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Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: Eight-day randomized clinical trial in Korea

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ABSTRACT

A randomized, controlled, open-label parallel-group, single-center study to determine biomarkers of exposure to 12 selected harmful and potentially harmful constituents (HPHC) in cigarette smoke and urinary excretion of mutagenic material in 72 male and female Korean subjects smoking *Lark One* cigarettes (1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO) at baseline. Subjects were randomized to continue smoking *Lark One* cigarettes, or switch to an Electrically Heated Cigarette Smoking System (EHCSS) and EHCSS-K3 cigarette (3 mg tar, 0.2 mg nicotine, and 0.6 mg CO), or to no-smoking. The mean decreases from baseline to Day 8 were statistically significant (all $p < 0.05$) for 10 of 12 HPHC in mainstream cigarette smoke including CO (the primary objective) in the EHCSS-K3 group (range: −1.5% to −74.2%). Exposure to the other determined HPHC was not significantly different. In the *Lark One* group, the mean exposure to 6 of 12 HPHC in cigarette smoke was significantly (all $p < 0.05$) decreased; however, exposure to CO was significantly increased. The largest mean reductions in biomarkers of exposure to HPHC occurred in smokers who switched to no-smoking (−3.4% to −98.9%). The mean excretion of mutagenic material was significantly decreased ($p < 0.05$) in the EHCSS-K3 and no-smoking groups (−31.8% and −45.3%, respectively), and increased in the *Lark One* group (+31.5%).

1. Introduction

There is overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases in smokers (Ha et al., 2003; US Department of Health and Human Services, 2010). In the US the Family Smoking Prevention and Tobacco Control Act (FSPTCA) (Family Smoking Prevention and Tobacco Control Act, 2009) has empowered the Food and Drug Administration (FDA) to evaluate and regulate modified risk tobacco products (MRTPs) (Deyton et al., 2010). The FDA, in consultation with the Institute of Medicine (IOM), has also been charged to issue guidance and regulations on the scientific evidence required for the assessment and ongoing review of MRTPs (Food and Drug Administration, 2012; Institute of Medicine, 2012).

The Electrically Heated Cigarette Smoking System (EHCSS) reduces many of the toxicologically important HPHC present in mainstream cigarette smoke and significantly lowers the biological activity of the smoke aerosol compared to conventional lit-end cigarettes in laboratory-based test systems (Werley et al., 2008; Zenzen et al., 2012). Electrical heating of the tobacco reduces pyrolysis, and produces smoke that contains lower amounts of most cigarette smoke HPHC. The current third-generation EHCSS is a puff-activated electrical heater that can only be used to smoke EHCSS series-K cigarettes, but not conventional lit-end cigarettes.

The current assessment, the second in a series of five clinical evaluations describing data from investigations performed under both controlled and real-life smoking conditions (Martin Leroy et al., 2012; Tricker et al., 2012a,b,c), reports a randomized, controlled, open-label, parallel-group, single-center study to evaluate differences in the exposure to selected HPHC in cigarette smoke and excretion of mutagenic material in urine. Subjects usually smoking the *Lark One* non-menthol cigarette (Lark1) at baseline were randomized to continue smoking the Lark1 cigarette, or switch to use the EHCSS heater to smoke the EHCSS-K3 cigarette, or to switch to no-smoking, for a duration of 8 days. The study was designed to examine changes in selected tobacco-specific and tobacco-related biomarkers of exposure to HPHC present both in the gas–vapor phase (1,3-butadiene, acrolein, benzene, CO, and crotonaldehyde) and particulate phase (2-naphthylamine, 4-aminobiphenyl, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK], acrylamide, nicotine, pyrene, and *o*-toluidine) of mainstream cigarette smoke, as well as excretion of mutagenic material in urine.

The primary objective of the study was to assess exposure to CO, determined as carboxyhemoglobin concentration in blood at

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17:00 ($COHb_{17:00}$), between the study groups on Day 8. Exposure to CO was selected as the primary objective based on the reduction of CO in mainstream smoke compared to conventional cigarettes (Werley et al., 2008; Zenzen et al., 2012) and the previous observation that COHb is reduced in smokers after switching to the EHCSS (Frost-Pineda et al., 2008a,b).

2. Materials and methods

2.1. Subjects

Adult male and female Korean smokers (aged 20–50) with acceptable health conditions who smoked 10–30 conventional lit-end non-menthol cigarettes (1.0–3.0 mg tar) per day and the Lark1 (1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO) as their exclusive brand for at least 2 weeks prior to admission to the clinic were recruited. All enrolled subjects signed an informed consent form prior to screening procedures. Subjects were compensated for study participation and were free to withdraw from the study at any time. Screening was performed within a 2 week prior to study enrolment and included medical history, physical examination, vital signs, electrocardiogram (ECG), pulmonary function tests, clinical laboratory, COHb, and the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Women of childbearing potential who used a reliable method of contraception were considered as eligible for study inclusion; pregnant or lactating women were excluded. Other exclusion criteria included existence of a clinically significant disease, clinically relevant abnormal findings on physical examination, medical history, and clinical laboratory results, alcohol or drug abuse, and a positive test for human immunodeficiency virus (HIV) or hepatitis. Subjects using a nicotine-containing product other than cigarettes within 3 months prior to screening, or having <1.5% COHb saturation (suggestive of being a non-smoker) were also excluded. The use of any medication with the exception of hormonal contraceptives for female subjects was prohibited in the week before the study.

