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Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: A one-month, randomized, ambulatory, controlled clinical study in Poland

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ABSTRACT

This randomized, open-label, ambulatory, controlled clinical study investigated biomarkers associated with cardiovascular risk and biomarkers of exposure to 10 selected harmful and potentially harmful constituents (HPHC) in cigarette smoke in 316 male and female Polish smokers. Subjects were randomized to continue smoking conventional cigarettes (CC; N = 79) or switch to smoking the Electrically Heated Cigarette Smoking System series-K cigarette (EHCSS-K6; N = 237). Biomarker assessments were performed at several time points during the study at baseline and during the 1-month investigational period. The primary biomarkers were high-sensitivity C-reactive protein and white blood cell counts. No statistically significant differences in the two primary biomarkers were found between the study groups at the end of the study. End-of-study comparisons of secondary biomarkers between study groups indicated an increase in high-density lipoprotein cholesterol, and reductions in red blood cell count, hemoglobin, and hematocrit levels in the EHCSS-K6 group. All biomarkers of exposure to cigarette smoke HPHC were decreased in the EHCSS-K6 group, despite an increase in cigarette consumption, compared to the CC group. There were no apparent differences in any of the safety assessment parameters between the groups, and the overall incidence of study-related adverse events was low.

1. Introduction

There is overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases in smokers (US Department of Health and Human Services, 2010). The Family Smoking Prevention and Tobacco Control Act (FSPTCA) (Family Smoking Prevention and Tobacco Control Act, 2009) in the United States 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 association between cigarette smoking and cardiovascular disease (CVD) is well documented. For example, smoking is a cause of premature atherosclerosis, acute myocardial infarction, sudden death, and stroke (Burns, 2003; Hatsukami et al., 2006a,b). Significant changes in biomarkers related to oxidative stress, endothelial damage, thrombosis, inflammation, and lipid metabolism have been found in smokers (Benowitz, 2003; Hatsukami et al., 2006a,b; US Department of Health and Human Services, 2010).

Use of the Electrically Heated Cigarette Smoking System (EHCSS) series-K heater and the EHCSS series-K6 cigarette results in reduced levels of a wide range of toxicologically important cigarette smoke HPHC and significantly lowers the biological activity of mainstream smoke compared to conventional lit-end cigarettes in laboratory-based test systems (Werley et al., 2008; Zenzen et al., 2012). By heating tobacco, the temperature reached is lower than that reached in the burning cone of a conventional lit-end cigarette. Up to 8 puffs can be obtained by smoking an EHCSS series-K cigarette with the EHCSS heater. Previous clinical investigations with the EHCSS have found that there are reductions in biomarkers of exposure to selected cigarette smoke HPHC (Frost-Pineda et al., 2008a,b; Roethig et al., 2005, 2007). Smokers who switched to an earlier version of the EHCSS over 12 months also had favorable changes in several biomarkers associated with CVD (Roethig et al., 2008). Additionally, the use of an EHCSS results in reductions of the levels of environmental tobacco smoke (ETS) constituents in indoor air (Frost-Pineda et al., 2008c; Tricker et al., 2009).

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The current study investigated the effect of switching to the EHCSS series-K heater and the EHCSS-K6 cigarette for 1 month on the levels of biomarkers associated with CVD and selected biomarkers of exposure to cigarette smoke HPHC in smokers. The biomarkers associated with CVD included those (white blood cell count, hematocrit, urine 11-dehydrothromboxane B_2, and high-density lipoprotein cholesterol) for which statistically significant changes were observed in a previous 12-month study evaluating a second-generation EHCSS (series-JLI) (Roethig et al., 2008). Biomarkers of exposure were selected for the HPHC 1,3-butadiene, 2-naphthylamine (2-NA), 4-aminobiphenyl (4-ABP), acrolein, benzene, carbon monoxide (CO), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), nicotine, pyrene, and *o*-toluidine.

The primary biomarkers investigated were white blood cell (WBC) count and high-sensitivity C-reactive protein (*hs*-CRP), two biomarkers which indicate an inflammatory response associated with CVD and have been shown to be influenced by smoking (Abel et al., 2005; Andrews and Tingen, 2006; Bakhru and Erlinger, 2005; Bazzano et al., 2003; Hatsukami et al., 2005).

This is the final manuscript in a series of five clinical evaluations of the EHCSS describing data from clinical investigations performed under both controlled (Tricker et al., 2012a,b,c,d) and actual use smoking conditions (this study).

2. Materials and methods

2.1. Subjects

Subjects were eligible for enrollment if they were Caucasian smokers aged 30–60 years with acceptable health conditions. Subjects were current smokers of commercially available, non-mentholated conventional cigarettes with a 3–10 mg tar yield with a smoking history of at least 10 years prior to screening.

