratory, vital signs, or ECG assessments. Three subjects had CS findings on physical examination on Day 6 that were associated with mild AEs that were not considered to be related to product use.

(b) *Serious Adverse Events*

There were no deaths or serious AEs.

(c) *Discontinuations*

There were no AEs that led to discontinuation.

Table VIII.D-64. Summary of AEs from VLN™ King abuse liability study (A = VLN™; B = Usual Brand; C = Nicorette Gum).

| Parameter | Study Product A (N=66) | Study Product B (N=65) | Study Product C (N=65) | Overall (N=66) |
|---|---------------------------|---------------------------|---------------------------|-------------------|
| Adverse Events Reported [n] | | | | 80 |
| Subjects With At Least One AE [n(%)] [1] | | | | 41 (62.1) |
| Study Product Use-Emergent Adverse Events (SPUEAEs) Reported [n] | 10 | 31 | 29 | 70 |
| Subjects With At Least One SPUEAE [n(%)] [1] | 10 (15.2) | 20 (30.8) | 21 (32.3) | 37 (56.1) |
| SPUEAEs Relationship [2] | | | | |
| Unrelated [n(%)] | 8 (80.0) | 11 (35.5) | 7 (24.1) | 26 (37.1) |
| Unlikely Related [n(%)] | 1 (10.0) | 2 (6.5) | 1 (3.4) | 4 (5.7) |
| Possibly Related [n(%)] | 1 (10.0) | 3 (9.7) | 0 | 4 (5.7) |
| Probably Related [n(%)] | 0 | 15 (48.4) | 21 (72.4) | 36 (51.4) |
| SPUEAEs Severity/Intensity [2] | | | | |
| Mild [n(%)] | 8 (80.0) | 23 (74.2) | 28 (96.6) | 59 (84.3) |
| Moderate [n(%)] | 2 (20.0) | 8 (25.8) | 1 (3.4) | 11 (15.7) |
| Severe [n(%)] | 0 | 0 | 0 | 0 |
| Study Product Use-Emergent Serious Adverse Events (SPUESAEs) Reported [n] [2] | 0 | 0 | 0 | 0 |
| Subjects With At Least One SPUESAE [n(%)] [1] | 0 | 0 | 0 | 0 |
| SPUEAEs Leading To Study Discontinuation Reported [n] [2] | 0 | 0 | 0 | 0 |
| SPUEAEs Leading To Death Reported [n] [2] | 0 | 0 | 0 | 0 |

ii. Evaluation of the Abuse Liability of Menthol Very Low Nicotine Cigarettes

In an acute study (Altasciences 2019 [pg297]) designed to evaluate the abuse liability of VLN™ menthol cigarettes, subjects used VLN™ Menthol Kings (Product A), their usual menthol brand (Product B) and nicotine gum (Product C) under controlled and *ad libitum* smoking conditions over 6 days. This was a randomized, two-part, 3-way crossover design to evaluate the abuse liability, PK, and product use behavior associated in healthy adult male and female exclusive smokers. Subjects participated in a standard Screening visit and one 7-day Confined Assessment Phase, which included a product trial session (Day -1), and two study parts (Part A and Part B). Spontaneous AE reporting was continuous throughout the study, beginning with the time the subject gave informed consent; however, at regular intervals, AE checks were performed using a non-leading question.

The study products were relatively well tolerated; no subjects experienced SAEs or AEs leading to discontinuation. Mentholated own-brand cigarette was associated with the highest

incidence of AEs overall (28.3%), followed by nicotine gum (19.7%) and VLN™ Menthol cigarette (18.3%). Overall, the only AEs reported in 2 or more subjects following use of the VLN™ Menthol cigarettes were those classified as nervous system disorders (11.7%), and musculoskeletal and connective tissue disorders (3.3%). The most common AEs with mentholated own-brand cigarette were nervous system disorders (20.0%), followed by gastrointestinal disorders and general disorders and catheter site conditions (6.7% for both). The most commonly observed AEs with nicotine gum were nervous system disorders (6.6%), followed by musculoskeletal and connective tissue disorders (4.9%) and general disorders and catheter site conditions (3.3%).

(a) *Adverse Events*

Table VIII.D-65 summarizes the AEs. The majority of AEs were mild in severity and no severe AEs were reported during the study. Most AEs were considered unrelated (unrelated or unlikely to be related) to product use. The overall incidence of AEs was highest for mentholated own-brand cigarette (28%) and comparable for the VLN™ Menthol cigarette and nicotine gum (~18 to 20%). For VLN™ Menthol cigarettes and nicotine gum, the incidence of AEs was similar in Part A and Part B, while for mentholated own-brand cigarette, the incidence of AEs was higher in Part B compared with Part A.

The study products were relatively well tolerated; no subjects experienced SAEs or AEs leading to discontinuation. Mentholated own-brand cigarette was associated with the highest incidence of AEs overall (28.3%), followed by nicotine gum (19.7%) and VLN™ Menthol cigarette (18.3%). Overall, the only AEs reported in 2 or more subjects following use of the VLN™ mentholated cigarettes were those classified as nervous system disorders (11.7%), and musculoskeletal and connective tissue disorders (3.3%).

The most common AEs with mentholated own-brand cigarette were nervous system disorders (20.0%), followed by gastrointestinal disorders and general disorders and catheter site conditions (6.7%). The most commonly observed AEs with nicotine gum were nervous system disorders (6.6%), followed by musculoskeletal and connective tissue disorders (4.9%) and general disorders and catheter site conditions (3.3%).

The most common AE reported following use of VLN™ Menthol cigarette was headache (6 [10%] subjects) followed by pain in extremity (2 [3.3%] subjects); all other AEs occurred in only one (1.7%) subject. The most common AEs with Menthol own-brand cigarette were dizziness (6 [10%] subjects), headache (4 [6.7%] subjects), presyncope (3 [5.0%] subjects), and nausea and vomiting (2 [3.3%] subjects each); all other AEs occurred in only one (1.7%) subject. For nicotine gum, the most common AEs were headache (4 [6.7%] subjects), followed by pain in extremity (2 [3.3%] subjects); all other AEs occurred in only one (1.6%) subject.

The majority of AEs were mild in severity. Two moderate AEs were reported following use of the VLN™ Menthol cigarette (2 subjects with headache). Three subjects experienced moderate AEs with mentholated own-brand cigarette (2 subjects with headache and one subject with syncope). One subject experienced a moderate AE of headache with nicotine gum. No subjects experienced severe or life-threatening AEs during the study. The majority of AEs following use of all products were considered unrelated to study product (unrelated or unlikely related).

All mean laboratory, vital signs, and ECG values were within normal ranges at all assessments. In addition, no subjects had CS findings for laboratory, vital signs, or ECG

assessments. Four subjects had CS findings upon physical examination on Day 6 associated with mild AEs that were not considered to be related to product use.

(b) *Serious Adverse Events*

There were no deaths or serious AEs.

(c) *Discontinuations*

There were no AEs that led to discontinuation.

Table VIII.D-65. Summary of AEs from VLN™ Menthol King abuse liability study (A = VLN™ Menthol; B = Usual Brand; C = Nicorette Gum).

| Parameter | Study Product A (N=60) | Study Product B (N=60) | Study Product C (N=61) | Overall (N=61) |
|--|---------------------------|---------------------------|---------------------------|-------------------|
| Adverse Events Reported [n] | | | | 62 |
| Subjects With At Least One AE [n(%)] [1] | | | | 31 (50.8) |
| Study Product Use- Emergent Adverse Events (SPUEAEs) Reported [n] | 12 | 26 | 18 | 56 |
| Subjects With At Least One SPUEAE [n(%)] [1] | 11 (18.3) | 17 (28.3) | 12 (19.7) | 28 (45.9) |
| SPUEAEs Relationship [2] | | | | |
| Unrelated [n(%)] | 5 (41.7) | 11 (42.3) | 9 (50.0) | 25 (44.6) |
| Unlikely Related [n(%)] | 4 (33.3) | 2 (7.7) | 3 (16.7) | 9 (16.1) |
| Possibly Related [n(%)] | 1 (8.3) | 6 (23.1) | 3 (16.7) | 10 (17.9) |
| Probably Related [n(%)] | 2 (16.7) | 7 (26.9) | 3 (16.7) | 12 (21.4) |
| SPUEAEs Severity/Intensity [2] | | | | |
| Mild [n(%)] | 10 (83.3) | 23 (88.5) | 17 (94.4) | 50 (89.3) |
| Moderate [n(%)] | 2 (16.7) | 3 (11.5) | 1 (5.6) | 6 (10.7) |
| Severe [n(%)] | 0 | 0 | 0 | 0 |
| Study Product Use- Emergent Serious Adverse Events (SPUESAEs) Reported [n] [2] | 0 | 0 | 0 | 0 |
| Subjects With At Least One SPUESAE [n(%)] [1] | 0 | 0 | 0 | 0 |
| SPUEAEs Leading To Study Discontinuation Reported [n] [2] | 0 | 0 | 0 | 0 |
| SPUEAEs Leading To Death Reported [n] [2] | 0 | 0 | 0 | 0 |

iii. Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure: A Randomized Clinical Trial

This study (Hatsukami *et al.* 2018 [pg300]) was a randomized, parallel, double-blind trial conducted at 10 sites throughout the United States. Participants (N = 1,250) 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). Adverse event data may be found in the Esupplement on the journal website (Hatsukami *et al.* 2018 eSupplement [pg300]).

(a) Adverse Events

Significantly greater numbers of adverse events were observed in the immediate versus gradual nicotine reduction and control groups and between gradual versus control group. The differences between the immediate compared to the other two groups occurred during the first week, but not thereafter (Figure VIII.D-98). No differences were observed across groups for out of range blood pressure, heart rate or CO levels (Table VIII.D-66). These results would indicate that more self-reported adverse events would likely be experienced with immediate reduction, but many of these events might be associated with withdrawal from nicotine (Figure VIII.D-99). Other safety concerns were not evident. The number of adverse events by system are shown in Table VIII.D-67. The number one symptom was cough. The number of participants with adverse events

is shown in Table VIII.D-68. Seventeen per cent of the immediate group (88/503) reported cough as compared to 11 percent in the control (28/249).

(b) *Serious Adverse Events*

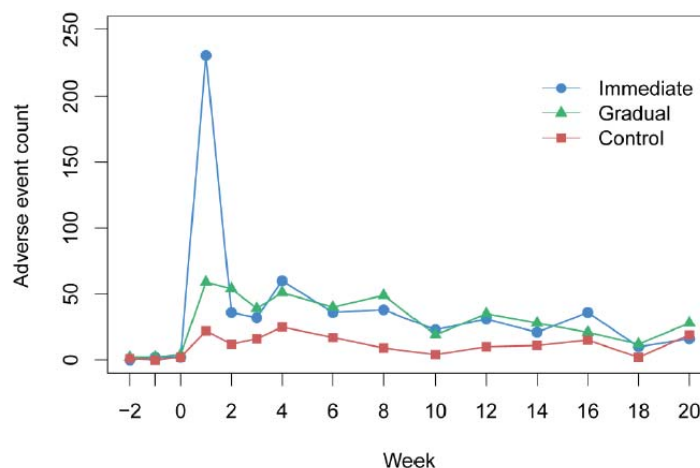
There was a total of 22/503 (4.3%) serious adverse events in the immediate group compared to 14/249 (5.6%) in the control (Table VIII.D-69). Table VIII.D-70 lists the serious adverse events. Table VIII.D-71 lists the non-serious and related adverse events.

(c) *Discontinuations*

Table VIII.D-72 lists the participants withdrawn after randomization due to a non-serious adverse event.

