Supplemental Data

Materials and Methods: Inclusion exclusion criteria
Potential subjects who met the following criteria at Screening were included in the study.

1. Males and females between the ages of 30 and 50 years, inclusive.
2. Subjects met one (a, b, c, or d) of the following tobacco or non-tobacco use conditions based on self-report:
    a. SMK who exclusively smoked 10 - 20 combustible filtered cigarettes per day (CPD) 83 – 100 mm in length, non-menthol or menthol, for at least 3 years prior to Screening. Brief periods of abstinence more than 30 days prior to Screening due to illness, quit attempt, or clinical study participation were allowed at the discretion of the Investigator.
    b. MSC who exclusively consumed ≥ 1 can of moist snuff per week for at least 6 months prior to Screening. Brief periods of abstinence more than 30 days prior to Screening due to illness, quit attempt, or clinical study participation were allowed at the discretion of the Investigator.
    c. VAP who exclusively used a nicotine-containing "cig-a-like" and/or tank system daily for at least 3 months prior to Screening. Subjects reported using only products with the characterizing flavors of tobacco, menthol, or fruit (e.g., berry, strawberry, blueberry, banana). Brief periods of abstinence more than 30 days prior to Screening due to illness, quit attempt, or clinical study participation were allowed at the discretion of the Investigator.
    d. NTC who had used no tobacco or nicotine-containing products for at least the past 5 years prior to Screening and did not plan to use any tobacco or nicotine-containing products throughout the study.
3. Subjects met one (a, b, c, or d) of the following conditions:
    a. SMK had an ECO ≥ 15 ppm and ≤ 100 ppm and had a positive urine cotinine test (> 500 ng/mL).
    b. MSC had an ECO ≤ 5 ppm and had a positive urine cotinine test (> 500 ng/mL).
    c. VAP had an ECO ≤ 5 ppm and had a positive urine cotinine test (> 500 ng/mL).
    d. NTC had an ECO ≤ 5 ppm and had a negative urine cotinine test (≤ 200 ng/mL).
4. Generally healthy (i.e., free of any acute or chronic health conditions in the opinion of the Investigator).
5. Females had a negative serum pregnancy test result.
6. Females of childbearing potential were willing to use a form of contraception acceptable to the Investigator for the timing as noted below through study discharge.

Potential subjects who met any of the following criteria at Screening were excluded from the study:

1. Subjects who met one of the following based upon their cohort:
    a. For SMK, use of any tobacco- or nicotine-containing products (e.g., e-cigs, moist snuff, chewing tobacco, nicotine replacement therapy (NRT), tobacco cigarettes that are heated but not burned, dissolvable nicotine products) other than combustible cigarettes within 30 days prior to Screening. *NOTE: Subjects*

who smoked ≤ 6 cigars in the past 12 months prior to Screening were NOT excluded. Subjects who received short-term administration of or used a NRT as a temporary bridging treatment/aid were NOT excluded.

b. For MSC, use of any tobacco- or nicotine-containing products (e.g., combustible or heated cigarettes, e-cigs, chewing tobacco, NRTs, dissolvable nicotine products) other than moist snuff within 30 days prior to Screening or regular exposure to cigarette smoke within 60 days prior to Screening (e.g., lived with a smoker who smoked in the home). *NOTE: Subjects who received short-term administration of or used a NRT as a temporary bridging treatment/aid were NOT excluded*.

c. For VAP, use of any tobacco- or nicotine-containing products (e.g., combustible or heated cigarettes, moist snuff, chewing tobacco, NRTs, dissolvable nicotine products) other than nicotine-containing vaping products within 30 days prior to Screening or regular exposure to cigarette smoke within 60 days prior to Screening (e.g., lived with a smoker who smoked in the home). *NOTE: Subjects who received short-term administration of or used a NRT as a temporary bridging treatment/aid were NOT excluded*.

d. For NTC, use of any tobacco- or nicotine-containing products (e.g., combustible or heated cigarettes, e-cigs, moist snuff, chewing tobacco, NRTs, dissolvable nicotine products) within 5 years prior to Screening or regular exposure to cigarette smoke within 60 days prior to Screening (e.g., lived with a smoker who smoked in the home).

2. Clinically significant or unstable/uncontrolled acute or chronic medical conditions, as determined by the Investigator, that precluded a subject from participating safely in the study (e.g., uncontrolled hypertension, asthma or other lung disease, or cardiac disease) based on safety assessments such as clinical laboratory tests, medical history, and physical/nasopharyngeal examinations.
3. History, presence, or clinical laboratory test results indicating diabetes.
4. Presence of environmental allergies that result in allergic rhinitis which had been treated with any medication within 2 weeks of sample collection.
5. Observed or report of a heavy cough that precluded a subject from successfully completing the lung permeability assessment.
6. Use of any NRT or smoking cessation medication (e.g., nicotine gum, lozenge, or patch; varenicline [Chantix®], bupropion [Wellbutrin®, Zyban®]) within 30 days prior to Screening through completion of the study.
7. A female who was pregnant, planned to become pregnant during the course of the study, or was breast feeding.
8. Females ≥ 35 years of age currently using systemic, estrogen-containing contraception or hormone replacement therapy.
9. Post-bronchodilator FEV1:FVC ratio < 0.7 and FEV1 < 80% of predicted.
10. Post-bronchodilator FEV1:FVC ratio < 0.75 and FEV1 increase ≥ 12% (or > 200 mL) from pre- to post-bronchodilator.
11. Systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg.
12. Fever (i.e., body temperature > 100.5°F).
13. Body mass index (BMI) < 18.5 or > 40.0 kg/m^2.
14. Estimated creatinine clearance (by Cockcroft-Gault equation) < 80 mL/minute.
15. Positive urine drug screen or alcohol test.
16. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

17. Postponing a decision to quit tobacco product use (defined as planning a quit attempt within 30 days of Screening) to participate in this study or previous attempt within 30 days prior to Screening.
18. Had received radiolabeled substances or had been exposed to radiation sources over the past 12 months or was likely to receive radiation exposure or radioisotopes within the next 12 months, such that participation in this study would increase the subject's total exposure beyond the recommended levels considered safe (i.e., weighted annual limit recommended by the International Commission on Radiological Protection of 3000 mrem).

