

RESEARCH ARTICLE

Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology

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Abstract

A randomized, multi-center study was conducted to assess potential improvement in health status measures, as well as changes in biomarkers of tobacco exposure and biomarkers of biological effect, in current adult cigarette smokers switched to tobacco-heating cigarettes, snus or ultra-low machine yield tobacco-burning cigarettes (50/group) evaluated over 24 weeks. Study design, conduct and methodology are presented here along with subjects' disposition, characteristics, compliance and safety results. This design and methodology, evaluating generally healthy adult smokers over a relatively short duration, proved feasible. Findings from this randomized study provide generalized knowledge of the risk continuum among various tobacco products (ClinicalTrials.gov Identifier: NCT02061917).

Keywords

Biomarkers, compliance, feasibility, health status measures, multi-center randomized study, risk continuum

History

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Introduction

The most effective way to prevent the health consequences from smoking is not to start, and for smokers who are concerned about their health, the best course of action is to quit. Although smoking prevalence has decreased over the last few decades, approximately 19% of the US adult population currently smokes (King et al., 2011). For individuals who do not quit, a tobacco product that may reduce health risks would be advantageous. Although no tobacco product has been shown to be safe and without risks, a continuum of risk exists among these products (Nutt et al., 2014; Zeller et al., 2009). For individuals who are unwilling or unable to quit tobacco consumption, the use of a lower risk tobacco product could mitigate some of the adverse health consequences of smoking and thereby would benefit the public health.

More research is needed to describe the existing tobacco product risk spectrum and to develop better tools for evaluating the potential health risks of emerging products. However, the complex task of assessing the effect of different tobacco products on disease incidence requires the evaluation of a large number of individuals over a long period of time. Accordingly, a practical approach to provide meaningful health information related to the use of different tobacco products is needed. One

method would be to assess effects of different tobacco products on health-related outcomes in a relatively healthy sample of tobacco consumers over a shorter period than would be required if disease incidence was assessed.

This article documents the design, conduct and methodology used in a randomized, multi-center study (ClinicalTrials.gov Identifier: NCT02061917). This study investigated whether current adult cigarette smokers, randomly switched to a tobacco-heating cigarette or snus, had improvement in health status measures and/or changes in levels of biomarkers of tobacco exposure and biological effect, relative to baseline (i.e. smoking their usual brand of cigarettes) and compared with subjects randomly switched to an ultra-low machine yield tobacco-burning (control) cigarette [i.e. 5 mg “tar” by the Cambridge Filter Method (CFM) (FTC, 1967, 1980)]. A group of never smokers was included for baseline comparisons. Subjects' disposition, characteristics, compliance and safety results are presented herein. Results from changes in exposure measures (Ogden et al., 2015a) and biomarkers of biological effect (Ogden et al., 2015b) are reported elsewhere.

Methods

The primary objectives of the study were to: (1) determine the feasibility of the study design and the analysis methodology; (2) assess subject compliance with study products and (3) obtain data on the ability of a tobacco-heating cigarette and/or snus to modify patient-reported chronic obstructive pulmonary disease (COPD)-related health status [as measured by the St. Georges Respiratory Questionnaire (SGRQ)]. Secondary objectives were to: (1) obtain data on product switching related modification of self-reported health status as measured by the SGRQ, the Leicester Cough Questionnaire

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(LCQ), and the Smoking Cessation Quality of Life Questionnaire (SCQoL); (2) obtain data in a comparison of health status measures (SGRQ, LCQ, SCQoL) among the three tobacco-using groups; (3) evaluate selected biomarkers (i.e. tobacco exposure and biological effect) among the three tobacco-using groups; (4) compare baseline data from all three tobacco-using groups to baseline data from a never smoking group; (5) measure amount and repeatability of smoke components yielded from tobacco-burning cigarettes (yield-in-use), and determine the relative uptake of selected smoke components and (6) assess issues related to subjects' switching from their usual brand cigarette to either a tobacco-heating cigarette or snus. Results from the SGRQ, LCQ and SCQoL are beyond the scope of the current manuscript and are not reported herein.

Subjects

The target enrollment for this study was 50 subjects per group, i.e. 50 subjects switching from usual brand cigarettes to tobacco-heating cigarettes, 50 subjects switching from usual brand cigarettes to snus and 50 subjects switching from usual brand cigarettes to ultra-low machine yield tobacco-burning cigarettes. This allowed for an approximately 25% drop out rate to complete 30–40 subjects per tobacco-using group. The target completion for never smokers was 30 subjects. Potential subjects were screened within 28 days prior to study entry to assess eligibility to participate at five clinical research units (CRUs) in the USA (Boise, ID; Dallas, TX; Daytona Beach, FL; Portland, OR and Austin, TX) managed by Covance Early Clinical Development (Madison, WI). Enrollment across the five CRUs was competitive.

Eligible study subjects included males and females 28–55 years of age and free of clinically significant health problems, in the opinion of the investigators. Subjects with a history or clinical manifestations of significant metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological, neurological or psychiatric disorders were excluded, as well as subjects taking medication for a chronic, clinically significant medical disorder. Eligible subjects tested negative for selected drugs of abuse at Screening and Enrollment (i.e. Week 0); and subjects' results of pulmonary function tests (i.e. spirometry) indicated forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow levels were $\geq 70\%$ of predicted values at Screening and Enrollment. Subjects were able to read and complete questionnaires in English. Subjects in the never smoker group were self-reported never smokers, per the American Thoracic Society Division of Lung Disease questionnaire (ATS-DLD-78A) definition (i.e. less than 20 packs of cigarettes, lifetime) (Ferris, 1978), with subsequent confirmation by a urinary cotinine measurement of ≤ 50 ng/mL. Eligible smoking subjects reported smoking at least 15 cigarettes daily for 10 or more years prior to Week 0 (i.e. were chronic cigarette smokers) and not using any other tobacco or nicotine-containing product or device 6 months prior to Week 0. Randomized subjects did not intend to quit smoking (i.e. intend to make or making a quit attempt within one month prior to Week 0), but were willing to switch to an alternate tobacco product for the duration of the study.