Figure VIII.D-98. Count of adverse events reported by week (From Hatsukami *et al* 2018 eSupplement [pg300])

eFigure 3. Count of Related Adverse Events Reported by Week (Safety Endpoint) ^{a,b}

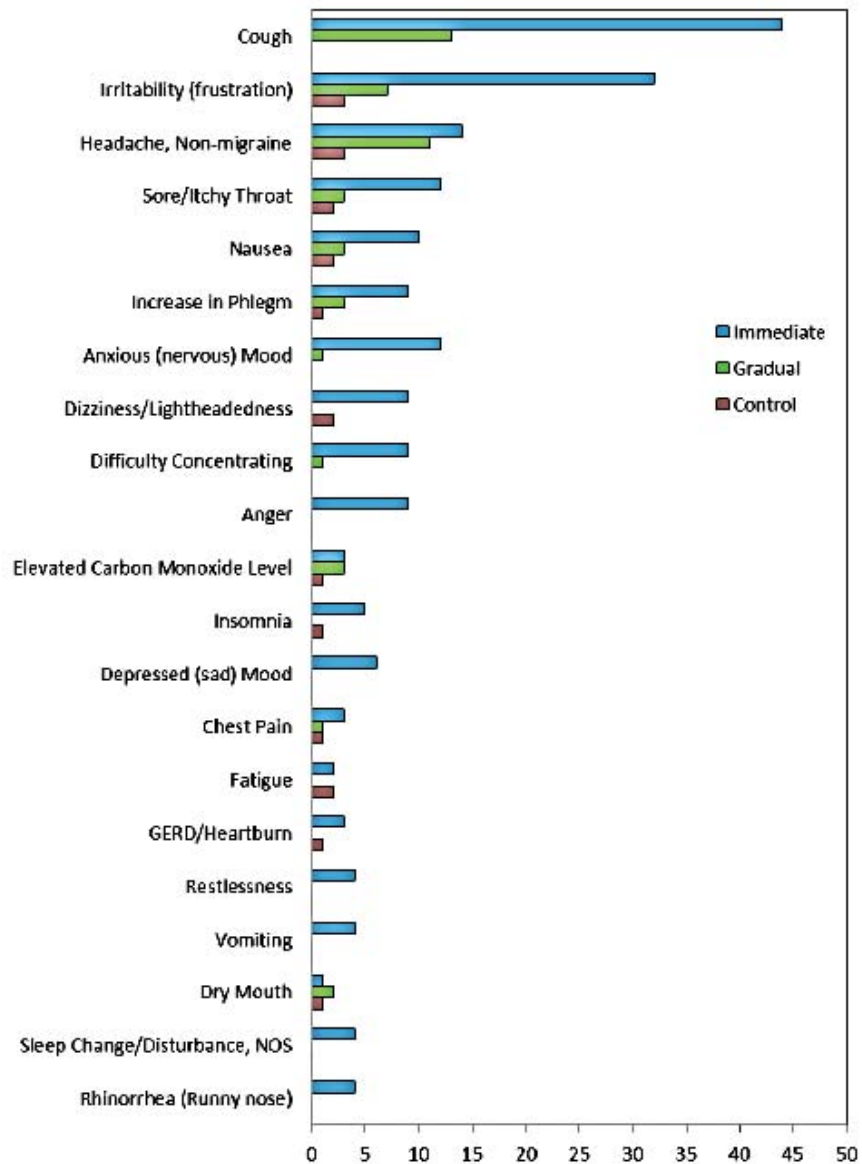


^aEvents that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Related events in the same participants would be counted as multiple events. Baseline (-2, 0) includes only events in participants that went on to be randomized.

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

Summary: Significantly greater number of AEs was observed in the immediate versus gradual and control groups, particularly at Week 1. See eTable 4.

eFigure 4. Top 20 Adverse Events Reported at Week 1 (Safety Endpoint) ^{a,b}



^aEvents that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Concurrent adverse events (e.g., cold symptoms) in the same participant would be counted as multiple events.

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

Summary: The greater rate of adverse symptoms in the immediate reduction group appears to be primarily related to symptoms of withdrawal from nicotine (e.g., mood and cough).

Table VIII.D-66. Adverse event counts (From Hatsukami *et al* 2018 eSupplement [pg300])

eTable 4. Adverse Events Counts, Out of Range Blood Pressure or Heart Rate, and Elevated Carbon Monoxide (Safety Endpoints)^{a,b}

| Measures | Week | Immediate vs. Gradual | | Immediate vs. Control | | Gradual vs. Control | |
|---|------|---------------------------|---------|---------------------------|---------|---------------------------|---------|
| | | Estimated IRR/OR (95% CI) | P Value | Estimated IRR/OR (95% CI) | P Value | Estimated IRR/OR (95% CI) | P Value |
| Total AE count during the experimental period ^c | 1-20 | 1.62 (1.29, 2.04) | <.0167 | 2.33 (1.74, 3.11) | <.0167 | 1.44 (1.08, 1.92) | <.0167 |
| AE count during 1st week of intervention ^c | 1 | 4.01 (2.78, 5.79) | <.0167 | 5.34 (3.18, 8.99) | <.0167 | 1.33 (0.76, 2.34) | .32 |
| Any out of range blood pressures or heart rates during the experimental period ^{d,e} | 1-20 | 0.68 (0.41, 1.13) | .14 | 1.09 (0.55, 2.16) | .81 | 1.60 (0.83, 3.10) | .16 |
| Any carbon monoxide levels \geq 50 ppm during the experimental period ^e | 1-20 | 0.56 (0.33, 0.96) | .033 | 0.54 (0.29, 1.00) | .051 | 0.96 (0.55, 1.69) | .89 |
| Any carbon monoxide levels \geq 70 ppm during the experimental period ^e | 1-20 | 0.49 (0.09, 2.70) | .42 | 0.49 (0.07, 3.52) | .48 | 1.00 (0.18, 5.50) | >.99 |

^aPs<.0167 were considered significant for safety endpoints, note that non-significant p values do not indicate absence of differences; Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=248).

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

^cNegative binomial regression of total adverse event (AE) count (Definitely Related/Possibly Related/Relationship Unknown), adjusting for AE count at baseline (Week 0), with estimated incidence rate ratio (IRR) between groups being presented.

^dOut of range blood pressure or heart rate was defined as either systolic \geq 160 or $<$ 90 or diastolic \geq 100 or $<$ 50 or heart rate \geq 105 or $<$ 45 bpm.

^eLogistic regression of any out of range events during Weeks 1-20, adjusting for any out of range events at baseline (Week 0), with estimated odds ratio (OR) between groups being presented.

Summary: Significantly greater numbers of adverse events were observed in the immediate versus gradual nicotine reduction and control groups and between gradual versus control group. The differences between the immediate compared to the other two groups occurred during the first week, but not thereafter (data not shown). No differences were observed across groups for out of range blood pressure, heart rate or CO levels. These results would indicate that more self-reported adverse events would likely be experienced with immediate reduction, but many of these events might be associated with withdrawal from nicotine (see eFigure 4). Other safety concerns were not evident.

Table VIII.D-67. Number of adverse events (From Hatsukami *et al* 2018 eSupplement [pg300])

eTable 5. Number of Adverse Events^{a,b}

| | Overall | Baseline n=1250 | Post Randomization | | |
|--|---------|--------------------|--------------------|------------------|------------------|
| | | | Immediate n=503 | Gradual n=498 | Control n=249 |
| Total Number of Person-Weeks of Follow-up | - | - | 7884 | 8812 | 4464 |
| Total Number of Events | 1182 | 15 | 570 | 435 | 162 |
| Number of Events per Symptom | | | | | |
| Cough | 229 | 4 | 105 | 90 | 30 |
| Elevated CESD ^c Score | 141 | 3 | 58 | 55 | 25 |
| Headache, Non-migraine | 76 | 0 | 31 | 36 | 9 |
| Irritability (Frustration) | 72 | 0 | 43 | 23 | 6 |
| Sore/Itchy Throat | 67 | 2 | 32 | 23 | 10 |
| Increase in Phlegm | 62 | 2 | 28 | 23 | 9 |
| Nausea | 40 | 0 | 23 | 13 | 4 |
| Depressed (Sad) Mood | 30 | 0 | 15 | 14 | 1 |
| Dizziness/Lightheadedness | 29 | 0 | 18 | 6 | 5 |
| Nasal Congestion | 25 | 1 | 11 | 7 | 6 |
| Rhinorrhea (Runny Nose) | 23 | 1 | 10 | 8 | 4 |
| Shortness of Breath | 23 | 0 | 7 | 12 | 4 |
| Elevated Carbon Monoxide Level | 21 | 1 | 6 | 9 | 5 |
| Fatigue | 20 | 0 | 12 | 3 | 5 |
| Insomnia | 20 | 0 | 9 | 7 | 4 |
| Anxious (Nervous) Mood | 18 | 0 | 13 | 4 | 1 |
| Chest Congestion | 17 | 0 | 8 | 6 | 3 |
| Anger | 15 | 0 | 13 | 2 | 0 |
| Difficulty Concentrating | 15 | 0 | 10 | 5 | 0 |
| Chest Pain | 13 | 0 | 6 | 4 | 3 |
| Sleep Change/Disturbance, NOS ^d | 13 | 0 | 8 | 4 | 1 |
| Gastroesophageal Reflux Disease/Heartburn | 11 | 0 | 7 | 3 | 1 |
| Headache, Migraine | 11 | 0 | 4 | 3 | 4 |
| Abnormal Blood Test, NOS ^d | 9 | 0 | 3 | 3 | 3 |
| Loss of Appetite | 9 | 0 | 6 | 2 | 1 |
| Vivid Dreams | 8 | 0 | 3 | 3 | 2 |
| Vomiting | 8 | 0 | 5 | 3 | 0 |
| Dry Mouth | 7 | 0 | 2 | 4 | 1 |
| Hypertension | 7 | 0 | 2 | 4 | 1 |
| Increased Appetite/Hunger | 7 | 0 | 2 | 3 | 2 |
| Stress | 7 | 0 | 4 | 2 | 1 |
| Suicidal Ideation | 7 | 0 | 4 | 2 | 1 |
| Mouth Problem, NOS ^d | 6 | 0 | 2 | 4 | 0 |
| Restlessness | 6 | 0 | 5 | 1 | 0 |
| Wheezing | 6 | 0 | 1 | 4 | 1 |
| Numbness/Tingling/Neuropathy | 5 | 0 | 2 | 3 | 0 |
| Gastrointestinal Pain | 5 | 0 | 3 | 2 | 0 |

| | | | Post Randomization | | |
|---|---------|--------------------|--------------------|------------------|------------------|
| | Overall | Baseline n=1250 | Immediate n=503 | Gradual n=498 | Control n=249 |
| Sneezing | 5 | 1 | 2 | 1 | 1 |
| Weight Change | 5 | 0 | 4 | 1 | 0 |
| Constipation | 5 | 0 | 4 | 1 | 0 |
| Panic/Anxiety Attack | 4 | 0 | 2 | 0 | 2 |
| Change in Taste/Smell | 4 | 0 | 2 | 1 | 1 |
| Asthma | 3 | 0 | 0 | 3 | 0 |
| Bacterial Infection | 3 | 0 | 2 | 0 | 1 |
| Bronchitis | 3 | 0 | 1 | 2 | 0 |
| Diarrhea | 3 | 0 | 1 | 1 | 1 |
| Dyspepsia | 3 | 0 | 2 | 1 | 0 |
| Eye Problem/Infection | 3 | 0 | 2 | 0 | 1 |
| Nose/Throat Problem, NOS ^d | 3 | 0 | 2 | 1 | 0 |
| Rash | 3 | 0 | 1 | 2 | 0 |
| Skin Issue, NOS ^d | 3 | 0 | 0 | 3 | 0 |
| Bipolar Disorder | 2 | 0 | 2 | 0 | 0 |
| Bruxism | 2 | 0 | 1 | 1 | 0 |
| Drug Use Problem | 2 | 0 | 2 | 0 | 0 |
| Fainting | 2 | 0 | 2 | 0 | 0 |
| Mood Swings | 2 | 0 | 2 | 0 | 0 |
| Nightmare/Terror | 2 | 0 | 0 | 1 | 1 |
| Lung Pain | 2 | 0 | 0 | 2 | 0 |
| Musculoskeletal Pain | 2 | 0 | 1 | 1 | 0 |
| Changes in Saliva Production | 2 | 0 | 2 | 0 | 0 |
| Alcohol Use Problem | 1 | 0 | 0 | 0 | 1 |
| Allergies (Seasonal) | 1 | 0 | 1 | 0 | 0 |
| Binge Eating | 1 | 0 | 0 | 1 | 0 |
| Bloating | 1 | 0 | 1 | 0 | 0 |
| Chronic Obstructed Airway Disease | 1 | 0 | 1 | 0 | 0 |
| Dehydration | 1 | 0 | 0 | 1 | 0 |
| Dental/Teeth Problem | 1 | 0 | 0 | 1 | 0 |
| Depression, Clinical Diagnosis | 1 | 0 | 0 | 1 | 0 |
| Erectile Dysfunction | 1 | 0 | 1 | 0 | 0 |
| Excessive Sweating | 1 | 0 | 1 | 0 | 0 |
| Fever | 1 | 0 | 0 | 1 | 0 |
| Hair Loss | 1 | 0 | 0 | 1 | 0 |
| Hot Flashes | 1 | 0 | 0 | 1 | 0 |
| Kidney/Bladder/Urinary Problems, NOS ^d | 1 | 0 | 1 | 0 | 0 |
| Laryngitis | 1 | 0 | 1 | 0 | 0 |
| Lung "Fullness" | 1 | 0 | 0 | 1 | 0 |
| Mania | 1 | 0 | 0 | 1 | 0 |
| Nasal/Sinus Drainage | 1 | 0 | 0 | 1 | 0 |
| Nosebleed/Dry Nasal Membrane | 1 | 0 | 0 | 1 | 0 |