2.2. Cigarette products

A leading commercial conventional cigarette (CC) brand (*Lark One*) was chosen to represent the Korean cigarette market in which smokers have a preference for smoking cigarettes with very low International Organization for Standardization (ISO) tar and nicotine yields. Lark1 also has a similar tobacco blend to that used in the EHCSS test cigarettes. Lark1 was analyzed for tar and nicotine according to ISO methods. All study cigarettes were conditioned according to ISO standard 3402 (International Organization for Standardization, 1991). Lark1 was smoked on a smoking machine according to ISO standard 3308 (International Organization for Standardization, 2000a). Tar, nicotine and CO were determined according to ISO standards 4387, 10315, and 8454, respectively (International Organization for Standardization, 2000b,c, 1995). Mainstream smoke from EHCSS cigarettes was generated on a modified smoking machine with a carousel adapted to use the EHCSS series-K lighter. The EHCSS smoke generation conformed with ISO standard 3308; some slight technical deviations were required. The ISO yields as declared on the cigarette packaging were as follows: *Lark One* (Lark1; 1.0 mg tar, 0.1 mg nicotine, and 1.5 mg CO) and EHCSS-K3 (3 mg tar, 0.2 mg nicotine, and 0.6 mg CO).

2.3. Study design and conduct

Enrolled subjects ($N = 99$, 75 males and 24 females) completed a 7-day smoking diary prior to check-in on Day -2 (Fig. 1). The median daily cigarette consumption was used to determine the maximum number of cigarettes that the subject could smoke during the in-clinic confinement. On Day -2, subjects entered the clinic before 08:00. Vital signs and ECG were measured (08:00), clinical laboratory and a physical examination performed to re-confirm eligibility for study inclusion. All subjects were confined to the clinic from Day -2 to Day 9 under medical supervision. On Day -1 (baseline), assessments included determination of biomarkers of exposure in a 24-h urine sample (combined urine voids starting at 07:00), vital signs (07:00), COHb ($COHb_{0700}$ and $COHb_{17:00}$; 07:00 and 17:00), plasma cotinine and nicotine ($COT\text{-}P_{17:00}$ and $NIC\text{-}P_{17:00}$; 17:00). Seventy-two subjects (54 males and 18 females) were randomized into 1 of 3 parallel groups (Lark1: $N = 28$; EHCSS-K3: $N = 28$; and no-smoking: $N = 16$) using a stratification based on median daily cigarette consumption (10–19 and 20–30 cigarettes per day [CPD]). On randomization, subjects continuing to smoke Lark1 were 'blind' to the identity of the test cigarette. Non-randomized subjects were released from the study center after completion of all scheduled assessments. Subjects withdrawing from the study or those removed by the investigator after

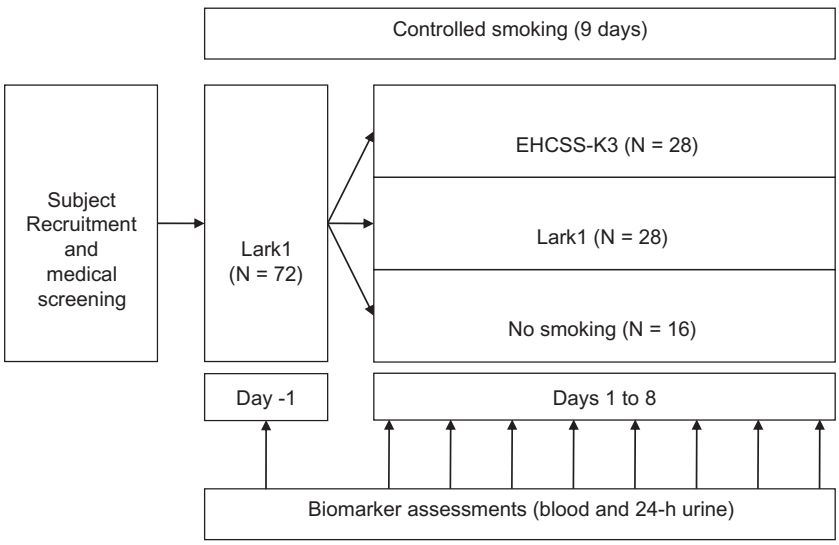

Fig. 1. Schedule of study events. Footnote: On Day-1 (baseline) all subjects smoked the Lark1 cigarette prior to randomization into the three study groups. All cigarettes described in Table 2.