Female subjects were not pregnant or breast-feeding. Any subject who was enrolled/randomized but subsequently decided to quit smoking was encouraged to do so and was withdrawn from the study; and any woman who became pregnant during the study was discontinued and counseled to quit smoking.

Study design and conduct

The study was conducted between February and November 2007 in accordance with applicable sections of the United States Code of Federal Regulations (21 CFR Parts 50, 54, 56), the International Conference on Harmonization Good Clinical Practice (ICH, 1996), and the Declaration of Helsinki (WMA, 2002). Study and subject materials, including protocol, protocol amendments, informed consent forms, study product information and recruitment literature, were reviewed and approved by Independent Investigational Review Board, Inc. (currently Shulman Associates IRB, Inc., Fort Lauderdale, FL). The Principal Investigator (or designee) at each CRU explained the purpose of the study, all study procedures to be carried out, and a description of the study products to the subjects. After subjects' questions regarding the study were answered, written informed consent was obtained from all subjects prior to any study-specific procedures being performed. Subjects were free to withdraw from the study at any time and for any reason and were compensated for their time and participation (i.e. each portion of the study had an assigned monetary value). All five Principal Investigators at the CRUs, as well as the study Medical Monitor (Medical Director, Covance Early Clinical Development, Madison, WI), were medical doctors.

This was a randomized, multi-center study of adult cigarette smokers randomly switched to tobacco-heating cigarettes, snus or ultra-low machine yield tobacco-burning cigarettes, with a comparison group of never smokers at baseline only. Subjects' experience with the assigned study products was followed for 24 weeks. There were no exercise, diet or fluid controls throughout the study, although excessive alcohol consumption (i.e. more than 14 drinks per week, with one drink equivalent to one ounce of hard liquor, six ounces of wine, and 12 ounces of beer) was discouraged. Basic safety monitoring included vital signs (i.e. oral temperature, respiratory rate, blood pressure and pulse), expired carbon monoxide concentration measurements, evaluation of adverse events (AEs) at every two-week visit, and an electrocardiogram (ECG) at Screening and Week 24. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized using MedDRA terms. Clinical laboratory evaluations (Covance Central Laboratory Services, Indianapolis, IN) for blood chemistry, complete blood count, urinalysis, urine drug screen/alcohol breathalyzer, and urine pregnancy test for females were also conducted at Weeks 0, 12 and 24, as well as general physical (i.e. height, weight and general appearance) and oral health examinations.

Spirometry was performed at Screening and at baseline Week 0 to determine whether a subject had significant pulmonary disease for inclusion/exclusion purposes, and at Weeks 12 and 24 to measure any potential changes in

pulmonary function that may have occurred during the course of the study. In this study, spirometry was performed before and after inhalation of a bronchodilator, per the protocol-specified procedures, in order to measure the degree of reversibility of potential airflow obstruction. Post-bronchodilator spirometry was performed 15 min after administering a bronchodilator (Proventil®) by metered dose inhaler. The ATS recommended criteria for a significant response to a bronchodilator in adults are $\geq 12\%$ improvement in FEV1 or FVC from baseline and an absolute improvement of ≥ 0.200 L (ATS, 1991).

A 24-h clinical confinement in the CRU occurred at Weeks 0, 12, and 24 for smokers and Week 0 for never smokers; check-in for the confinement periods was between 2 and 5 PM. Subjects were provided with standardized meals during confinement periods. Fasting blood samples and 24-h and spot urine samples were collected and analyzed for selected biomarkers of exposure and biological effect. Health-related quality of life questionnaires were administered at Week 0 and every four weeks thereafter.

Study products

Subjects provided their own usual brand of cigarettes for smoking from Screening up to the time of randomization at Week 0. Study products were provided by the study Sponsor (R.J. Reynolds Tobacco Company, Winston-Salem, NC) and were tobacco products commercially marketed in the USA as of December 2006. The products included a tobacco-heating cigarette (Eclipse brand cigarette; regular and menthol varieties), snus (Camel SNUS, 400 mg; Frost, Spice, and Original varieties), and an ultra-low machine yield tobacco-burning cigarette [5 mg “tar” by CFM; Camel “Ultra Lights”¹ (non-menthol variety) or Salem “Ultra Lights” (menthol variety)]. Different varieties (menthol, non-menthol cigarettes; Spice, Original and Frost snus) were offered to subjects in order to match consumer preferences for cigarettes and with the intention to maximize compliance across all arms of the study for subjects switched to a product that was not their usual tobacco form or brand. All cigarettes were produced in one lot each in either June 2006 (Eclipse) or August 2006 (Camel and Salem “Ultra Lights”). For snus, because of the 16-week “Best Before” date in effect at that time, all varieties were produced in multiple (5) lots across the time course of the study (from December 2006 to July 2007). Representative analytical characterization of each of the study products is shown in Supplemental Table 1 for the cigarettes and Supplemental Tables 2 and 3 for Camel SNUS including reference to previously published data (Borgerding et al., 2012).