| | | | Post Randomization | | |
|-------------------------|---------|--------------------|--------------------|------------------|------------------|
| | Overall | Baseline n=1250 | Immediate n=503 | Gradual n=498 | Control n=249 |
| Pain at Phlebotomy Site | 1 | 0 | 1 | 0 | 0 |
| Fibromyalgia Pain | 1 | 0 | 1 | 0 | 0 |
| Sinus Pain | 1 | 0 | 0 | 1 | 0 |
| Pneumonia | 1 | 0 | 0 | 1 | 0 |
| Tachycardia | 1 | 0 | 1 | 0 | 0 |
| Tremors | 1 | 0 | 1 | 0 | 0 |
| Vertigo/Disequilibrium | 1 | 0 | 1 | 0 | 0 |

*Events that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Concurrent adverse events (e.g., cold symptoms) in the same participant would be counted as multiple events. Baseline refers only to events in participants who went on to be randomized.

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

^cCenter for Epidemiological Studies Depression Scale

^dNot Otherwise Specified

eTable 6. Number of Participants with Adverse Events ^{a,b}

| | Overall | Baseline n=1250 | Post Randomization | | |
|---|-------------------|--------------------|--------------------|------------------|------------------|
| | | | Immediate n=503 | Gradual n=498 | Control n=249 |
| Total Number of Person-Weeks of Follow-up | - | - | 7884 | 8812 | 4464 |
| Number of Participants with any Symptom | 1056 ^c | 15 | 512 | 385 | 147 |
| Number of Participants with Each Symptom | | | | | |
| Cough | 196 ^c | 4 | 88 | 77 | 28 |
| Elevated CESD ^d Score | 110 ^c | 3 | 47 | 41 | 20 |
| Irritability (Frustration) | 68 | 0 | 40 | 22 | 6 |
| Headache, Non-migraine | 64 | 0 | 29 | 28 | 7 |
| Sore/Itchy Throat | 61 | 2 | 30 | 20 | 9 |
| Increase in Phlegm | 52 ^c | 2 | 24 | 20 | 7 |
| Nausea | 39 | 0 | 22 | 13 | 4 |
| Depressed (Sad) Mood | 29 | 0 | 15 | 13 | 1 |
| Dizziness/Lightheadedness | 27 | 0 | 17 | 5 | 5 |
| Rhinorrhea (Runny Nose) | 21 | 1 | 8 | 8 | 4 |
| Insomnia | 20 | 0 | 9 | 7 | 4 |
| Nasal Congestion | 20 | 1 | 8 | 7 | 4 |
| Shortness of Breath | 20 | 0 | 6 | 10 | 4 |
| Fatigue | 19 | 0 | 11 | 3 | 5 |
| Anxious (Nervous) Mood | 18 | 0 | 13 | 4 | 1 |
| Elevated Carbon Monoxide Level | 18 | 1 | 5 | 7 | 5 |
| Chest Congestion | 17 | 0 | 8 | 6 | 3 |
| Difficulty Concentrating | 15 | 0 | 10 | 5 | 0 |
| Anger | 14 | 0 | 12 | 2 | 0 |
| Chest Pain | 13 | 0 | 6 | 4 | 3 |
| Sleep Change/Disturbance, NOS ^e | 12 | 0 | 7 | 4 | 1 |
| Gastroesophageal Reflux Disease/Heartburn | 10 | 0 | 6 | 3 | 1 |
| Abnormal Blood Test, NOS ^e | 9 | 0 | 3 | 3 | 3 |
| Headache, Migraine | 9 | 0 | 3 | 3 | 3 |
| Loss of Appetite | 9 | 0 | 6 | 2 | 1 |
| Vivid Dreams | 8 | 0 | 3 | 3 | 2 |
| Dry Mouth | 7 | 0 | 2 | 4 | 1 |
| Hypertension | 7 | 0 | 2 | 4 | 1 |
| Increased Appetite/Hunger | 7 | 0 | 2 | 3 | 2 |
| Stress | 7 | 0 | 4 | 2 | 1 |
| Suicidal Ideation | 7 | 0 | 4 | 2 | 1 |
| Vomiting | 7 | 0 | 4 | 3 | 0 |
| Mouth Problem, NOS ^e | 6 | 0 | 2 | 4 | 0 |
| Restlessness | 6 | 0 | 5 | 1 | 0 |
| Wheezing | 6 | 0 | 1 | 4 | 1 |
| Constipation | 5 | 0 | 4 | 1 | 0 |
| Numbness/Tingling/Neuropathy | 5 | 0 | 2 | 3 | 0 |
| Sneezing | 5 | 1 | 2 | 1 | 1 |

| | | | Post Randomization | | |
|---|---------|--------------------|--------------------|------------------|------------------|
| | Overall | Baseline n=1250 | Immediate n=503 | Gradual n=498 | Control n=249 |
| Weight Change | 5 | 0 | 4 | 1 | 0 |
| Gastrointestinal Pain | 4 | 0 | 2 | 2 | 0 |
| Panic/Anxiety Attack | 4 | 0 | 2 | 0 | 2 |
| Bacterial Infection | 3 | 0 | 2 | 0 | 1 |
| Bronchitis | 3 | 0 | 1 | 2 | 0 |
| Diarrhea | 3 | 0 | 1 | 1 | 1 |
| Dyspepsia | 3 | 0 | 2 | 1 | 0 |
| Eye Problem/Infection | 3 | 0 | 2 | 0 | 1 |
| Nose/Throat Problem, NOS ^e | 3 | 0 | 2 | 1 | 0 |
| Rash | 3 | 0 | 1 | 2 | 0 |
| Skin Issue, NOS ^e | 3 | 0 | 0 | 3 | 0 |
| Change in Taste/Smell | 3 | 0 | 1 | 1 | 1 |
| Bruxism | 2 | 0 | 1 | 1 | 0 |
| Drug Use Problem | 2 | 0 | 2 | 0 | 0 |
| Fainting | 2 | 0 | 2 | 0 | 0 |
| Nightmare/Terror | 2 | 0 | 0 | 1 | 1 |
| Lung Pain | 2 | 0 | 0 | 2 | 0 |
| Musculoskeletal Pain | 2 | 0 | 1 | 1 | 0 |
| Changes in Saliva Production | 2 | 0 | 2 | 0 | 0 |
| Alcohol Use Problem | 1 | 0 | 0 | 0 | 1 |
| Allergies (Seasonal) | 1 | 0 | 1 | 0 | 0 |
| Asthma | 1 | 0 | 0 | 1 | 0 |
| Binge Eating | 1 | 0 | 0 | 1 | 0 |
| Bipolar Disorder | 1 | 0 | 1 | 0 | 0 |
| Bloating | 1 | 0 | 1 | 0 | 0 |
| Chronic Obstructed Airway Disease | 1 | 0 | 1 | 0 | 0 |
| Dehydration | 1 | 0 | 0 | 1 | 0 |
| Dental/Teeth Problem | 1 | 0 | 0 | 1 | 0 |
| Depression, Clinical Diagnosis | 1 | 0 | 0 | 1 | 0 |
| Erectile Dysfunction | 1 | 0 | 1 | 0 | 0 |
| Excessive Sweating | 1 | 0 | 1 | 0 | 0 |
| Fever | 1 | 0 | 0 | 1 | 0 |
| Hair Loss | 1 | 0 | 0 | 1 | 0 |
| Hot Flashes | 1 | 0 | 0 | 1 | 0 |
| Kidney/Bladder/Urinary Problems, NOS ^e | 1 | 0 | 1 | 0 | 0 |
| Laryngitis | 1 | 0 | 1 | 0 | 0 |
| Lung "Fullness" | 1 | 0 | 0 | 1 | 0 |
| Mania | 1 | 0 | 0 | 1 | 0 |
| Mood Swings | 1 | 0 | 1 | 0 | 0 |
| Nasal Sinus Drainage | 1 | 0 | 0 | 1 | 0 |
| Nosebleed/Dry Nasal Membrane | 1 | 0 | 0 | 1 | 0 |
| Pain at Phlebotomy Site | 1 | 0 | 1 | 0 | 0 |

| | Overall | Post Randomization | | | |
|------------------------|---------|--------------------|--------------------|------------------|------------------|
| | | Baseline n=1250 | Immediate n=503 | Gradual n=498 | Control n=249 |
| Fibromyalgia Pain | 1 | 0 | 1 | 0 | 0 |
| Sinus Pain | 1 | 0 | 0 | 1 | 0 |
| Pneumonia | 1 | 0 | 0 | 1 | 0 |
| Tachycardia | 1 | 0 | 1 | 0 | 0 |
| Tremors | 1 | 0 | 1 | 0 | 0 |
| Vertigo/Disequilibrium | 1 | 0 | 1 | 0 | 0 |

^aEvents that were Definitely Related, Probably Related or Relationship Unknown were counted on a per participant basis. Baseline reflects randomized participants.

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

^cSymptom reported by same subject during baseline and post randomization.

^dCenter for Epidemiological Studies Depression Scale

^eNot Otherwise Specified

Table VIII.D-69. Count of serious and severe adverse events (From Hatsukami *et al* 2018 eSupplement [pg300])

eTable 7. Count of Serious and Severe Adverse Events^{a,b}

| | Overall | | Post Randomization | | | Follow-up | | |
|---|------------------|--------------------|--------------------|------------------|------------------|--------------------|------------------|------------------|
| | | Baseline n=1250 | Immediate n=503 | Gradual n=498 | Control n=249 | Immediate N=340 | Gradual n=400 | Control n=210 |
| Serious Adverse Events | | | | | | | | |
| Number of serious adverse events (related/unrelated) | 74 | 4 | 21 | 25 | 13 | 4 | 5 | 2 |
| Number of serious adverse events (related, possibly related or unknown) | 6 | 0 | 1 | 3 | 1 | 0 | 1 ^c | 0 |
| Severe Adverse Events Including Serious Adverse Events | | | | | | | | |
| Number of severe adverse events (related/unrelated) | 317 ^d | 20 | 111 | 113 | 49 | 9 | 10 | 7 |
| Number of severe adverse events (related, possibly related or unknown) | 21 | 0 | 9 | 9 | 3 | 0 | 0 | 0 |

^aBaseline reflects randomized participants.

^bAdverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

^cSerious adverse event related to study procedure.

^dTwo participants reported the same symptom at baseline and post randomization.

Summary: Immediate reduction did not result in greater serious and/or severe adverse events, related and/or unrelated to study cigarettes, compared to gradual or control groups.

