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Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program

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ABSTRACT

This publication introduces a series of eight other publications describing the non-clinical assessment and initial clinical study of a candidate modified risk tobacco product (MRTP) – the Tobacco Heating System 2.2 (THS2.2). This paper presents background information on tobacco harm reduction, to complement the approaches aimed at increasing smoking cessation and reducing smoking initiation to reduce the morbidity and mortality caused by cigarette smoking. THS2.2 heats tobacco without combustion, and the resulting formation of harmful and potentially harmful constituents (HPHC) is greatly reduced compared with cigarette smoke. Assessment of the THS2.2 aerosol *in vitro* and *in vivo* reveals reduced toxicity and no new hazards. Additional mechanistic endpoints, measured as part of *in vivo* studies, confirmed reduced impact on smoking-related disease networks. The clinical study confirmed the reduced exposure to HPHCs in smokers switching to THS2.2, and the associated transcriptomic study confirmed the utility of a gene expression signature, consisting of only 11 genes tested in the blood transcriptome of subjects enrolled in the clinical study, as a complementary measure of exposure response. The potential of THS2.2 as an MRTP is demonstrated by the assessment and additional publications cited in this series.

1. Introduction

1.1. General

The U.S. Family Smoking Prevention and Tobacco Control Act defines a Modified Risk Tobacco Product (MRTP) as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco related disease associated with commercially marketed tobacco products (Family Smoking Prevention and Tobacco Control Act). This publication is part of a series of nine publications describing the nonclinical and part of the clinical assessment of a candidate MRTP, THS2.2 regular and a mentholated version (THS2.2M). The series of publications provides part of the overall scientific program to assess the potential for THS2.2 to be a reduced risk product. This first publication in this series describes THS2.2 and the assessment program for MRTPs. This is followed by six publications that describe the nonclinical assessment of THS2.2 regular and THS2.2M (Kogel et al., 2016; Oviedo et al., 2016; Schaller et al., 2016a; Schaller et al., 2016b; Sewer et al., 2016; Wong et al., 2016). The eighth publication in the series describes a clinical study to assess whether the reduced formation of Harmful and Potentially Harmful Constituents (HPHC) for THS2.2 regular also leads to reduced exposure to HPHCs when the product is used in a clinical setting (Haziza, 2016). A final publication utilizes data gathered from the reduced exposure clinical study on THS2.2 regular to determine if a systems pharmacology approach can identify exposure response markers in peripheral blood of smokers switching to THS2.2 (Martin et al., 2016).

Abbreviations: MRTP, Modified Risk Tobacco Product; THS2.2, Tobacco Heating System version 2.2 regular; THS2.2M, Tobacco Heating System version 2.2 menthol version; HPHC, Harmful and potentially harmful constituents; PMI, Philip Morris International; FSPTCA, Family Smoking Prevention and Tobacco Control Act; FDA, Food and Drug Administration; CTP, Center for Tobacco Products; CDER, Center for Drug Evaluation and Research; CC, Combustible Cigarette; CVD, Cardiovascular disease; COPD, Chronic obstructive lung disease; NPA, Network perturbation amplitude; BIF, Biological Impact Factor; OECD, Organization for Economic Cooperation and Development; PHIM, Population health impact model; HCI, Health Canada intense smoking regime; 3R4F, University of Kentucky Reference Cigarette; miRNA, Micro-ribonucleic acid; MRC, Mentholated reference cigarettes; SA, Smoking abstinence.

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1.2. Tobacco harm reduction

Cigarette smoking is one of the leading causes of preventable death both in the United States and globally. For many decades, the foundational principles of reducing this harm have been focused on preventing smoking initiation and promoting smoking cessation. In recent years, a third opportunity to reduce the harm from combusted tobacco products has emerged, based on switching consumers to less harmful products that have significantly reduced levels of toxic and harmful compounds. The United States Surgeon General (US Department of Health and Human Services (2010)) concluded that '*Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation and oxidative stress.*' It has long been known that the best way for smokers to reduce the adverse health consequences of smoking is to quit. However, though many smokers are interested in and attempt to quit, it can be very difficult to quit smoking cigarettes and hence the rates of long-term smoking cessation remain low. For example, according to the United States Surgeon General (US Department of Health and Human Services (2010)) although about 45% of smokers quit for a day, only approximately 5% succeed in achieving long-term abstinence for one year or longer.