Orientation information about the tobacco-heating cigarette and snus was provided to the subjects by the clinical staff at Screening and Week 0. A randomization schedule was made available to each CRU through a telephone-based interactive voice response system (IVRS) (Covance InterActive Voice Response Services, Princeton, NJ). The randomization ratio was 1:1:1. Once randomly assigned to a

product category (i.e. tobacco-heating cigarette, snus or ultra-low machine yield tobacco-burning cigarette) at Week 0, all subjects were offered a choice from the varieties within that product category (i.e. three varieties of snus, and menthol/non-menthol varieties for cigarettes). The study products were unblinded because of their unique visual appearances; however, products were supplied in plain white, unbranded packaging without any trademark or style identifiers (other than variety) but marked with federally mandated health warnings and tax information. Study product was distributed every two weeks; all unused product was returned to the CRU at each visit and a new supply of study product was dispensed. Subjects collected used tobacco-heating cigarette rods, used snus pouches and smoked cigarette butts for 24 h preceding clinical confinement, and these were processed at each CRU. Clinical staff counted and recorded the number of used products (i.e. rods/pouches/butts) and visually assessed them for brand conformity. Any product determined to have been from a brand other than the subjects’ usual brand cigarette at Week 0 or the protocol-specified brand at Weeks 12 and 24 was counted and recorded as a deviation.

Usage and compliance

For the two-week period prior to Week 0 check-in, the smoking subjects recorded their typical smoking and other tobacco use habits via IVRS. After randomization at Week 0, subjects were instructed to use only the study product to which they were assigned. While on study, the tobacco use IVRS diary entries were made daily and reflected usage of the study product as well as outside-of-protocol smoking and any other tobacco or nicotine use. Every two weeks, the assigned study product was dispensed to subjects based on IVRS usage reported in the previous two weeks. If a subject used tobacco or nicotine-containing product(s) other than their protocol-specified product, they were instructed to honestly and accurately report this in their IVRS diary entries. Subjects were not discontinued from the study for product non-compliance; however, clinical staff reviewed the subjects’ IVRS diary entries and discussed compliance issues at each two-week product pick-up. For example, subjects were reminded that they were allowed to switch to another variety of their protocol-specified product to potentially improve compliance. For the one-week period prior to check-in, never smokers also completed diary questions via IVRS. Subjects were compensated for daily diary entries to incentivize compliance with both IVRS entry and assigned product use.

Determination of compliance was based upon the proportion of assigned study product used relative to the combined use of study product plus other tobacco or nicotine-containing products. Use of assigned product, other tobacco-containing products and other nicotine-containing products was based on subject self-report via daily IVRS calls. Compliance was calculated cumulatively from randomization until the time of assessments for the endpoint, i.e. at the end of Week $k = 4, 8, 12, 16, 20$ and 24 using the following equation:

$$\text{Percent compliance}_k = \left(\frac{\text{SPU}_k}{\text{SPU}_k + \text{ONP}_k} \right) \times 100,$$

¹Under the Family Smoking Prevention and Tobacco Control Act (United States Congress, 2009), the term “Ultra Lights” was banned as a cigarette descriptor as of 22 June 2010. However, this term is included in this report, as it accurately reflects the product descriptors in use at the time of the study.

Table 1. Subject demographics summary.

| | Smokers | | | | Never smokers | Total | <i>p</i> Value |
|---------------------------------|--------------|--------------|--------------|--------------|---------------|--------------|----------------|
| | TH | S | TB | Overall | | | |
| <i>Intent-to-treat sample</i> | | | | | | | |
| Age, years <i>n</i> | 44 | 43 | 44 | 131 | 32 | 163 | 0.96* |
| Mean | 42 | 41 | 41 | 42 | 42 | 42 | |
| Min | 29 | 30 | 28 | 28 | 29 | 28 | |
| Max | 55 | 55 | 55 | 55 | 54 | 55 | |
| BMI, kg/m ² <i>n</i> | 44 | 40 | 43 | 127 | 30 | 157 | 0.18* |
| Mean | 27.4 | 29.8 | 30.0 | 29.0 | 30.5 | 29.3 | |
| Min | 18.2 | 20.8 | 16.2 | 16.2 | 20.9 | 16.2 | |
| Max | 51.3 | 46.9 | 62.0 | 62.0 | 45.0 | 62.0 | |
| Gender | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | –‡ |
| Male | 21 (47.7) | 22 (51.2) | 23 (52.3) | 66 (50.4) | 14 (43.8) | 80 (49.1) | |
| Female | 23 (52.3) | 21 (48.8) | 21 (47.7) | 65 (49.6) | 18 (56.3) | 83 (50.9) | |
| Ethnicity | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | –‡ |
| Hispanic/Latino | 2 (4.5) | 2 (4.7) | 4 (9.1) | 8 (6.1) | 5 (15.6) | 13 (8) | |
| Not Hispanic/Latino | 33 (75) | 32 (74.4) | 32 (72.7) | 97 (74) | 22 (68.8) | 119 (73) | |
| Unknown | 9 (20.5) | 9 (20.9) | 8 (18.2) | 26 (19.8) | 5 (15.6) | 31 (19) | |
| Race | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | –‡ |
| White | 39 (88.6) | 35 (81.4) | 36 (81.8) | 110 (84) | 23 (71.9) | 133 (81.6) | |
| African American | 2 (4.5) | 6 (14) | 3 (6.8) | 11 (8.4) | 4 (12.5) | 15 (9.2) | |
| Other | 3 (6.9) | 2 (4.6) | 5 (11.4) | 10 (7.8) | 5 (15.5) | 17 (10.3) | |
| <i>Per-protocol sample</i> | | | | | | | |
| Age, years <i>n</i> | 33 | 20 | 35 | 88 | 32 | 120 | 0.96* |
| Mean | 42 | 41 | 41 | 41 | 42 | 42 | |
| Min | 29 | 30 | 28 | 28 | 29 | 28 | |
| Max | 55 | 52 | 55 | 55 | 54 | 55 | |
| BMI, kg/m ² <i>n</i> | 33 | 18 | 35 | 86 | 30 | 116 | 0.32* |
| Mean | 27.5 | 29.6 | 29.6 | 28.8 | 30.5 | 29.3 | |
| Min | 18.2 | 21.1 | 16.2 | 16.2 | 20.9 | 16.2 | |
| Max | 51.3 | 46.9 | 50.7 | 51.3 | 45.0 | 51.3 | |
| Gender | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | 0.25† |
| Male | 14 (42.4) | 13 (65) | 16 (45.7) | 43 (48.9) | 14 (43.8) | 57 (47.5) | |
| Female | 19 (57.6) | 7 (35) | 19 (54.3) | 45 (51.1) | 18 (56.3) | 63 (52.5) | |
| Ethnicity | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | –‡ |
| Hispanic/Latino | 1 (3) | 2 (10) | 2 (5.7) | 5 (5.7) | 5 (15.6) | 10 (8.3) | |
| Not Hispanic/Latino | 27 (81.8) | 15 (75) | 27 (77.1) | 69 (78.4) | 22 (68.8) | 91 (75.8) | |
| Race | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | –‡ |
| White | 31 (93.9) | 17 (85) | 30 (85.7) | 78 (88.6) | 23 (71.9) | 101 (84.2) | |
| African American | 0 | 2 (10) | 3 (8.6) | 5 (5.7) | 4 (12.5) | 9 (7.5) | |
| Other | 2 (6.0) | 1 (5) | 2 (5.8) | 5 (5.6) | 5 (15.5) | 10 (8.3) | |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette; BMI, body mass index.