Table VIII.D-70. Serious adverse events: related, possibly related and unknown (From Hatsukami *et al* 2018 eSupplement [pg300])

eTable 8. Serious Adverse Events (SAE): Related, Possibly Related and Unknown

| # | Week | Seriousness | Relatedness | Event Description |
|---|-----------------------|----------------------------|------------------|--|
| SAE's Post Randomization – Immediate Group (N | | | | |
| 1 | 12 | Hospitalization | Unknown | Surgery unknown etiology |
| SAE's Post Randomization – Gradual Group | | | | |
| 1 | 12 | Hospitalization | Possibly Related | Pneumonia / lung infection |
| 2 | 8 | Hospitalization | Possibly Related | Asthma exacerbation |
| 3 | 18 | Hospitalization | Possibly Related | Flu-like symptoms and shortness of breath due to reactive airway disease |
| SAE's Post Randomization – Control Group | | | | |
| 1 | 18 | Hospitalization | Possibly Related | Chest pain secondary to anxiety attack |
| SAE's During Follow-up – Gradual Group^c | | | | |
| 1 | Exit Visit (~Week 18) | Other Serious Intervention | Related | Seizure during breath holding for CO test |

eTable 9. Non-Serious Severe and Related^a Adverse Events

| # | Week reported | Event |
|------------------------|---------------|-----------------------------------|
| Immediate Group | | |
| 1 | 10 | Depressed (sad) mood |
| 2 ^b | 6, 8 | Worsening of psychiatric symptoms |
| 3 ^b | 8 | Suicidal ideation |
| 4 | 4 | Drug use problem |
| 5 | 4 | Dizziness/Lightheadedness |
| 6 | 1 | Anxious (nervous) mood |
| 7 | 1 | Irritability |
| 8 | 2 | Elevated carbon monoxide level |
| Gradual Group | | |
| 1 | 2 | Headache, Non-migraine |
| 2 ^c | 8 | Cough |
| 3 ^c | 8 | Increased phlegm |
| 4 ^c | 8 | Rhinitis (runny nose) |
| 5 ^c | 8 | Shortness of breath |
| 6 | 4 | Rash |
| Control Group | | |
| 1 | 18 | Depressed (sad) mood |
| 2 | 20 | Cough |

^aOnly includes Related, Possibly Related or Relationship Unknown.

^bSame participant, multiple symptoms reported

^cSame participant, multiple symptoms reported

Table VIII.D-72. Participants withdrawn due to non-serious adverse events (From Hatsukami *et al* 2018 eSupplement [pg300])

eTable 10. Participants Withdrawn, Post-Randomization, Due to Non-Serious Adverse Events

| # | Week Withdrawn | Severity | Relatedness | Event description |
|---|----------------|----------|-----------------------------|--|
| Immediate Group – Subject Self Withdrawn | | | | |
| 1 | 2 | Mild | Related | Withdrawal symptoms |
| 2 | 3 | Mild | Possibly Related | Cough, throat irritation |
| 3 | 2 | Mild | Remotely (Unlikely) Related | Muscle spasm |
| 4 | 2 | Severe | Unrelated | Traumatic injury |
| 5 | 3 | Severe | Remotely (Unlikely) Related | Kidney stones/pancreatitis |
| Immediate Group – PI Withdrawn due to AE | | | | |
| 1 | 2 | Severe | Related | CO exceeded study safety standards |
| 2 | 1 | Mild | Possibly Related | Suicidal ideation (history of depressive symptoms) |
| 3 | 1 | Mild | Possibly Related | Suicidal ideation (history of depression) |
| Gradual Group – Subject Self Withdrawn | | | | |
| 1 | 2 | Mild | Related | Headaches |
| 2 | 6 | Mild | Possibly Related | Racing thoughts and risk of relapse to drug use |
| 3 | 6 | Moderate | Remotely (Unlikely) Related | Sublingual growths |
| Gradual Group – PI Withdrawn due to AE | | | | |
| 1 | 8 | Moderate | Unrelated | Unstable health |
| 2 | 3 | Mild | Unrelated | Untreated high blood pressure |

iv. Reduced Nicotine Standards for Cigarettes: A Randomized Trial

Donny *et al.*, (2015) [pg299] conducted a double-blind, parallel, randomized clinical trial at 10 sites enrolling 840 subjects. Subjects were randomly assigned to smoke either their usual brand of cigarettes or one of six types SPECTRUM cigarettes, provided free, for 6 weeks. The investigational cigarettes had nicotine content ranging from 0.4 mg per gram of tobacco to 15.8 mg per gram (typical of commercial brands). The primary outcome was the number of cigarettes smoked per day during week 6. Subjective measures of dependence, withdrawal, and smoking urges were collected. Biomarkers of exposure and were measured in urine at 2- and 6-weeks. Topography was also measured at 2- and 6-weeks. Abstinence (no smoking for ≥ 18 hours) was measured after 6 weeks of product use. Adverse event data may be found in the supplement available on the journal website.

(a) Adverse Events

The number of adverse events and the number of participants with an adverse event are shown in Table VIII.D-73 and Table VIII.D-74, respectively. No significant differences between the groups were found in the total number of related or possibly related events ($p=0.37$). Participant ratings of overall health and symptoms specific to respiratory health (cough, phlegm production, shortness of breath, and irritation in throat and lungs) were not significantly related to condition.

(b) Serious Adverse Events

None of the serious events were judged to be related or possibly related (Table VIII.D-75).

(c) *Discontinuations*

Table VIII.D-76 lists the Serious Events, Severe Events and Withdrawals. One subject in the 0.4 mg/g group was withdrawn from the study after hospitalization for suicidal ideation. The investigator concluded that this event was remotely (unlikely) related.

Table VIII.D-73. Number of adverse events (From Donny *et al.* 2015 [pg299]).

Table S46. Number of events

| Description | Overall | Baseline | Post-randomization | | | | | | |
|--|---------|----------|--------------------|-----------|----------|----------|----------|----------|-------------------|
| | | | Usual brand | 15.8 mg/g | 5.2 mg/g | 2.4 mg/g | 1.3 mg/g | 0.4 mg/g | 0.4 mg/g high tar |
| TOTAL EVENTS (PER SYMPTOM) | 2609 | 620 | 221 | 312 | 276 | 288 | 292 | 287 | 313 |
| Abdominal aortic aneurysm | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abscess, Dental | 8 | 3 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Abscess, Other | 3 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Acne | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Acute myeloid leukemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Alcohol use problem | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Allergic Reaction | 6 | 1 | 1 | 0 | 2 | 0 | 0 | 1 | 1 |
| Allergies (seasonal) | 28 | 14 | 1 | 0 | 3 | 3 | 2 | 3 | 2 |
| Anaphylactic shock | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anger | 10 | 2 | 1 | 1 | 2 | 0 | 1 | 1 | 2 |
| Angina | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxiety, clinical diagnosis | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxious (nervous) mood* | 42 | 4 | 8 | 5 | 5 | 5 | 8 | 3 | 4 |
| Arthritis | 4 | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 0 |
| Asthma | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Binge eating | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bladder cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bloating | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Body aches | 30 | 5 | 3 | 3 | 7 | 2 | 2 | 5 | 3 |
| Bone fracture | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Bradycardia (Slow heart rate) | 4 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| Bronchitis | 5 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Burn | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Candidiasis | 5 | 0 | 1 | 1 | 1 | 0 | 0 | 2 | 0 |
| Cervical cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills | 21 | 4 | 1 | 4 | 0 | 5 | 2 | 1 | 4 |
| Chronic obstructed airway disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cold sore | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cold/clammy/pale skin | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Congenital anomaly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 9 | 0 | 1 | 1 | 3 | 1 | 2 | 1 | 0 |
| Coronary heart disease | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Cough | 273 | 67 | 17 | 25 | 26 | 36 | 34 | 29 | 39 |
| Death | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Decreased Libido | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Deep vein thrombosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dehydration | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Delirium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dental Procedure | 21 | 7 | 3 | 4 | 1 | 2 | 2 | 0 | 2 |
| Depressed (sad) mood* | 48 | 11 | 6 | 5 | 5 | 4 | 8 | 6 | 3 |
| Depression (clinical diagnosis; CESD > 15) | 277 | 124 | 18 | 24 | 20 | 20 | 25 | 20 | 26 |
| Diarrhea | 32 | 7 | 3 | 5 | 5 | 4 | 2 | 2 | 4 |
| Difficulty concentrating* | 5 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 |
| Dizziness | 23 | 1 | 1 | 4 | 1 | 3 | 6 | 3 | 4 |
| Drug use problem | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dry Mouth | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Dyspepsia | 15 | 1 | 4 | 0 | 5 | 1 | 3 | 1 | 0 |
| Ear infection | 6 | 2 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |

| | | | | | | | | | |
|---|-----|----|----|----|----|----|----|----|----|
| Elevated carbon monoxide level | 11 | 0 | 0 | 3 | 1 | 2 | 2 | 1 | 2 |
| Emphysema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Esophageal cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Excessive sweating | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Eye irritation | 19 | 4 | 0 | 4 | 6 | 0 | 4 | 1 | 0 |
| Fainting | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Fall | 5 | 2 | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| Fatigue | 54 | 6 | 5 | 9 | 9 | 7 | 3 | 7 | 8 |
| Fever | 30 | 10 | 3 | 3 | 1 | 2 | 3 | 5 | 3 |
| Foamy Saliva | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Frequent bowel movements | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| Gagging | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Gastroesophageal reflux disease (GERD) | 8 | 1 | 0 | 2 | 0 | 2 | 1 | 1 | 1 |
| Gum sensitivity | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hallucination | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache, Migraine | 18 | 2 | 2 | 1 | 3 | 2 | 1 | 5 | 2 |
| Headache, Non-migraine | 128 | 17 | 9 | 18 | 17 | 18 | 14 | 16 | 19 |
| Hearing loss | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Heart palpitation | 4 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| Heat exhaustion | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hemorrhoids | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Hernia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Homicidal Ideation | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hospitalization | 12 | 4 | 0 | 2 | 0 | 1 | 1 | 3 | 1 |
| Hot Flashes | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hypercholesterolemia (High Cholesterol) | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperglycemia (High blood sugar) | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hypertension (High BP) | 65 | 16 | 10 | 10 | 4 | 11 | 6 | 3 | 5 |
| Hypoglycemia (Low blood sugar) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypotension (Low BP) | 4 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 |
| Impotence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Increased appetite/hunger | 9 | 0 | 0 | 3 | 1 | 0 | 0 | 4 | 1 |
| Injury, Musculoskeletal | 15 | 1 | 4 | 3 | 2 | 1 | 0 | 1 | 3 |
| Injury, Other | 12 | 0 | 1 | 4 | 3 | 0 | 1 | 3 | 0 |
| Injury, Traumatic | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Insomnia* | 30 | 2 | 2 | 5 | 4 | 2 | 3 | 7 | 5 |
| Irritability (frustration)* | 34 | 2 | 3 | 4 | 4 | 5 | 4 | 6 | 6 |
| Itchy Skin | 6 | 0 | 2 | 2 | 0 | 0 | 1 | 0 | 1 |
| Jaundice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Kidney cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Kidney or bladder problem | 4 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 |
| Laryngitis | 9 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 1 |
| Larynx cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of Appetite | 7 | 0 | 0 | 3 | 1 | 1 | 1 | 1 | 0 |
| Low birth weight | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Low bone density | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lung cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mania | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Medical Procedure | 41 | 14 | 5 | 5 | 2 | 6 | 3 | 3 | 3 |
| Medication change | 248 | 80 | 25 | 22 | 23 | 29 | 13 | 23 | 33 |
| Menstrual cramps | 8 | 1 | 0 | 0 | 2 | 1 | 1 | 2 | 1 |
| MRSA | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle spasm | 8 | 0 | 4 | 2 | 1 | 0 | 1 | 0 | 0 |
| Myocardial infarction (Heart attack) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasal congestion | 119 | 34 | 8 | 14 | 10 | 16 | 9 | 14 | 14 |
| Nasal sinus drainage | 30 | 7 | 1 | 4 | 5 | 2 | 4 | 5 | 2 |
| Nausea | 66 | 7 | 1 | 11 | 9 | 11 | 10 | 14 | 3 |

