Nicotine Pharmacokinetics and Pharmacodynamic Effects of P4M3 Compared with Subjects’ Own Electronic Cigarette

Philip Morris International (PMI) is developing and scientifically substantiating Reduced-Risk Products (RRP). RRPs are the term we can refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to products continued versus smoking. Such RRPs aim to substantially reduce or eliminate exposure to harmful and potentially harmful constituents while providing an acceptable option as substitutes for cigarettes. One of these RRPs is the electronic nicotine delivery system P4M3. P4M3 is based on the principle of heating an e-liquid mainly composed of propylene glycol, glycerin, flavors, and nicotine to generate a nicotine-containing aerosol. In P4M3, a metallic mesh is used as a heating element. P4M3 uses puff-activated heating and low-level liquid detection that ensures the consistency and quality of the aerosol. The goal of the study was to evaluate the nicotine pharmacokinetic profiles and derived PK parameters, subjective and behavioral effects, and puffing topography parameters of P4M3 variants and to compare to subjects’ own e-cigarettes.

Introduction and Objectives

A total of 35 subjects signed the Informed Consent Form for this study. 15 subjects (5 female and 10 male) were enrolled and randomly assigned to one of two product use sequences. All subjects in this study were White, with a mean age of 40 years. All subjects were current daily e-cigarette users, with an average cigarette smoking history of 15.6 years. The most commonly used e-cigarette product was Vuse® (53.3% of subjects, followed by Blu® (33.3%). The mean nicotine concentration of subjects’ own e-cigarettes was 2.98%.

Methods

This was a single-center (High Point Clinical Trials Center, 4160 Mendhenhall Oaks Pkwy #105, High Point, NC, USA), open-label, concentration-ranging study to evaluate the nicotine pharmacokinetic profile and pharmacodynamic effects in healthy, White, adult, experienced users of closed-cartridge e-cigarettes using four different variants of P4M3 differing in e-liquid nicotine concentration or their own e-cigarette. ClinicalTrials.gov NCT03379740

Results

A puffing regimen comprising 12 puffs in total at a rate of one puff every 30 seconds (±5 seconds) was used. For each session, the start of the puffing session was at approximately the same time (±30 minutes) for the fixed puffing regimen in the morning and for ad libitum in the afternoon. There was a washout period of at least 10 hours between each product use regimen.

Pharmacokinetics

- Fixed puffing regimen, Ten venous blood samples: prior to product use –15 minutes, thereafter in relation to T1 at 2, 4, 7, 10, 15, and 30 minutes and at 1, 2, and 4 hours.
- Ad libitum use, Eight venous blood samples: prior to product use –15 minutes, thereafter in relation to T1 at 10, 20, 30, and 40 minutes and at 1, 2, and 4 hours.
- Day 5: Five venous blood samples: in relation to T1 from ad libitum use on Day 4 at 14, 16, 18, 20, and 24 hours for determination of terminal elimination rate constant and half-life. Background nicotine concentration correction was applied for adjust for carry-over effects. The determination of nicotine in human plasma samples was conducted using a calibration range of 0.2 ng/mL to 25.0 ng/mL, using a validated method (CeleroLincoln, NE, USA). Nicotine exposure parameters were derived from background-corrected plasma nicotine concentrations versus time data by non-compartmental analysis using Phoenix WinNonlin version 7.0 (Certara USA, Inc., Princeton, NJ, USA).

Human puffing topography

- A portable puffing behavior tracking device (SOMID SPA-M) was connected to subjects’ own e-cigarette and P4M3 during the fixed puffing regimen and ad libitum use to gather puffing topography data (e.g., puff parameters, average flow, puff duration, total puff volume).

Pharmacodynamics

- Subjective effects and related behavioral assessments of the P4M3 variants and subjects’ own e-cigarette (Visual Analog Scale (VAS) of craving and adapted version of modified Cigarette Elevation Questionnaire (MECQ)).

Safety

- Adverse events (AE), physical examination, vital signs, spirometry, electrocardiography, cough assessment, clinical chemistry, hematology, and urine analysis safety panel were assessed.

Conclusions

During the fixed puffing regimen, increasing Cmax and AUC0-24h values were associated with increasing e-liquid nicotine concentrations of P4M3 variants. Plasma nicotine concentration-time profile of subjects’ own e-cigarette was comparable to the profiles of P4M3-1.7% and P4M3-1.7%LA. Time to maximal concentration (tmax) was between 7 and 9 minutes after the first puff for all subjects. Plasma nicotine concentration-time profiles from P4M3-3.5%LA and 4%LA appeared to be comparable, with peak plasma nicotine concentrations (Cmax) after 60 minutes ad libitum use higher than those of the two 1.7%LA variants and subjects’ own e-cigarettes.

Subjects’ own e-cigarette provided a similar maximal level of craving reduction to P4M3 variants. Higher nicotine concentration in the e-liquid or higher nicotine exposure were not indicative of a greater reduction in craving. The results for the ad libitum use suggest that when using P4M3 variants, subjects did not substantially self-regulate their puffing behavior. The adapted MECQ subscale score for Aversion was higher for the P4M3 variants, while subscale scores for Product Satisfaction, Psychological Reward, Enjoyment, and Sensory Sensation and Craving Reduction were lower following the use of the P4M3 variants compared to subjects’ own e-cigarettes.

There were no serious or severe adverse events (SAE) reported during the study, and no subjects discontinued from the study due to an AE. No AE was considered related to P4M3 variants or subjects’ own e-cigarette. There were no clinically notable findings in the physical examination, clinical laboratory, vital signs, ECG, or spirometry assessments in this study.