**p* Value is from the *F*-test to assess if mean values of the continuous variables are equivalent across product groups.

†*p* Value is from chi-square test for equal proportions of gender in each group.

‡–, not reported.

where SPU_k is the sum of study products used from Week 0 to Week *k* (inclusive) and ONP_k is the sum of other tobacco and nicotine-containing products used from Week 0 through Week *k* (inclusive). Cumulative compliance data were then categorized as:

- Compliant = Proportion of amount of assigned study product used relative to combined use of study product and other products was $\geq 75\%$.
- Somewhat compliant = Proportion of amount of assigned study product used relative to combined use of study product and other products was $>50\%$ to $<75\%$.
- Non-compliant = Proportion of amount of assigned study product used relative to combined use of study product and other products was $\leq 50\%$.

Analysis and statistical methods

Data were evaluated for both the intent-to-treat sample and the per-protocol sample. The intent-to-treat sample included all randomized subjects in the groups to which they were assigned, regardless of adherence with the compliance criteria, deviation from protocol and/or subsequent withdrawal from the study. The per-protocol sample was defined by mean compliance greater than 50% over the 24 study weeks. A subject's per-protocol variable in the model was set to "non-compliant" when the subject was not cumulatively compliant at Week 24 or when the Week 24 data were missing (i.e. subject discontinued).

Appropriate statistical analyses were performed to assess differences between all groups. For descriptive analysis, the

Table 2. Smokers by usual brand cigarette “tar” category^a.

| “Tar” category | TH | S | TB | Overall |
|--|----|----|----|---------|
| Intent-to-treat sample | | | | |
| Full flavor ^b | 17 | 15 | 19 | 51 |
| Full flavor low machine yield ^c | 25 | 26 | 24 | 75 |
| Ultra-low machine yield ^d | 1 | 1 | 1 | 3 |
| Per-protocol sample | | | | |
| Full flavor ^b | 14 | 10 | 16 | 40 |
| Full flavor low machine yield ^c | 17 | 9 | 18 | 44 |
| Ultra-low machine yield ^d | 1 | 0 | 1 | 2 |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette.

^a“Tar” category as determined by the Cambridge Filter Method (CFM) (FTC, 1967, 1980). CFM “tar” ratings for two brands (subjects) were unknown.

^b>13 mg CFM “tar”.

^c6–13 mg CFM “tar”.

^d<6 mg CFM “tar”.

Table 3. Usual brand “tar” yield (mg/cigarette) summary statistics by group.

| | Sample size | Mean (mg) | Standard deviation | Minimum | Maximum |
|------------------------|-----------------|-----------|--------------------|---------|---------|
| Intent-to-treat sample | | | | | |
| TH | 44 ^a | 12.2 | 2.7 | 4.4 | 17.6 |
| S | 43 ^a | 12.1 | 2.9 | 4.4 | 19.9 |
| TB | 44 | 13.1 | 4.0 | 5.9 | 31.0 |
| Per-protocol sample | | | | | |
| TH | 33 ^a | 12.2 | 2.8 | 4.4 | 17.6 |
| S | 20 ^a | 13.0 | 2.5 | 9.6 | 17.3 |
| TB | 35 | 12.8 | 2.7 | 5.9 | 19.4 |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette.

^aCount includes one unknown CFM “tar” yield.

two comparison groups of interest were smokers versus never smokers and smokers by assigned study product (i.e. tobacco-heating cigarette, snus, ultra-low machine yield tobacco-burning cigarette).

Results

Subject demographics and other baseline characteristics

Subject demographics are summarized in Table 1. In both the intent-to-treat and per-protocol samples, the three tobacco-using groups and never smokers were not different in terms of mean age, mean body mass index and gender proportions. Additionally, 33 (25%) subjects smoked menthol cigarettes and 98 (75%) smoked non-menthol cigarettes as their usual brand. Although all smokers in the study had a history of smoking for 10 or more years, the reported duration of usual brand smoking ranged between less than 1 and 43 years. Smokers by usual brand CFM “tar” category are presented in Table 2. The usual brand for the majority of subjects within each group was full flavor low machine yield (i.e. 6–13 mg CFM “tar”) in both the intent-to-treat and per-protocol samples.