| | | | | | | | | | |
|-------------------------------|-----|----|----|----|----|----|----|----|----|
| Nightmare/terror* | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Nosebleed | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Numbness | 6 | 1 | 0 | 0 | 1 | 0 | 3 | 0 | 1 |
| Other | 4 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 1 |
| Pain, Arthritis | 13 | 2 | 3 | 3 | 0 | 1 | 3 | 1 | 0 |
| Pain, Chest | 11 | 2 | 1 | 1 | 1 | 3 | 1 | 2 | 0 |
| Pain, Fibromyalgia | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain, Musculoskeletal | 84 | 19 | 9 | 10 | 6 | 12 | 11 | 8 | 9 |
| Pain, Other | 43 | 5 | 4 | 8 | 3 | 5 | 7 | 6 | 5 |
| Pain, Sinus | 20 | 4 | 1 | 0 | 3 | 2 | 2 | 3 | 5 |
| Pancreatic cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Peripheral vascular disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia | 5 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Pregnancy | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Preterm delivery | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary congestion | 41 | 7 | 2 | 7 | 3 | 3 | 8 | 4 | 7 |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Purging | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash | 5 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| Reduced blood circulation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory depression | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rhinorrhea (Runny nose) | 120 | 35 | 6 | 8 | 15 | 15 | 13 | 14 | 14 |
| Ruptured Cyst | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Seizure/convulsion | 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| Sensitivity to Light | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Shingles | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Shortness of breath | 27 | 3 | 4 | 4 | 3 | 4 | 1 | 1 | 7 |
| Sight loss | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sneezing | 37 | 10 | 3 | 6 | 5 | 4 | 1 | 2 | 6 |
| Sore throat | 108 | 23 | 10 | 11 | 13 | 13 | 16 | 9 | 13 |
| Sprain | 8 | 3 | 1 | 0 | 0 | 0 | 3 | 0 | 1 |
| Stillbirth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomach cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomach cramps | 6 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 2 |
| Stroke | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Suicidal ideation | 10 | 2 | 0 | 0 | 2 | 1 | 3 | 2 | 0 |
| Suicide | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Surgery, emergency | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Surgery, non-emergency | 8 | 3 | 0 | 1 | 1 | 0 | 1 | 0 | 2 |
| Swelling | 11 | 2 | 1 | 1 | 0 | 1 | 3 | 2 | 1 |
| Tachycardia (Fast heart rate) | 3 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Throat cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tonsillitis | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Toothache | 39 | 5 | 5 | 7 | 6 | 3 | 4 | 3 | 6 |
| Tremors | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Ulcer | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Ulcerative Colitis | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Urinary Tract Infection | 7 | 2 | 0 | 1 | 0 | 0 | 1 | 2 | 1 |
| Vision blurred | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vivid Dreams | 3 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| Vomiting | 46 | 7 | 4 | 6 | 6 | 5 | 7 | 5 | 6 |
| Weakness | 5 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 |

* Symptom had a significant impact on daily life, caused major disruption of functioning, or a medication was taken for it.

Note: events were counted on a per symptom basis. Related events in the same participants would be counted as multiple events. Baseline refers only to participants that were randomized.

Table S47. Number of participants with an event

| Description | Overall | Post-randomization | | | | | | | |
|--|---------|--------------------|-------------|-----------|----------|----------|----------|----------|-------------------|
| | | Baseline | Usual brand | 15.8 mg/g | 5.2 mg/g | 2.4 mg/g | 1.3 mg/g | 0.4 mg/g | 0.4 mg/g high tar |
| NUMBER OF PARTICIPANTS WITH ANY EVENT | 692 | 351 | 82 | 97 | 84 | 87 | 93 | 93 | 92 |
| Abdominal aortic aneurysm | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abscess, Dental | 8 | 3 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Abscess, Other | 3 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Acne | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Acute myeloid leukemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Alcohol use problem | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Allergic Reaction | 6 | 1 | 1 | 0 | 2 | 0 | 0 | 1 | 1 |
| Allergies (seasonal) | 25 | 14 | 1 | 0 | 3 | 3 | 2 | 2 | 2 |
| Anaphylactic shock | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anger | 10 | 2 | 1 | 1 | 2 | 0 | 1 | 1 | 2 |
| Angina | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxiety, clinical diagnosis | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxious (nervous) mood* | 38 | 4 | 7 | 5 | 4 | 4 | 7 | 3 | 4 |
| Arthritis | 4 | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 0 |
| Asthma | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Binge eating | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bladder cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bloating | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Body aches | 29 | 5 | 3 | 3 | 7 | 2 | 2 | 5 | 3 |
| Bone fracture | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Bradycardia (Slow heart rate) | 4 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| Bronchitis | 5 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Burn | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Candidiasis | 5 | 0 | 1 | 1 | 1 | 0 | 0 | 2 | 0 |
| Cervical cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills | 21 | 4 | 1 | 4 | 0 | 5 | 2 | 1 | 4 |
| Chronic obstructed airway disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cold sore | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cold/clammy/pale skin | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Congenital anomaly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 9 | 0 | 1 | 1 | 3 | 1 | 2 | 1 | 0 |
| Coronary heart disease | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Cough | 236 | 65 | 14 | 22 | 24 | 32 | 31 | 26 | 33 |
| Death | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Decreased Libido | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Deep vein thrombosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dehydration | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Delirium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dental Procedure | 21 | 7 | 3 | 4 | 1 | 2 | 2 | 0 | 2 |
| Depressed (sad) mood* | 46 | 11 | 6 | 4 | 5 | 4 | 8 | 6 | 3 |
| Depression, clinical diagnosis (CESD > 15) | 226 | 124 | 18 | 24 | 19 | 20 | 25 | 20 | 25 |
| Diarrhea | 30 | 7 | 3 | 4 | 5 | 4 | 2 | 2 | 4 |
| Difficulty concentrating* | 5 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 |
| Dizziness | 22 | 1 | 1 | 4 | 1 | 3 | 5 | 3 | 4 |
| Drug use problem | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dry Mouth | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Dyspepsia | 15 | 1 | 4 | 0 | 5 | 1 | 3 | 1 | 0 |
| Ear infection | 6 | 2 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |

| | | | | | | | | | |
|---|-----|----|----|----|----|----|----|----|----|
| Elevated carbon monoxide level | 10 | 0 | 0 | 3 | 1 | 2 | 2 | 1 | 1 |
| Emphysema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Esophageal cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Excessive sweating | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Eye irritation | 17 | 4 | 0 | 3 | 6 | 0 | 4 | 1 | 0 |
| Fainting | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Fall | 5 | 2 | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| Fatigue | 53 | 6 | 5 | 9 | 8 | 7 | 3 | 7 | 8 |
| Fever | 30 | 10 | 3 | 3 | 1 | 2 | 3 | 5 | 3 |
| Foamy Saliva | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Frequent bowel movements | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| Gagging | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Gastroesophageal reflux disease (GERD) | 7 | 1 | 0 | 2 | 0 | 2 | 1 | 1 | 1 |
| Gum sensitivity | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hallucination | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache, Migraine | 18 | 2 | 2 | 1 | 3 | 2 | 1 | 5 | 2 |
| Headache, Non-migraine | 113 | 17 | 9 | 17 | 15 | 18 | 10 | 14 | 17 |
| Hearing loss | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Heart palpitation | 4 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| Heat exhaustion | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hemorrhoids | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hernia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Homicidal Ideation | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hospitalization | 10 | 3 | 0 | 2 | 0 | 1 | 1 | 2 | 1 |
| Hot Flashes | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hypercholesterolemia (High Cholesterol) | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperglycemia (High blood sugar) | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hypertension (High BP) | 55 | 16 | 8 | 8 | 4 | 8 | 6 | 3 | 4 |
| Hypoglycemia (Low blood sugar) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypotension (Low BP) | 4 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 |
| Impotence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Increased appetite/hunger | 9 | 0 | 0 | 3 | 1 | 0 | 0 | 4 | 1 |
| Injury, Musculoskeletal | 14 | 1 | 4 | 2 | 2 | 1 | 0 | 1 | 3 |
| Injury, Other | 12 | 0 | 1 | 4 | 3 | 0 | 1 | 3 | 0 |
| Injury, Traumatic | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Insomnia* | 30 | 2 | 2 | 5 | 4 | 2 | 3 | 7 | 5 |
| Irritability (frustration)* | 33 | 2 | 3 | 4 | 4 | 5 | 4 | 6 | 5 |
| Itchy Skin | 6 | 0 | 2 | 2 | 0 | 0 | 1 | 0 | 1 |
| Jaundice | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Kidney cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Kidney or bladder problem | 4 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 |
| Laryngitis | 7 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 1 |
| Larynx cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Loss of Appetite | 7 | 0 | 0 | 3 | 1 | 1 | 1 | 1 | 0 |
| Low birth weight | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Low bone density | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lung cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mania | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Medical Procedure | 32 | 12 | 2 | 5 | 2 | 5 | 3 | 3 | 2 |
| Medication change | 168 | 58 | 20 | 18 | 17 | 16 | 10 | 19 | 22 |
| Menstrual cramps | 8 | 1 | 0 | 0 | 2 | 1 | 1 | 2 | 1 |
| MRSA | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle spasm | 7 | 0 | 4 | 1 | 1 | 0 | 1 | 0 | 0 |
| Myocardial infarction (Heart attack) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasal congestion | 115 | 34 | 7 | 13 | 10 | 16 | 8 | 14 | 13 |
| Nasal sinus drainage | 28 | 7 | 1 | 4 | 4 | 2 | 4 | 5 | 2 |
| Nausea | 61 | 7 | 1 | 10 | 9 | 10 | 9 | 13 | 3 |

| | | | | | | | | | |
|-------------------------------|-----|----|----|----|----|----|----|----|----|
| Nightmare/terror* | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Nosebleed | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Numbness | 5 | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 1 |
| Other | 3 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| Pain, Arthritis | 13 | 2 | 3 | 3 | 0 | 1 | 3 | 1 | 0 |
| Pain, Chest | 11 | 2 | 1 | 1 | 1 | 3 | 1 | 2 | 0 |
| Pain, Fibromyalgia | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain, Musculoskeletal | 76 | 19 | 9 | 9 | 6 | 11 | 10 | 8 | 9 |
| Pain, Other | 40 | 5 | 4 | 7 | 3 | 5 | 6 | 5 | 5 |
| Pain, Sinus | 17 | 4 | 1 | 0 | 3 | 2 | 2 | 3 | 5 |
| Pancreatic cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Peripheral vascular disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia | 5 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Pregnancy | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Preterm delivery | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary congestion | 40 | 7 | 2 | 6 | 3 | 3 | 8 | 4 | 7 |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Purging | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| Reduced blood circulation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory depression | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rhinorrhea (Runny nose) | 112 | 35 | 6 | 8 | 13 | 15 | 13 | 14 | 13 |
| Ruptured Cyst | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Seizure/convulsion | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Sensitivity to Light | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Shingles | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Shortness of breath | 27 | 3 | 4 | 4 | 3 | 4 | 1 | 1 | 7 |
| Sight loss | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sneezing | 36 | 10 | 3 | 6 | 5 | 4 | 1 | 2 | 6 |
| Sore throat | 100 | 23 | 10 | 10 | 13 | 12 | 14 | 9 | 12 |
| Sprain | 8 | 3 | 1 | 0 | 0 | 0 | 3 | 0 | 1 |
| Stillbirth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomach cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomach cramps | 6 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 2 |
| Stroke | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Suicidal ideation | 9 | 2 | 0 | 0 | 2 | 1 | 2 | 2 | 0 |
| Suicide | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Surgery, emergency | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Surgery, non-emergency | 7 | 3 | 0 | 1 | 1 | 0 | 1 | 0 | 2 |
| Swelling | 11 | 2 | 1 | 1 | 0 | 1 | 3 | 2 | 1 |
| Tachycardia (Fast heart rate) | 3 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Throat cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tonsillitis | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Toothache | 34 | 5 | 4 | 7 | 4 | 3 | 4 | 2 | 6 |
| Tremors | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Ulcer | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Ulcerative Colitis | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Urinary Tract Infection | 7 | 2 | 0 | 1 | 0 | 0 | 1 | 2 | 1 |
| Vision blurred | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vivid Dreams | 3 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| Vomiting | 45 | 7 | 4 | 6 | 6 | 5 | 7 | 5 | 6 |
| Weakness | 5 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 |

* Symptom had a significant impact on daily life, caused major disruption of functioning, or a medication was taken for it.
Note: events were counted on a per symptom basis. Baseline refers only to participants that were randomized.