As outlined by the U.K. Royal College of Physicians (Royal College of Physicians (2016)), '*Smoking is completely preventable, yet, more than half a century after the health harm of smoking first became widely known, almost 1 billion people worldwide still smoke. They do so primarily because they are addicted to the nicotine in tobacco smoke and, as this addiction can be extremely difficult to overcome, many will continue to smoke until they die.*'

Referring to an earlier report (Royal College of Physicians (2007)) that promoted the principle of harm reduction in nicotine addiction, the Tobacco Advisory Group of the U.K. Royal College of Physicians (Royal College of Physicians (2016)) stated that '*as most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke, the health and life expectancy of today's smokers could be radically improved by encouraging as many as possible to switch to a smoke-free source of nicotine. While recognizing the primacy of complete cessation of all tobacco and nicotine use as the ultimate goal to prevent harm from smoking, the report argued that promoting widespread substitution of cigarettes and other tobacco combustion products would, for smokers who made the change, achieve much the same thing. Harm reduction, as a complement to conventional tobacco control policies, could therefore offer a means to prevent millions of deaths among tobacco smokers in the UK alone.*'

As noted by McNeil (McNeil, 2012) '*Since nicotine itself is not a highly hazardous drug, encouraging smokers to obtain nicotine from sources that do not involve tobacco combustion is a potential means to reduce the morbidity and mortality they sustain, without the need to overcome their addiction to nicotine.*'

The harm reduction approach can be used to complement the existing strategies of reducing smoking related harm (i.e., preventing initiation and promoting cessation of smoking), to provide smokers with novel tobacco or nicotine containing products that are substantially less toxic than cigarettes. However, the potential public health benefit of such an approach will only be achieved if these novel nicotine products are scientifically substantiated to reduce risk and are acceptable alternatives that allow smokers to switch to the reduced-risk products.

Philip Morris International (PMI) is developing a portfolio of such novel nicotine products to address a wide range of adult smoker preferences where each product type is designed to significantly reduce or eliminate the formation of HPHCs in the inhaled aerosol while preserving as much as possible the taste, sensory experience, nicotine delivery profile and ritual characteristics of cigarettes.

The novel nicotine product described in this series of papers is a '*heat-not-burn*' tobacco product, which heats tobacco at a temperature below that required to initiate combustion. Different classes of tobacco constituents decompose at different temperatures, releasing chemical compounds into the aerosol. Heating at much lower temperatures than those found at the tip of a burning cigarette generates fewer and lower levels of HPHCs. The resulting aerosol contains nicotine but has significantly reduced levels of HPHCs compared with cigarette smoke.

The development of *heat-not-burn* tobacco products is not new and earlier efforts to develop such products (notably Premier and Eclipse products from R.J. Reynolds and Accord from Philip Morris) have been reviewed (Baker, 2006). Baker concluded that consumer acceptance of these products was low primarily because of sensory and usability issues, explaining their lack of commercial success. Consumer acceptance of reduced-risk products is crucially important if they are to be used in place of cigarettes and realize the potential to reduce risk for the individual smoker and for harm reduction at the population level (Fig. 1).

The studies presented in this series of papers form part of an assessment strategy to characterize a potentially reduced-risk product that generates an inhalable aerosol by heating tobacco instead of burning it. A description of this Tobacco Heating System (THS) version 2.2 is provided below, followed by an overview of our MRTP assessment strategy.

2. Product characteristics of THS2.2

THS 2.2 is a novel tobacco product type. It has three distinct components that perform different functions (Fig. 2): (i) a *tobacco stick* - a novel patent-pending tobacco product with processed tobacco made from tobacco powder, (ii) a *holder* into which the *tobacco stick* is inserted and which heats the tobacco material by means of an electronically controlled heating blade, and (iii) a *charger* that is used to recharge the *holder* after each use.

The THS2.2 product differs from a cigarette in significant ways. First, the *tobacco stick* does not contain tobacco cut-filler (tobacco leaf cut in small pieces found in cigarettes). Instead, the tobacco is ground and reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum and cellulose fibers. Second, the *tobacco stick* (Fig. 3) contains much smaller amounts of tobacco compared with a cigarette. The weight of the tobacco plug in the *tobacco stick* is approximately 320 mg compared with the 550–700 mg cut-filler found in conventional cigarettes. The reconstituted tobacco cast-leaf is fashioned into a small plug through a proprietary process known as '*crimping*'. Third, unlike a cigarette, the *tobacco stick* contains two unique and independent filters: (i) a polymer-film filter to cool the aerosol and (ii) a low-density cellulose acetate mouthpiece filter to mimic the sensory aspects of a cigarette. Furthermore, a hollow acetate tube separates the tobacco plug and the polymer-film filter.

To operate the THS2.2 product, the user inserts a *tobacco stick*

Fig. 1. The Harm Reduction Equation. Harm reduction at the population level is the result of the availability of a scientifically substantiated reduced-risk product that is an acceptable alternative to adult smokers and is not likely to attract non-smokers.