Table 3 presents summary statistics for subjects’ usual brand cigarettes CFM “tar” yield by sample and group. For the intent-to-treat sample, CFM “tar” levels of their usual brand cigarettes ranged between 4.4 and 31 mg. Among the per-protocol sample, CFM “tar” levels ranged between 4.4

Table 4. Subjects by COPD classification,^a Week 0.

| | Smokers | Never smokers | All |
|------------------------|---------|---------------|-----|
| Intent-to-treat sample | | | |
| No COPD ^b | 117 | 30 | 147 |
| COPD ^c | 13 | 2 | 15 |
| COPD classification | | | |
| Mild | 10 | 1 | 11 |
| Moderate | 3 | 1 | 4 |
| Severe | 0 | 0 | 0 |
| Per-protocol sample | | | |
| No COPD ^b | 79 | 30 | 109 |
| COPD ^c | 9 | 2 | 11 |
| COPD classification | | | |
| Mild ^d | 6 | 1 | 7 |
| Moderate ^e | 3 | 1 | 4 |
| Severe ^f | 0 | 0 | 0 |

COPD, chronic obstructive pulmonary disease; FEV1_{post}, forced expiratory volume, post-bronchodilator; FVC_{post}, forced vital capacity, post-bronchodilator. FER_{post}=100 × FEV1_{post}/FVC_{post}.

^aAmerican Thoracic Society (Ferris, 1978); data for one subject was unknown.

^bForced expiratory ratio, post-bronchodilator (FER_{post}) ≥ 70%.

^cFER_{post} < 70%.

^dFER_{post} < 70% and FEV1_{post} ratio ≥ 80%.

^eFER_{post} < 70% and 50% ≤ FEV1_{post} ratio < 80%.

^fFER_{post} < 70% and 30% ≤ FEV1_{post} ratio < 50%.

and 19.4 mg. In addition, average CFM “tar” yields of usual brand cigarettes in all three groups were approximately the same at study entry, in both the intent-to-treat (i.e. range of 12.1–13.1) and per-protocol samples (i.e. range of 12.2–13.0).

As noted, the study subjects were determined to be eligible to participate based on protocol-specified inclusion and exclusion criteria as well as the Screening spirometry results. Therefore, the study subjects were prescreened to be relatively healthy or to have only mild COPD. By the ATS classification system (Ferris, 1978), 15 of the 163 enrolled subjects (9.2%) and 11 of 120 (9.2%) of per-protocol subjects had classifiable COPD and most of those (11 of 15 and 7 of 11, respectively) had mild COPD (Table 4).

None of the self-reported never smokers had urinary cotinine > 50 ng/mL, no randomized subjects decided to quit smoking while on-study, and no women became pregnant during the study. Twenty-two subjects withdrew consent, six subjects were discontinued for other reasons, three subjects were lost to follow-up, the Sponsor discontinued one subject, and the Principal Investigator discontinued one subject due to an AE of sepsis (Table 5). The counts for subjects who withdrew consent for non-product-related reasons were approximately equal among the three product groups. However, the counts for subjects who withdrew consent for product-related reasons increased from the ultra-low machine yield tobacco-burning cigarette group (*n* = 0), to the tobacco-heating cigarette group (*n* = 3), to the snus group (*n* = 7).

In the intent-to-treat sample, completion rates were 77% for the tobacco-heating cigarette group, 67% for the snus group and 80% for the ultra-low machine yield tobacco-burning cigarette group. Of the 131 subjects randomized, 88 subjects met the product usage compliance criteria for inclusion in the per-protocol sample, 33 subjects withdrew before study completion and 10 subjects completed the study but failed to meet the per-protocol product usage criteria.

Table 5. Subject disposition summary.

| | Smokers | | | Overall n (%) | Never smokers n (%) | Total n (%) |
|-----------------------------------|-------------|------------|-------------|------------------|------------------------|----------------|
| | TH n (%) | S n (%) | TB n (%) | | | |
| Intent-to-treat | | | | | | |
| Overall | 44 (27) | 43 (26) | 44 (27) | 131 (80) | 32 (20) | 163 (100) |
| Randomized | 44 (100) | 43 (100) | 44 (100) | 131 (100) | NA ^d | 131 (100) |
| Completed | 34 (77) | 29 (67) | 35 (80) | 98 (75) | 32 (100) | 130 (80) |
| Withdrawal | 10 (23) | 14 (33) | 9 (21) | 33 (25) | 0 | 33 (20) |
| Adverse events ^a | 0 | 0 | 1 (2) | 1 (1) | 0 | 1 (1) |
| Sponsor discontinued ^b | 1 (2) | 0 | 0 | 1 (1) | 0 | 1 (1) |
| Consent withdrawn | 6 (14) | 11 (26) | 5 (11) | 22 (17) | 0 | 22 (14) |
| Product related | 3 | 7 | 0 | 10 | 0 | 10 |
| Not product related | 3 | 4 | 5 | 12 | 0 | 12 |
| Lost to follow-up | 0 | 1 (2) | 2 (5) | 3 (2) | 0 | 3 (2) |
| Other ^c | 3 (7) | 2 (5) | 1 (2) | 6 (5) | 0 | 6 (4) |
| Per-protocol | | | | | | |
| Overall | 33 (28) | 20 (17) | 35 (29) | 88 (73) | 32 (27) | 120 (100) |
| Randomized | 33 (100) | 20 (100) | 35 (100) | 88 (100) | NA ^d | 88 (73) |
| Completed | 33 (100) | 20 (100) | 35 (100) | 88 (100) | 32 (100) | 120 (100) |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette. Percent values have been rounded.

^aSepsis; a serious AE, not study product nor procedure related; subject required hospitalization and was discontinued by the Principal Investigator.

^bSubject developed benign mouth sores; off study product long enough that subject was discontinued from study.