Table VIII.D-75. Count of serious and severe adverse events (From Donny *et al.* 2015 [pg299])

Table S48. Count of serious and severe adverse events

| | Overall | Post-randomization | | | | | | | |
|---|---------|--------------------|-------------|-----------|----------|----------|----------|----------|-------------------|
| | | Baseline | Usual brand | 15.8 mg/g | 5.2 mg/g | 2.4 mg/g | 1.3 mg/g | 0.4 mg/g | 0.4 mg/g high tar |
| Number serious adverse events | 15 | 4 | 0 | 1 | 0 | 3 | 1 | 4 | 2 |
| Number serious adverse events (related or possibly related) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number severe adverse events | 24 | 4 | 1 | 2 | 1 | 4 | 3 | 8 | 1 |
| Number severe adverse events (related or possibly related) | 4 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |

Note: Multiple symptoms related to the same event in the same participant are only counted once. Baseline refers only to participants that were randomized.

Table VIII.D-76. Description of serious events, severe events and withdrawals (From Donny *et al.* 2015 [pg299])

Table S49. Description of serious events, severe events and withdrawals

| Seriousness | Severity | Relatedness | Withdrawn | Group | Description |
|----------------------------|--------------------------|-----------------------------|-----------|--------------------|--|
| Serious - Death | Severe | Unrelated | Yes | 0.4 mg/g | Cocaine and alcohol overdose |
| Serious - Life threatening | Severe | Unrelated | Yes | 2.4 mg/g | Tonic clonic seizure; manic episode (6) |
| Serious - Hospitalization | Severe | Unrelated | No | 2.4 mg/g | Atypical chest pain; negative EKG |
| Serious - Hospitalization | Severe | Unrelated | No | Baseline | Elective orthopedic surgery |
| Serious - Hospitalization | Severe | Unrelated | No | Baseline | Bowel obstruction |
| Serious - Hospitalization | Severe | Remotely (Unlikely) Related | Yes | 0.4 mg/g | Suicidal ideation |
| Serious - Hospitalization | Severe | Unrelated | Yes | 0.4 mg/g | Stomach ulcers |
| Serious - Hospitalization | Severe | Unrelated | No | 1.3 mg/g | Illicit drug impairment |
| Serious - Hospitalization | Severe | Unrelated | No | 0.4 mg/g | Cyst draining (2) |
| Serious - Hospitalization | Moderate (1), Severe (2) | Unrelated | No | Baseline | Influenza (3) |
| Serious - Hospitalization | Moderate | Unrelated | No | 0.4 mg/g, high tar | Fall; cellulitis |
| Serious - Hospitalization | Moderate | Unrelated | No | 2.4 mg/g | Hypertension |
| Serious - Hospitalization | Moderate | Unrelated | No | 0.4 mg/g, high tar | Running injury |
| Serious - Hospitalization | Moderate | Unrelated | No | Baseline | Infection |
| Serious - Hospitalization | Mild | Unrelated | No | 15.8 mg/g | Stomach virus |
| Not Serious | Severe | Related | Yes | 15.8 mg/g | Chest pain; headache; cough; sore throat |
| Not Serious | Severe | Possibly Related | Yes* | 0.4 mg/g | Unstable cardiovascular disease; myocardial infarction ruled out |
| Not Serious | Severe | Unrelated | No | 1.3 mg/g | Kidney infection |
| Not Serious | Severe | Possibly Related | No | 5.2 mg/g | Numbness in left arm and leg |
| Not Serious | Severe | Remotely (Unlikely) Related | No | 0.4 mg/g | Nausea; migraine headache (2) |
| Not Serious | Severe | Unrelated | No | 0.4 mg/g | Nausea, vomiting (2) |
| Not Serious | Severe | Remotely (Unlikely) Related | No | 2.4 mg/g | Laryngitis |
| Not Serious | Severe | Unrelated | No | 2.4 mg/g | Vomiting |
| Not Serious | Severe | Unrelated | No | Baseline | Depression, clinical diagnosis |
| Not Serious | Severe | Possibly Related | No | 0.4 mg/g, high tar | Anger |
| Not Serious | Severe | Unrelated | No | 15.8 mg/g | Dislocated shoulder due to fall |
| Not Serious | Severe | Unrelated | No | Usual Brand | Ruptured spleen during sporting activity |
| Not Serious | Severe | Unrelated | No | 1.3 mg/g | Tonsillitis; arthritis pain (6) |
| Not Serious | Moderate | Unrelated | No | 2.4 mg/g | MRSA contracted prior to randomization (post-randomization) |
| Not Serious | Mild | Possibly Related | Yes | 1.3 mg/g | expired carbon monoxide=116 |
| Not Serious | Mild | Remotely (Unlikely) Related | Yes | 0.4 mg/g, high tar | Hives; vomiting |
| Not Serious | Not Applicable | Not Applicable | Yes | 15.8 mg/g | non-medical; prior screening ineligibility |
| Not Serious | Not Applicable | Not Applicable | Yes | 15.8 mg/g | non-medical; inappropriate behavior towards staff |

All serious adverse events listed by category. Baseline refers only to participants that were randomized.

In parentheses: number of events (per symptom) if more than one per participant

*individual was withdrawn, but continued to complete interactive voice response (IVR) calls and therefore was included in the final analyses per intent-to-treat principles

v. *A Prospective, Double-blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of Quest Alone and in Combination with Nicotine Replacement Therapy as a Smoking Cessation Aid (IND 69185 [pg304])*

Results of this study were published by Becker, *et al.*, (2008) [pg297]. The IND report was filed by Vector Tobacco (Vector Tobacco Inc. 2006 [pg304]). This study was a randomized, double-blind, active controlled, parallel group, multi-center phase II clinical trial to evaluate the efficacy of reduced-nicotine cigarettes as a novel smoking cessation treatment under IND 69,185. Treatment consisted of 6 weeks of smoking a series of cigarettes with progressively lower nicotine content (Quest 1, Quest 2, and Quest 3, with smoking yields of 0.6, 0.3 and ≤ 0.05 mg nicotine/cigarette), either in combination with nicotine patch therapy (NRT) or placebo patches. Three hundred forty-six smokers of non-menthol cigarettes who were motivated to quit were randomized to one of 3 treatments:

- Group 1: Quest plus NRT patch,
- Group 2: Quest plus placebo patch, or
- Group 3: active control (conventional cigarette) plus NRT patch.

The primary endpoint was 4 weeks of continuous abstinence (Weeks 7 to 10), with follow-up at 3 and 6 months.

(a) *Adverse Events*

The proportion of treatment-emergent adverse events was 61.2% in Group 1, 52.6% in Group 2, and 60.5% in Group 3 (Table VIII.D-77).

(b) *Serious Adverse Events*

Serious AEs were reported for two subjects in Group 1 and for one subject in Group 3 (Table VIII.D-79). None of the SAEs were considered treatment related. The proportion of subjects reporting at least one treatment-related AE was 44% in Group 1, 27.6% in Group 2, and 36.8% in

Group 3 (Table VIII.D-77). The most common treatment-related AE consisted of psychiatric disorders (most frequently specified as insomnia, abnormal dreams, irritability, and anxiety), nervous system disorders, and general disorders and administration site problems. Headache was the most predominantly reported nervous system disorder. Application site problems were related to the NRT/placebo patch application included pruritis, dermatitis, discomfort, irritation, discoloration, and erythema (Table VIII.D-80).

Table VIII.D-77. Summary of adverse effects. (From Vector 2006, IND 69,185 [pg304]) (Columns are group 1, 2, and 3, respectively.)

**Table 25 Summary of Adverse Events
(Safety Population)**

| | Group 1 (N=116) | Group 2 (N=116) | Group 3 (N=116) |
|--------------------------------------|--------------------|--------------------|--------------------|
| Treatment-emergent AEs | 71 (61.2%) | 61 (52.6%) | 69 (60.5%) |
| | | | |
| Treatment-related AEs | 51 (44.0%) | 32 (27.6%) | 42 (36.8%) |
| Possibly Related | 38 (32.8%) | 24 (20.7%) | 34 (29.8%) |
| Probably Related | 10 (8.6%) | 7 (6.0%) | 8 (7.0%) |
| Definitely Related | 12 (10.3%) | 5 (4.3%) | 9 (7.9%) |
| | | | |
| Serious AEs | 2 (1.7%) | 0 | 1 (0.9%) |
| | | | |
| Treatment-related serious AEs | 0 | 0 | 0 |
| | | | |
| AEs leading to study product stopped | 4 (3.4%) | 1 (0.9%) | 4 (3.5%) |
| AEs leading to study discontinuation | 3 (2.6%) | 2 (1.7%) | 3 (2.6%) |

N = number of randomized subjects who received study treatment

% = $n/N \times 100\%$

Table VIII.D-78. Individual subjects who experienced adverse events leading to study termination (From Vector 2006, IND 69,185 [pg304]) (Columns are group 1, 2, and 3, respectively.)

Table 26 Subjects Who Experienced Adverse Events Directly or Indirectly Leading to Study Discontinuation

| Subject ID | Group | Adverse Event | Study Discontinued Due to AE? | Discontinued Due to AE? |
|------------|-------|--|-------------------------------|-------------------------|
| 01295 | 1 | Nausea | Yes | Yes |
| 03051 | 1 | Nausea / vivid dreams | Yes | No |
| 03067 | 1 | Rash, itchiness under patch site | Yes | Yes |
| 04015 | 1 | Chest urticaria | Yes | No |
| 03060 | 2 | Itchiness on chest and legs / redness under patch site | Yes | Yes |
| 01311 | 3 | Headache and cough | Yes | Yes |
| 02043 | 3 | Contact dermatitis | Yes | Yes |
| 05110 | 3 | Localized muscle aches under patch site | Yes | Yes |
| 05245 | 3 | Rash under patch site | Yes | No |
| 03064 | 1 | Chest pressure | No | Yes |
| 04003 | 2 | Shortness of breath / chest pain / insomnia | No | Yes |

Table VIII.D-79. Summary of serious adverse events by system organ. (From Vector 2006, IND 69,185 [pg304]))
(Columns are group 1, 2, and 3, respectively.)

Table 27 Summary of Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

| | Group 1 (N = 116) | Group 2 (N = 116) | Group 3 (N = 114) |
|--|----------------------|----------------------|----------------------|
| Subjects with Any Serious Adverse Events | 2 (2%) | 0 | 1 (<1%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 1 (<1%) | 0 | 0 |
| CHEST DISCOMFORT | 1 (<1%) | 0 | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 0 | 0 | 1 (<1%) |
| FIBULA FRACTURE | 0 | 0 | 1 (<1%) |
| TIBIA FRACTURE | 0 | 0 | 1 (<1%) |
| INVESTIGATIONS | 1 (<1%) | 0 | 0 |
| BLOOD PRESSURE INCREASED | 1 (<1%) | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 1 (<1%) | 0 | 0 |
| BLADDER NEOPLASM | 1 (<1%) | 0 | 0 |

N = number of randomized subjects who received study treatment

% = n/N x 100%

Table VIII.D-80. Summary of adverse events leading to discontinuation (From Vector 2006, IND 69,185 [pg304])
(Columns are group 1, 2, and 3, respectively.)

**Table 28 Summary of Adverse Events Leading Directly to Study Discontinuation
by System Organ Class and Preferred Term
(Safety Population)**

| | Group 1 (N = 116) | Group 2 (N = 116) | Group 3 (N = 124) |
|---|----------------------|----------------------|----------------------|
| Subjects with Any Adverse Events Leading to Study Product Stopped | 4 (3%) | 1 (<1%) | 4 (4%) |
| GASTROINTESTINAL DISORDERS | 2 (2%) | 0 | 0 |
| NAUSEA | 2 (2%) | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 1 (<1%) | 1 (<1%) | 2 (2%) |
| APPLICATION SITE DERMATITIS | 1 (<1%) | 0 | 1 (<1%) |
| APPLICATION SITE DISCOMFORT | 0 | 0 | 1 (<1%) |
| APPLICATION SITE ERYTHEMA | 0 | 1 (<1%) | 0 |
| APPLICATION SITE PRURITUS | 1 (<1%) | 0 | 0 |
| NERVOUS SYSTEM DISORDERS | 0 | 0 | 1 (<1%) |
| HEADACHE | 0 | 0 | 1 (<1%) |
| PSYCHIATRIC DISORDERS | 1 (<1%) | 0 | 0 |
| ABNORMAL DREAMS | 1 (<1%) | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| DERMATITIS CONTACT | 0 | 0 | 1 (<1%) |
| PRURITUS | 0 | 1 (<1%) | 0 |
| URTICARIA | 1 (<1%) | 0 | 0 |

N = number of randomized subjects who received study treatment

% = n/N x 100%

(c) *Discontinuation*

Table VIII.D-78 shows subjects who experienced adverse events leading to study termination. Table VIII.D-80 summarizes the results of AEs leading to discontinuation.

vi. *A Prospective, Double-Blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of X-22 as a Smoking Cessation Aid (IND 103589 [pg297])*

This study was designed to investigate the potential efficacy of X-22 cigarettes as a cessation aid. Subjects smoked a control cigarette or X-22 VLN™ tobacco cigarettes prior to their quit date. This study was not published. Data for the adverse events was taken from the 2012 Annual Report (22nd Century Group 2012 [pg297]).