Final eligibility was at the discretion of the Investigator based on whether or not the subject's participation in the study would compromise his or her safety or limit his or her ability to complete the study.

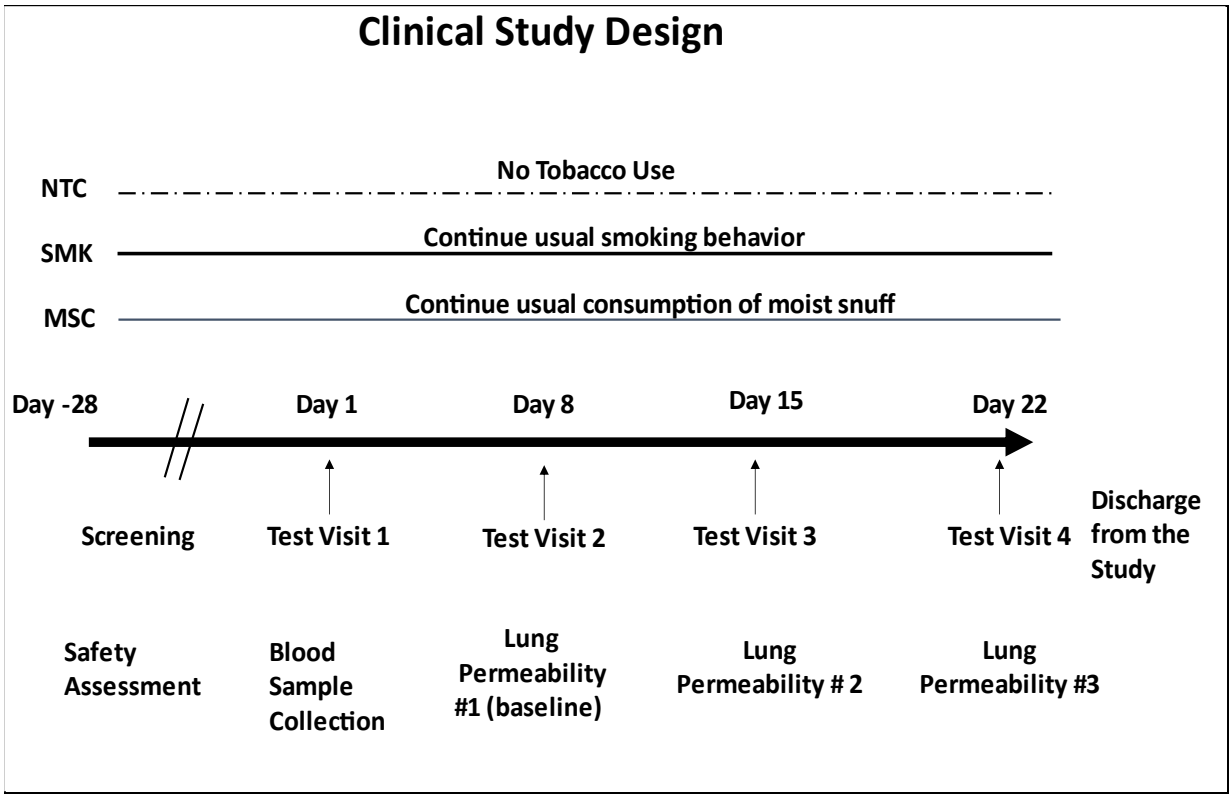
Supplemental Table S1: Subject disposition

One female subject (SMK) was discontinued by the PI on Day 1 of Period 3 due to positive alcohol screen. Another subject, also a female (SMK) was an alternate subject to complete the cohort but was not needed. A male subject (NTC) was discontinued by the PI on Day 1.

	Tobacco user group				
Category	**SMK**	**MSC**	**VAP**	**NTC**	**Overall**
Enrolled	8 (100.0%)	5 (100.0%)	1 (100.0%)	7 (100.0%)	21 (100.0%)
Completed Study	6 (75.0%)	5 (100.0%)	1 (100.0%)	6 (85.7%)	18 (85.7%)
Dropped From Study	2 (25.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	3 (14.3%)
Other	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
Physician Decision	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (9.5%)

Supplemental Figures

Supplemental Figure 1. Clinical Study Design:



Supplemental Figure 1: The outline of clinical design shows study timelines, study groups and key procedures performed during the study period as described in Materials and Methods section. The SMK and MSC continued their usual tobacco use behavior throughout the study, while the NTC did not use any tobacco products. One vapor consumer also completed all the study procedures (not shown in the diagram). Safety Assessments were conducted at Screening and AEs were monitored through the entire study period. Three measurements of lung permeability were performed by DTPA inhalation method at test visits 2, 3 and 4. Expired carbon monoxide was measured at all test visits. Blood samples were collected to determine nicotine and cotinine at test visits 1-4.