^cNon-compliance, family emergency.

^dNot applicable. Never smokers were not randomized.

Table 6. Mean daily tobacco product use (counts)^a.

| Week | Product | Intent-to-treat sample | | | Per-protocol sample | | |
|------|--------------------|------------------------|----------------|----------------|---------------------|----------------|----------------|
| | | TH | S | TB | TH | S | TB |
| 0 | Assigned product | – ^b | – ^b | – ^b | – ^b | – ^b | – ^b |
| | Cigarette | 19.4 | 17.2 | 17.0 | 18.9 | 18.3 | 16.8 |
| | Other ^c | 1.0 | 0.1 | 0.04 | 1.4 | 0 | 0.02 |
| 12 | Assigned product | 18.1 | 9.0 | 24.3 | 19.3 | 10.8 | 24.1 |
| | Cigarette | 3.3 | 5.8 | 0.5 | 2.6 | 3.9 | 0.5 |
| | Other ^c | 0 | 0.1 | 0 | 0 | 0.1 | 0 |
| 24 | Assigned product | 23.0 | 8.3 | 27.0 | 23.5 | 10.2 | 26.6 |
| | Cigarette | 3.2 | 6.8 | 2.6 | 2.9 | 4.8 | 2.6 |
| | Other ^c | 0 | 0 | 0.3 | 0 | 0 | 0.3 |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette.

^aCalculated over two-week intervals leading up to the week.

^b–, not applicable.

^cAny other tobacco or nicotine-containing product.

Product usage

Assigned study product and all other product usage was tracked daily and reviewed by study staff at two-week intervals. Data at each time-point were based on reported usage from the previous two weeks (Table 6).

Among the per-protocol sample, tobacco product usage at baseline was approximately evenly matched among the three product groups, with cigarettes per day consumed averaging 18.9 for the tobacco-heating cigarette group, 18.3 for the snus group and 16.8 for the ultra-low machine yield tobacco-burning cigarette group. Over the duration of the study (i.e. Weeks 1–24), average daily counts of assigned product usage were 20.8 (range 18.2–23.5) for the tobacco-heating cigarette

group, 10.6 (range 9.5–11.5) for the snus group and 24.6 (range 21.5–26.6) for the ultra-low machine yield tobacco-burning cigarette group. Occasional usage of other nicotine products was reported during nine of the 13 two-week intervals. The most commonly used other products were cigarettes or nicotine gum. Mean daily use of the tobacco-heating cigarette and ultra-low machine yield tobacco-burning cigarette increased over time from 18.2 and 21.5, respectively, at the Week 2 interval to 23.5 and 26.6, respectively, at the Week 24 interval. No increase in daily snus usage was noted over the same time. Results were similar for the intent-to-treat sample.

Compliance

For all reported daily data within two-week intervals for the per-protocol sample, percentages of assigned product used (i.e. out of total product usage) through Week 24 were

Table 7. Subject cumulative compliance.

| Week | Product | Intent-to-treat | | | Per-protocol | | |
|------|------------------------|-----------------|---------|----------------|----------------|----------------|----------------|
| | | TH | S | TB | TH | S | TB |
| 4 | Sample size (%) | 44 (34) | 43 (33) | 44 (34) | 33 (38) | 20 (23) | 35 (40) |
| | Compliant ^a | 34 (77) | 12 (28) | 44 (100) | 30 (91) | 11 (55) | 35 (100) |
| | Somewhat ^b | 7 (16) | 11 (26) | — ^d | 2 (6) | 7 (35) | — ^d |
| 12 | Non ^c | 3 (7) | 19 (44) | — ^d | 1 (3) | 2 (10) | — ^d |
| | Compliant ^a | 34 (77) | 14 (33) | 41 (94) | 30 (91) | 13 (65) | 35 (100) |
| | Somewhat ^b | 4 (9) | 10 (23) | — ^d | 3 (9) | 6 (30) | — ^d |
| 24 | Non ^c | 1 (2) | 10 (23) | — ^d | — ^d | 1 (5) | — ^d |
| | Compliant ^a | 32 (73) | 11 (26) | 35 (80) | 32 (97) | 11 (55) | 35 (100) |
| | Somewhat ^b | 1 (2) | 9 (21) | — ^d | 1 (3) | 9 (45) | — ^d |
| | Non ^c | 1 (2) | 8 (19) | — ^d | — ^d | — ^d | — ^d |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette. Percent values have been rounded.

^aCompliant: $\geq 75\%$ of tobacco product use was assigned product.

^bSomewhat compliant: $>50\%$ to $<75\%$ of tobacco product use was assigned product.

^cNon-compliant: $\leq 50\%$ of tobacco product use was assigned product.

^d—, not applicable.

Table 8. Summary of AEs, incidences (number of distinct subjects), intent-to-treat sample.

| Adverse events | TH | S | TB | Overall ^a |
|------------------------------|----------------|----------------|---------|----------------------|
| Any | 82 (32) | 92 (24) | 77 (32) | 251 (88) |
| Mild | 63 (26) | 57 (20) | 58 (29) | 178 (75) |
| Moderate | 18 (15) | 35 (16) | 16 (12) | 69 (43) |
| Severe | — ^b | — ^b | 3 (2) | 3 (2) |
| Product-related ^c | 17 (8) | 31 (15) | 13 (7) | 61 (30) |
| Led to study discontinuation | — ^b | — ^b | 1 (1) | — ^b |
| Serious | — ^b | — ^b | 1 (1) | 1 (1) |

TH, switched to tobacco-heating cigarette; S, switched to snus; TB, switched to ultra-low machine yield tobacco-burning cigarette.

^aNo AEs in never smokers were reported.

^b—none.