(a) *Adverse Events*

A summary of AEs by body system is presented in Table VIII.D-81. Adverse Events in Study X-22 by System Organ Class and Preferred Term (From IND 103589 [pg297]) A total of 114 subjects experienced an AE during this study (58 in the X-22 group and 56 in the control group). The most frequently reported adverse events were in the body systems of infections and infestations (62 events; 31 in the X-22 group and 31 in the control group), respiratory, thoracic and mediastinal disorders (26 events; 11 in the X-22 group and 15 in the control group), gastrointestinal disorders (22 events; 11 in the X-22 group and 11 in the control group), and nervous system disorders (20 events; 11 in the X-22 group and 9 in the control group). Overall, AEs were reported at similar frequencies in the X-22 and control groups across body systems.

Table VIII.D-81. Adverse Events in Study X-22 by System Organ Class and Preferred Term (From IND 103589 [pg297])

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Adverse Events by System Organ Class and Preferred Term
Safety Population

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|--------------------------------------|--|---|------------------|
| Any Adverse Event | 58 (54.7) | 56 (50.9) | 114 (52.8) |
| Blood and lymphatic system disorders | 1 (0.9) | 2 (1.8) | 3 (1.4) |
| Blood disorder | 0 | 1 (0.9) | 1 (0.5) |
| Leukocytosis | 1 (0.9) | 0 | 1 (0.5) |
| Lymphadenopathy | 0 | 1 (0.9) | 1 (0.5) |
| Ear and labyrinth disorders | 0 | 2 (1.8) | 2 (0.9) |
| Ear pain | 0 | 1 (0.9) | 1 (0.5) |
| Tympanic membrane perforation | 0 | 1 (0.9) | 1 (0.5) |
| Endocrine disorders | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Hypothyroidism | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Eye disorders | 2 (1.9) | 2 (1.8) | 4 (1.9) |
| Astigmatism | 1 (0.9) | 0 | 1 (0.5) |
| Dark circles under eyes | 1 (0.9) | 0 | 1 (0.5) |
| Myopia | 1 (0.9) | 0 | 1 (0.5) |
| Retinal disorder | 0 | 1 (0.9) | 1 (0.5) |
| Visual impairment | 0 | 1 (0.9) | 1 (0.5) |
| Gastrointestinal disorders | 11 (10.4) | 11 (10.0) | 22 (10.2) |
| Abdominal discomfort | 0 | 1 (0.9) | 1 (0.5) |
| Abdominal hernia obstructive | 1 (0.9) | 0 | 1 (0.5) |
| Abdominal pain lower | 0 | 1 (0.9) | 1 (0.5) |

Table Generation: 24AUG12 10:12

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Adverse Events by System Organ Class and Preferred Term
Safety Population

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|--|--|---|------------------|
| Abdominal pain upper | 0 | 2 (1.8) | 2 (0.9) |
| Constipation | 0 | 4 (3.6) | 4 (1.9) |
| Diarrhoea | 1 (0.9) | 0 | 1 (0.5) |
| Dyspepsia | 2 (1.9) | 0 | 2 (0.9) |
| Food poisoning | 2 (1.9) | 0 | 2 (0.9) |
| Gingival bleeding | 0 | 1 (0.9) | 1 (0.5) |
| Gingivitis | 1 (0.9) | 0 | 1 (0.5) |
| Nausea | 2 (1.9) | 1 (0.9) | 3 (1.4) |
| Oral pain | 1 (0.9) | 0 | 1 (0.5) |
| Tooth loss | 0 | 1 (0.9) | 1 (0.5) |
| Toothache | 0 | 1 (0.9) | 1 (0.5) |
| Vomiting | 2 (1.9) | 0 | 2 (0.9) |
| General disorders and administration site conditions | 3 (2.8) | 1 (0.9) | 4 (1.9) |
| Chest pain | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Irritability | 1 (0.9) | 0 | 1 (0.5) |
| Pyrexia | 1 (0.9) | 0 | 1 (0.5) |
| Immune system disorders | 0 | 1 (0.9) | 1 (0.5) |
| Seasonal allergy | 0 | 1 (0.9) | 1 (0.5) |
| Infections and infestations | 30 (28.3) | 31 (28.2) | 61 (28.2) |
| Abscess | 1 (0.9) | 0 | 1 (0.5) |
| Bronchitis | 1 (0.9) | 2 (1.8) | 3 (1.4) |
| Cellulitis | 1 (0.9) | 0 | 1 (0.5) |

Table Generation: 24AUG12 10:12

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Adverse Events by System Organ Class and Preferred Term
Safety Population

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|--|--|---|------------------|
| Ear infection | 0 | 1 (0.9) | 1 (0.5) |
| Gastroenteritis viral | 0 | 1 (0.9) | 1 (0.5) |
| Groin abscess | 0 | 1 (0.9) | 1 (0.5) |
| Influenza | 1 (0.9) | 0 | 1 (0.5) |
| Kidney infection | 0 | 1 (0.9) | 1 (0.5) |
| Laryngitis | 2 (1.9) | 0 | 2 (0.9) |
| Localised infection | 1 (0.9) | 0 | 1 (0.5) |
| Lower respiratory tract infection | 0 | 2 (1.8) | 2 (0.9) |
| Nasopharyngitis | 19 (17.9) | 17 (15.5) | 36 (16.7) |
| Oral herpes | 0 | 1 (0.9) | 1 (0.5) |
| Osteomyelitis | 0 | 1 (0.9) | 1 (0.5) |
| Pharyngitis | 0 | 1 (0.9) | 1 (0.5) |
| Pneumonia | 0 | 1 (0.9) | 1 (0.5) |
| Post procedural infection | 1 (0.9) | 0 | 1 (0.5) |
| Sepsis | 0 | 1 (0.9) | 1 (0.5) |
| Sinusitis | 2 (1.9) | 3 (2.7) | 5 (2.3) |
| Tooth infection | 3 (2.8) | 0 | 3 (1.4) |
| Upper respiratory tract infection | 0 | 1 (0.9) | 1 (0.5) |
| Urinary tract infection | 0 | 1 (0.9) | 1 (0.5) |
| Varicella | 1 (0.9) | 0 | 1 (0.5) |
| Injury, poisoning and procedural complications | 9 (8.5) | 4 (3.6) | 13 (6.0) |
| Ear injury | 1 (0.9) | 0 | 1 (0.5) |
| Excoriation | 1 (0.9) | 0 | 1 (0.5) |
| Eye injury | 1 (0.9) | 0 | 1 (0.5) |
| Foot fracture | 0 | 1 (0.9) | 1 (0.5) |

Table Generation: 24AUG12 10:12

Program source: T_ae.sas

Adverse Events by System Organ Class and Preferred Term
Safety Population

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|---|--|---|------------------|
| Head injury | 2 (1.9) | 0 | 2 (0.9) |
| Joint sprain | 2 (1.9) | 1 (0.9) | 3 (1.4) |
| Laceration | 3 (2.8) | 0 | 3 (1.4) |
| Limb injury | 0 | 1 (0.9) | 1 (0.5) |
| Muscle strain | 0 | 1 (0.9) | 1 (0.5) |
| Procedural pain | 1 (0.9) | 0 | 1 (0.5) |
| Investigations | 4 (3.8) | 6 (5.5) | 10 (4.6) |
| Blood carbon monoxide increased | 1 (0.9) | 0 | 1 (0.5) |
| Blood creatinine increased | 0 | 1 (0.9) | 1 (0.5) |
| Blood lactate dehydrogenase increased | 0 | 1 (0.9) | 1 (0.5) |
| Blood potassium increased | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Blood pressure increased | 1 (0.9) | 2 (1.8) | 3 (1.4) |
| Gamma-glutamyltransferase increased | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Haematocrit decreased | 0 | 1 (0.9) | 1 (0.5) |
| Haemoglobin decreased | 0 | 1 (0.9) | 1 (0.5) |
| Red blood cell count decreased | 0 | 1 (0.9) | 1 (0.5) |
| Metabolism and nutrition disorders | 3 (2.8) | 0 | 3 (1.4) |
| Glucose tolerance impaired | 1 (0.9) | 0 | 1 (0.5) |
| Hypercholesterolaemia | 1 (0.9) | 0 | 1 (0.5) |
| Increased appetite | 1 (0.9) | 0 | 1 (0.5) |
| Vitamin D deficiency | 1 (0.9) | 0 | 1 (0.5) |
| Musculoskeletal and connective tissue disorders | 5 (4.7) | 3 (2.7) | 8 (3.7) |
| Arthralgia | 0 | 1 (0.9) | 1 (0.5) |

Table Generation: 24AUG12 10:12

Program source: T_ae.sas

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|--|--|---|------------------|
| Back pain | 1 (0.9) | 0 | 1 (0.5) |
| Myalgia | 1 (0.9) | 0 | 1 (0.5) |
| Pain in extremity | 2 (1.9) | 2 (1.8) | 4 (1.9) |
| Rheumatoid arthritis | 0 | 1 (0.9) | 1 (0.5) |
| Tendonitis | 1 (0.9) | 0 | 1 (0.5) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.9) | 0 | 1 (0.5) |
| Uterine leiomyoma | 1 (0.9) | 0 | 1 (0.5) |
| Nervous system disorders | 11 (10.4) | 7 (6.4) | 18 (8.3) |
| Dizziness | 3 (2.8) | 1 (0.9) | 4 (1.9) |
| Dysgeusia | 1 (0.9) | 0 | 1 (0.5) |
| Headache | 5 (4.7) | 6 (5.5) | 11 (5.1) |
| Nerve compression | 0 | 1 (0.9) | 1 (0.5) |
| Sinus headache | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| VIIth nerve paralysis | 1 (0.9) | 0 | 1 (0.5) |
| Psychiatric disorders | 3 (2.8) | 5 (4.5) | 8 (3.7) |
| Alcoholism | 1 (0.9) | 0 | 1 (0.5) |
| Anxiety | 2 (1.9) | 0 | 2 (0.9) |
| Attention deficit/hyperactivity disorder | 0 | 2 (1.8) | 2 (0.9) |
| Depression | 0 | 1 (0.9) | 1 (0.5) |
| Insomnia | 0 | 2 (1.8) | 2 (0.9) |
| Reproductive system and breast disorders | 0 | 1 (0.9) | 1 (0.5) |

Table Generation: 24AUG12 10:12

Program source: T_ae.sas

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=106) | Active Control Cigarettes (N=110) | Total (N=216) |
|---|--|---|------------------|
| Menorrhagia | 0 | 1 (0.9) | 1 (0.5) |
| Respiratory, thoracic and mediastinal disorders | 11 (10.4) | 15 (13.6) | 26 (12.0) |
| Cough | 7 (6.6) | 7 (6.4) | 14 (6.5) |
| Dysphonia | 0 | 1 (0.9) | 1 (0.5) |
| Increased upper airway secretion | 1 (0.9) | 0 | 1 (0.5) |
| Nasal congestion | 5 (4.7) | 3 (2.7) | 8 (3.7) |
| Oropharyngeal pain | 0 | 5 (4.5) | 5 (2.3) |
| Respiratory tract congestion | 2 (1.9) | 2 (1.8) | 4 (1.9) |
| Rhinorrhoea | 0 | 2 (1.8) | 2 (0.9) |
| Throat irritation | 0 | 1 (0.9) | 1 (0.5) |
| Upper-airway cough syndrome | 0 | 3 (2.7) | 3 (1.4) |
| Skin and subcutaneous tissue disorders | 0 | 2 (1.8) | 2 (0.9) |
| Dermatitis allergic | 0 | 1 (0.9) | 1 (0.5) |
| Pruritus | 0 | 1 (0.9) | 1 (0.5) |
| Vascular disorders | 2 (1.9) | 2 (1.8) | 4 (1.9) |
| Hypertension | 2 (1.9) | 2 (1.8) | 4 (1.9) |

Table Generation: 24AUG12 10:12

Program source: T_ae.sas

Source: Study X-22-201, Table 14.3.2.1

(b) *Serious Adverse Events*

A summary of SAEs reported during Study X-22 is presented in Table VIII.D-82 and a description of each SAE is provided below. Five of the AEs in the X-22 group and 1 in the control group were SAEs.