Subjects with clinically relevant abnormal findings based on the screening assessments were excluded. Pregnant or lactating women and women of child-bearing potential who were not using an acceptable method of contraception were also excluded. Subjects were recruited from the clinical site database and were compensated for their participation in the study. All subjects provided written informed consent and were advised that they were free to withdraw from the study at any time. Each subject was provided with advice and information about the risks of smoking, and counseling was made available.

2.2. Study design and conduct

This study was approved by the Independent Ethics Committee of the Regional Chamber of Physicians, Warsaw, Poland, and conducted at MTZ Clinical Research Ltd., Warsaw, Poland (MTZ) in compliance with the ethical principles that have their origin in the Declaration of Helsinki (World Medical Association, 1964, as amended 2004) and International Conference on Harmonisation Good Clinical Practice (GCP) guidelines (International Conference on Harmonisation, 1996). The study was conducted in two sessions between October 2007 and April 2008.

This was a randomized, open-label, controlled study with two study groups, EHCSS-K6 and conventional cigarettes (CC). The study schedule consisted of eight main study visits, screening (Visit 1), two baseline, weekly assessments (Visits 2 and 3), and five post-randomization weekly assessments (Visits 4–8). The whole study duration was approximately 8 weeks (Fig. 1), with the investigational period defined as 5 weeks from the date of randomization (Visit 3/Day 0) to the last study visit (Visit 8/Day 35).

The screening assessment at Visit 1 included the following assessments: physical examination, vital signs, chest X-ray, electrocardiography (ECG), clinical laboratory, drug screening, pregnancy test, and collection of demographic data and smoking history, including the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991). Blood and urine samples were taken for serum chemistry, hematology, serology, and urine analysis.

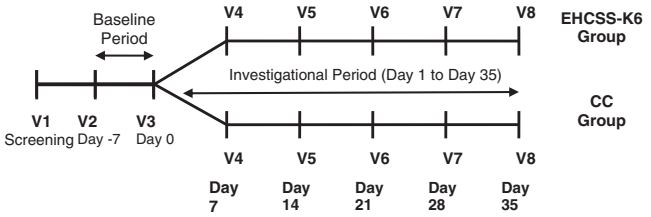

Fig. 1. Study design and assessment schedule. All subjects were scheduled to attend the study site on Visit 1 for screening assessments, Visits 2 and 3 for baseline assessments of biomarkers prior to randomization at Visit 3; and Visits 4 through 8 for study investigations. Study visits were scheduled 7 (±2) days apart.

Randomization of subjects was performed at Visit 3 after completion of the visit-specific assessments using an Interactive Voice Response System (IVRS) (Covance, Waterloo, Belgium). Subjects were randomized to either the EHCSS-K6 group or the CC group, respectively, stratified by gender (40–60% of each gender) and age (50% subjects aged 30–44 years and 50% aged 45–60 years). A randomization ratio of 3:1 (EHCSS-K6:CC) was used to account for possible non-compliance in the EHCSS-K6 group.

Subjects randomized to the CC group continued to smoke their own brand of cigarettes for the duration of the study. Subjects in the EHCSS-K6 group were asked to exclusively smoke the EHCSS-K6 cigarette from Visit 3 until the end of the study. Blinding was not possible due to the differences in physical appearance of the cigarettes to be used.

The assessment schedule of biomarkers over the course of the study consisted of blood sampling (in fasted state) on Visits 2, 3, 5, 7, and 8, and a 24-hour urine collection prior to Visits 3 and 8 (for urinary biomarkers). Carbon monoxide breath testing (Smokerlyzer®, Bedfont Scientific Ltd., Rochester, UK) was performed at all visits from Visit 2 through Visit 8.

Adherence to the study protocol and to Good Clinical Practice was ensured by regular monitoring visits by an independent monitor and by an independent audit of the investigational site.

2.3. Cigarette products and compliance

The EHCSS series-K cigarette was analyzed for tar, nicotine and CO mainstream smoke yields according to International Organization for Standardization (ISO) methods. All study cigarettes were conditioned according to ISO standard 3402 (International Organization for Standardization, 1991). 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 (International Organization for Standardization, 2000a); however, some slight technical deviations were required. Tar, nicotine and CO were determined according to ISO standards 4387, 10315, and 8454, respectively (International Organization for Standardization, 2000b, 2000c; International Organization for Standardization, 1995). The ISO yields as declared on the EHCSS-K6 pack were as follows: 5 mg tar, 0.3 mg nicotine, and 1.0 mg CO.

As EHCSS-K6 cigarettes were not commercially available on the Polish market they were provided free-of-charge to the subjects. Conventional cigarettes were not analyzed or provided to subjects in the CC group, and were purchased by the subjects according to their usual habits.