^cPossibly, probably, or definitely according to the Principal Investigator.

between 86% and 94% for tobacco-heating cigarette usage, between 65 and 76% for snus usage, and between 89% and 98% for ultra-low machine yield tobacco-burning cigarette usage. A summary of subject cumulative compliance is presented in Table 7; findings for Week 24 in the per-protocol sample are summarized here. In the tobacco-heating cigarette group, 97% of subjects were cumulatively classified as compliant (i.e. the proportion of amount of assigned study product used relative to combined use of study product and other products was $\geq 75\%$), and 3% were cumulatively classified as somewhat compliant (i.e. the proportion of amount of assigned study product used relative to combined use of study product and other products was $>50\%$ to $<75\%$). In the snus group, 55% were cumulatively classified as compliant, and 45% were cumulatively classified as somewhat compliant. Among the ultra-low machine yield tobacco-burning cigarette group subjects, 100% were cumulatively classified as compliant.

Adverse events

AEs are summarized in Table 8. Overall, there were 75 subjects with no reported AEs, and no subject in the never smoker group reported an AE. In the intent-to-treat smokers who switched to tobacco-heating cigarettes, snus or ultra-low machine yield tobacco-burning cigarettes, there were 82 (32

subjects), 92 (24 subjects) and 77 (32 subjects) AEs reported, respectively. For AEs considered by the Principal Investigator to be possibly, probably or definitely related to the study product, 17 (8 subjects), 31 (15 subjects) and 13 (7 subjects) were reported in the groups switched to tobacco-heating cigarettes, snus and ultra-low machine yield tobacco-burning cigarettes, respectively. Overall, there were 178 mild, 69 moderate and 3 severe AEs. The mild AEs were distributed evenly across the three product groups. There was a higher occurrence of moderate AEs in the group switched to snus ($n=35$) compared with the other two groups ($n=18$ in the tobacco-heating cigarette group and $n=16$ in the ultra-low machine yield tobacco-burning cigarette group), although the number of distinct subjects with moderate AEs was approximately the same across the three product groups. Additionally, the majority ($n=30$) of the moderate AE incidences reported in the group switched to snus were deemed to be not product-related, and the remaining five were deemed possibly product-related. The three severe AEs were all in the ultra-low machine yield tobacco-burning cigarette group, although none was related to the study product according to the Principal Investigator. There were no other differential patterns among the three product groups.

The most frequently reported system organ classes for product-related AEs were respiratory, thoracic, and mediastinal disorders (15 mild and 1 moderate) and gastrointestinal disorders (12 mild, 3 moderate). For respiratory, thoracic and mediastinal disorders, there were 3–4 subjects each in the tobacco-heating cigarette and ultra-low machine yield tobacco-burning cigarette groups, and there were nine subjects with product-related AEs in the snus group. Overall respiratory, thoracic and mediastinal disorders of note included hiccups and cough. There were none of either in the never smokers and no hiccups in either the tobacco-heating cigarette or ultra-low machine yield tobacco-burning cigarette groups; however, hiccups were 16.3% of the AEs in the snus group (4.3% overall). There were no other differential patterns among the three product groups.

Safety evaluations

Sporadic out-of-range values occurred in some subjects for various chemistry, hematology and urinalysis measures. These out-of-range values were considered not clinically significant and/or not study product-related by the Principal Investigator. Vital signs noted as AEs during the study included hypertension ($n=3$), pyrexia [fever] ($n=1$), vasovagal episode [fainting] ($n=1$) and subjective fever ($n=1$); none were considered product-related. All ECGs were determined by the Principal Investigator to be either normal or abnormal but not clinically significant.

As required for inclusion in the study, subjects had acceptable spirometry results at Screening and Week 0. The study sample was thus prescreened as relatively healthy to only mildly COPD-afflicted. No subjects with asthma were on study. Spirometry was additionally performed at Weeks 12 and 24 to measure any change in pulmonary function during the course of the study. Some subjects showed a significant change ($\geq +12\%$) in percent FEV1 predicted or percent FVC predicted from pre-bronchodilator to post-bronchodilator response at either Week 12 or Week 24. Approximately the same number of subjects ($n=5$ tobacco-heating; $n=6$ snus; $n=6$ ultra-low machine yield tobacco-burning cigarette) experienced a notable positive response to bronchodilation in the three groups, and these were subjects who responded to bronchodilation at levels that had been considered notable by the Medical Monitor at Screening. Percent FEV1 predicted and percent FVC predicted over time (i.e. from Week 0 to Week 24) for either pre-bronchodilation or post-bronchodilation were also evaluated. There were no evident trends in the subjects who had at least $\pm 12\%$ change over time for either variable.

Discussion

Study conduct, methodology and subject disposition for a 24-week randomized study of adult cigarette smokers switched to an alternate tobacco product have been described here. The study design and its analytical methodology proved feasible. In general, the results from safety monitoring throughout the study indicated no unexpected side effects due to study products, as study products were generally well-tolerated by the subjects.

Overall, recruiting subjects into the study was more difficult than anticipated, as the original plan was to randomize 50 subjects per tobacco product group. After follow-up consultation with each CRU, this difficulty was primarily attributed to the 24-week duration of the study and the extensive inclusion and exclusion criteria. After extended and enhanced recruiting efforts, 44 smokers were randomized into each of the tobacco-heating cigarette and ultra-low machine yield tobacco-burning cigarette product groups and 43 into the snus product group. On the other hand, completion rates were better than initially anticipated, as the target was to complete at least 60% (30 of 50) of those randomized to each study product. Completion rates in the tobacco-heating and ultra-low machine yield tobacco-burning cigarette product groups were higher (80% and 77%, respectively) than in the snus product group (67%).