- Subject 1049 (obstructive abdominal hernia)

Subject 1049, a 47-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 08 Aug 2011 and stopped on 26 Sep 2011. The patient had a medical history of previous hernia repair. On (b) (6) (b) (6) the patient developed severe abdominal pain while exercising and went to an emergency room later that day. The patient was admitted to the hospital and hernia repair surgery was completed on (b) (6). She was released on 14 Oct 2011. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 13 Oct 2011.

- Subject 1073 (traumatic coma)

Subject 1073, a 37-year-old black female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 15 Sep 2011. On 22 Sep 2011, the site was notified by the subject's daughter that the subject had been in a motor vehicle accident on (b) (6), was hospitalized in an intensive care unit, had a brain injury, and was in a coma. No further information was available. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as ongoing at the conclusion of the study.

- Subject 1083 (uterine leiomyoma)

Subject 1083, a 33-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 14 Sep 2011. The patient had an active history of dysmenorrhea at screening. On 22 Dec 2011, the study site was

notified that the subject had uterine fibroid tumors and had elected to have a hysterectomy, requiring hospitalization. The start date of the event was reported as (b) (6). The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 18 Dec 2011.

- Subject 2009 (alcoholism)

Subject 2009, a 55-year-old Caucasian male, was enrolled in the study and randomized to the X-22 group. He began smoking the double-blind study cigarettes on 09 Aug 2011. The subject had a history of alcoholism from 1996 to 23 Aug 2010. On 20 Sep 2011, the subject notified the study site that he had admitted himself to (b) (6) for alcohol detox on (b) (6). He started drinking again on 04 Sep 2011. When he realized “what road he was traveling down” he decided to admit himself for detox. The start date of the event was reported as 04 Sep 2011. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 21 Sep 2011.

- Subject 2061 (head injury)

Subject 2061, a 33-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 14 Sep 2011 and stopped on 05 Oct 2011. On 13 Oct 2011, the study site was notified that the subject had been a passenger in a motor vehicle accident on (b) (6). She was admitted to a hospital on that date for severe head trauma and seizures. She was released on 12 Oct 2011. The investigator

determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as not resolved on 12 Oct 2011.

- Subject 3022 (sepsis)

Subject 3022, a 42-year-old Caucasian Hispanic male, was enrolled in the study and randomized to the control group. He began smoking the double-blind study cigarettes on 14 Sep 2011. The study site received a telephone call from the subject's partner reporting that the subject had complained of bilateral leg numbness and was taken to the emergency room, where he died soon after. A follow-up report identified the cause of death as sepsis most likely secondary to pancreatitis. Diagnoses prior to death included paraplegia secondary to large intrathecal hematoma, subarachnoid hemorrhage (stable), hypertension (stable), substance abuse (specifically methamphetamine), chest pain (myocardial infarction ruled out), acute pancreatitis, and sepsis most likely due to acute pancreatitis. Subarachnoid hemorrhage also occurred during the hospitalization and may have contributed to the cause of death. The date of hospital admission was not provided. On 06 Oct 2011, the subject chose to receive comfort care only and ongoing antibiotic therapy was discontinued. He expired on the evening of 07 Oct 2011 (Study Day 23). The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as fatal on 07 Oct 2011.

Table VIII.D-82. Summary of serious adverse events in study X-22-201 (From IND 103589 [pg297])

| System Organ Class Preferred Term | X-22 Smoking Cessation Product (N=118) | Active Control Cigarettes (N=116) | Total (N=234) |
|--|--|---|------------------|
| Any Serious Adverse Event | 5 (4.2) | 1 (0.9) | 6 (2.6) |
| Gastrointestinal disorders | 1 (0.8) | 0 | 1 (0.4) |
| Abdominal hernia obstructive | 1 (0.8) | 0 | 1 (0.4) |
| Infections and infestations | 0 | 1 (0.9) | 1 (0.4) |
| Sepsis | 0 | 1 (0.9) | 1 (0.4) |
| Injury, poisoning and procedural complications | 2 (1.7) | 0 | 2 (0.9) |
| Head injury | 1 (0.8) | 0 | 1 (0.4) |
| Traumatic coma | 1 (0.8) | 0 | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.8) | 0 | 1 (0.4) |
| Uterine leiomyoma | 1 (0.8) | 0 | 1 (0.4) |
| Psychiatric disorders | 1 (0.8) | 0 | 1 (0.4) |
| Alcoholism | 1 (0.8) | 0 | 1 (0.4) |

Source: Study X-22-201 Table 14.3.2.1

(c) *Deaths*

One subject died of sepsis during this study. The investigator determined that the event was not related to the active control cigarette.

(d) *Discontinuations Due to Adverse Events*

A total of 5 subjects discontinued the use of investigational product during Study X-22-201 due to an AE. A list of these subjects is provided below:

| <u>Subject Number</u> | <u>Treatment Group</u> | <u>Adverse Event</u> |
|-----------------------|------------------------|----------------------|
| 1047 | X-22 | Laryngitis |
| 1073 | X-22 | Traumatic coma |
| 2061 | X-22 | Head injury |
| 2009 | X-22 | Alcoholism |
| 3022 | Control | Sepsis |

5. Ongoing Studies

Table VIII.D-83 list the ongoing studies with VLN™. It is anticipated that the studies will be submitted at the end of the first quarter in 2019. Clinicaltrials.gov lists the following studies as underway with VLNC cigarettes:

i. Facilitating Smoking Cessation With Reduced Nicotine Cigarettes

ClinicalTrials.gov Identifier: NCT02796391

Sponsor: H. Lee Moffitt Cancer Center and Research Institute

Collaborator: James and Esther King Biomedical Research Program

ii. Novel Approaches to Reducing Tobacco Related Harm

ClinicalTrials.gov Identifier: NCT02600273

Sponsor: Duke University

Collaborator: National Institute of Allergy and Infectious Diseases (NIAID)

iii. Abuse Liability of Reduced Nicotine Content Cigarettes in the Context of Concurrent E-Cigarette Use

ClinicalTrials.gov Identifier: NCT02870218

Sponsor: Rose Research Center, LLC

Collaborators: National Institutes of Health (NIH) and Food and Drug Administration (FDA)

iv. Effects of Nicotine Reduction on Smoking Behavior in ADHD Smokers

ClinicalTrials.gov Identifier: NCT02599571

Sponsor: Duke University

Collaborators: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Food and Drug Administration (FDA), and University of Pittsburgh

v. Evaluation of Very Low Nicotine Content Cigarettes in Adolescent Smokers

ClinicalTrials.gov Identifier: NCT02587312

Sponsor: Brown University

Collaborator: National Cancer Institute (NCI)

vi. Manipulating Tobacco Constituents in Female Menthol Smokers

ClinicalTrials.gov Identifier: NCT02048852
Sponsor: University of Connecticut Health Center
Collaborator: National Institute on Drug Abuse (NIDA)

vii. Manipulating Tobacco Constituents in Male Menthol Smokers

ClinicalTrials.gov Identifier: NCT02592772
Sponsor: University of Connecticut Health Center
Collaborator: National Institute on Drug Abuse (NIDA)

viii. Project 1, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Childbearing Age Women

ClinicalTrials.gov Identifier: NCT02250534
Sponsor: University of Vermont
Collaborators: National Institute on Drug Abuse (NIDA) and Johns Hopkins University

ix. Project 1, Study 2: The Combined Impact of Nicotine Replacement and Spectrum Cigarettes

ClinicalTrials.gov Identifier: NCT02301325
Sponsor: University of Pittsburgh

x. Project 2, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Opioid Abusers

ClinicalTrials.gov Identifier: NCT02250664
Sponsor: University of Vermont
Collaborators: National Institute on Drug Abuse (NIDA) and Johns Hopkins University

xi. Project 3, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in People With Current Affective Disorders

ClinicalTrials.gov Identifier: NCT02232737
Sponsor: Brown University
Collaborator: University of Vermont

xii. Reduced Nicotine Content Cigarettes in Smokers of Lower Socioeconomic Status

ClinicalTrials.gov Identifier: NCT01928719
Sponsor: Milton S. Hershey Medical Center
Collaborator: George Washington University

xiii. Reduced Nicotine Cigarettes in Smokers With Mood and Anxiety Disorders

ClinicalTrials.gov Identifier: NCT01928758
Sponsor: Milton S. Hershey Medical Center
Collaborator: National Institute on Drug Abuse (NIDA)

xiv. Strengthening Instrumental Extinction to Prevent Smoking Relapse (VLNCCue)

ClinicalTrials.gov Identifier: NCT02538042
Sponsor: Francis McClernon
Collaborators: National Institutes of Health (NIH) and National Institute on Drug Abuse (NIDA)

xv. Switching to Reduced Oxidant or Nicotine Content Cigarettes in Smokers

ClinicalTrials.gov Identifier: NCT02415270
Sponsor: Milton S. Hershey Medical Center
Collaborators: Food and Drug Administration (FDA), National Institutes of Health (NIH), and National Institute on Drug Abuse (NIDA)

xvi. Very-Low Nicotine Cigarettes and Non-Daily Smokers

ClinicalTrials.gov Identifier: NCT02228824
Sponsor: University of Pittsburgh
Collaborator: National Cancer Institute (NCI)

xvii. Very Low Nicotine Cigarettes in Smokers With Schizophrenia

ClinicalTrials.gov Identifier: NCT02019459
Sponsor: Brown University
Collaborators: National Institute on Drug Abuse (NIDA) and University of Pittsburgh

xviii. Very Low-Nicotine Cigarettes in Smokers With SUD

ClinicalTrials.gov Identifier: NCT01989507
Sponsor/Collaborator: Brown University

xix. Neuroimaging Reward, Behavioral Treatment, and Smoking Cessation

ClinicalTrials.gov Identifier: NCT02927847
Sponsor: Maggie M. Sweitzer, PhD
Collaborator: National Institute on Drug Abuse (NIDA)

xx. Abuse Liability of Reduced Nicotine Content Cigarettes Within a Complex Tobacco Marketplace: Experiment 1

ClinicalTrials.gov Identifier: NCT02951143

Sponsor: Virginia Polytechnic Institute and State University

xxi. Concomitant Use of Very Low Nicotine Content Cigarettes and e-Cigarettes

ClinicalTrials.gov Identifier: NCT02964182

Sponsor: M.D. Anderson Cancer Center

Collaborator: National Institute on Drug Abuse (NIDA)

xxii. Reactions to Reduced Nicotine Cigarettes in Young Adult Low-Frequency Smokers (NicRed)

ClinicalTrials.gov Identifier: NCT02989038

Sponsor: Duke University

Collaborator: National Institute on Drug Abuse (NIDA)

xxiii. Reduced Nicotine Cigarettes in Smokers With and Without Alcohol Use Disorder (RedNic)

ClinicalTrials.gov Identifier: NCT02990455

Sponsor: Battelle Memorial Institute

xxiv. Switching to Very Low Nicotine Content Cigarettes vs Reducing Cigarettes Per Day

ClinicalTrials.gov Identifier: NCT03060083

Sponsor: University of Vermont

Table VIII.D-83. Status of ongoing studies with VLN™.

| Study | Status |
|---|--|
| Evaluation of the Abuse Liability of Very Low Nicotine Mentholated Cigarettes | Enrollment complete; Analysis under; Submission 1Q2019 |
| A Longitudinal Ambulatory Study to Assess Changes in Cigarettes Consumption Behavior and Biomarkers of Exposure during a 6-Week switch to Very Low Nicotine | Enrollment complete; Analysis under; Submission 1Q2019 |

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