The counts for subjects who withdrew consent for non-product-related reasons were approximately equal among the three product groups. However, subjects withdrawing consent increased as the assigned study product became less like their usual tobacco product form (i.e. tobacco-burning cigarettes). This pattern may impact biomarker and health-related questionnaire data interpretations and conclusions.

Overall compliance with the assigned product usage in the per-protocol sample was highest in the ultra-low machine yield tobacco-burning cigarette group (89–98%), followed by the tobacco-heating cigarette group (86–94%) and the snus group (65–76%). These data also indicate that some caution may be required when interpreting observed effects (or lack of observed effects) – for example, any changes in biomarkers (Ogden et al., 2015a,b) – especially for the snus per-protocol subset. For snus, observed effects are likely only partially attributable to the actual use of snus, and correspondingly, failure to observe effects for snus may be due to the continued use of other tobacco products. Use of multiple tobacco products would likely obscure the true effects of switching completely from cigarettes to snus. Although subjects in the snus group are labeled as “switched to snus”, the data should be understood to be estimates of the effects due to dual or poly-tobacco product use, rather than as estimates of effects due to snus use alone. Of note, cigarette consumption decreased among the smokers switched to snus. Biomarker changes in the snus group were generally positive (e.g. indications of reductions in exposure) or not different (Ogden et al., 2015a,b); thus it would be expected that with complete switching to snus, additional positive responses would be observed.

Within the per-protocol sample, tobacco product usage at baseline was approximately evenly matched among the three product groups (18.9 for tobacco-heating cigarette group, 18.3 for snus group and 16.8 for the ultra-low machine yield tobacco-burning cigarette group). There was evidence of increased daily cigarette consumption at Week 24 in the ultra-low machine yield tobacco-burning cigarette (29.2 assigned study product plus other cigarettes) and tobacco-heating cigarette groups (26.4 assigned study product plus other cigarettes); however, many tobacco-related biomarkers of exposure decreased in both groups (Ogden et al., 2015a). That the study products were provided at no expense to the subjects over the course of study might have affected this behavioral pattern of increased cigarette usage. In all groups, average cigarette consumption decreased between Week 0 and Week 24, indicating a substantial cigarette reduction, with the balance of tobacco product consumption constituted by the assigned study product. In the snus group, dual use of non-study cigarettes was a larger percentage of the overall tobacco product consumption compared with the other two groups (32% in snus compared with 9% and 11% in the ultra-low machine yield tobacco-burning cigarette and tobacco-heating cigarette groups, respectively).

Measurement of spirometry parameters in this study was primarily for establishing subject eligibility for participation and for ongoing safety monitoring. Pulmonary function was not included as an outcome measure, as it was not expected to be responsive to switching to an alternate tobacco product over the 24-week duration of this study. This notwithstanding,

results of FER_{post} (%) indicated that the metric was not affected by any of the study products. Of note, the study sample was screened as fairly healthy relative to the general population of long-term smokers.

This article documents a practical approach for the assessment of potential exposure and health effects from the use of tobacco products. The design and methodology, evaluating reasonably healthy adult smokers over 24 weeks, proved feasible. Many elements of the study outcomes (e.g. compliance with assigned study product usage) appeared to be essentially stable at Week 12. Accordingly, although the 24-week duration of the study is one of its strengths, similar study designs in the future may consider a shortened study duration, which might also improve recruitment efforts. Results presented here provide insight for further development of relevant tools (e.g. improved study design, optimized outcome measures) for the assessment of human exposure and health effects from the use of tobacco products. Additionally, biomarker findings from this randomized study (Ogden et al., 2015a,b) provide generalized knowledge of the risk continuum among various tobacco products.

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Declaration of interest

All authors are current employees of RAI Services Company or R.J. Reynolds Tobacco Company.

References

- American Thoracic Society (ATS). (1991). Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 144:1202–18.
- Borgerding MF, Bodnar JA, Curtin GM, Swauger JE. (2012). The chemical composition of smokeless tobacco: a survey of products sold in the United States in 2006 and 2007. *Regul Toxicol Pharmacol* 64: 367–87.
- Federal Trade Commission (FTC). (1967). Cigarettes: testing for tar and nicotine content. *Federal Register* 32:11178 August 1.
- Federal Trade Commission (FTC). (1980). Cigarettes and related matters: carbon monoxide, tar and nicotine content of cigarette smoke; description of new machines and methods to be used in testing. *Federal Register* 45:46483 July 10.
- Ferris BG. (1978). Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 118:1–120.
- International Conference on Harmonization (ICH). (1996). Guidance for industry E6 good clinical practice: consolidated guidance. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf> [last accessed 2 Aug 2014].
- King B, Dube S, Kaufmann R, et al. (2011). Vital signs: current cigarette smoking among adults aged ≥ 18 years – United States, 2005–2010. *MMWR* 60:1207–12.
- Nutt DJ, Phillips LD, Balfour D, et al. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. *Eur Addict Res* 20:218–25.
- Ogden MW, Marano KM, Jones BA, et al. (2015a). Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: part 2. Biomarkers of exposure. *Biomarkers*. [Epub ahead of print]. doi: 10.3109/1354750X.2015.1094134.
- Ogden MW, Marano KM, Jones BA, et al. (2015b). Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: part 3. Biomarkers of biological effect. *Biomarkers*. [Epub ahead of print]. doi: 10.3109/1354750X.2015.1094135.
- United States Congress. (2009). Family smoking prevention and tobacco control act. Available from: <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm237092.htm> [last accessed 14 Aug 2014].
- World Medical Association (WMA). (2002). Declaration of Helsinki – ethical principles for medical research involving human subjects. Available from: <http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC20-Attach-1.pdf> [last accessed 14 Aug 2014].
- Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction Group. (2009). The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the US. *Tob Control* 18:324–32.

Supplementary material available online

Supplementary Tables 1–3