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

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## Introduction and Objectives

Philip Morris International (PMI) is developing and scientifically substantiating Reduced-Risk Products (RRP). RRPs is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to those products versus continued 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, glycerol, flavor, 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-liquid level 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.

## Methods

This was a single-center (High Point Clinical Trials Center, 4160 Mendenhall 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-tank/cartridge e-cigarettes using four different variants of P4M3 differing in e-liquid nicotine concentration or their own e-cigarette. ClinicalTrials.gov Identifier: NCT03379740

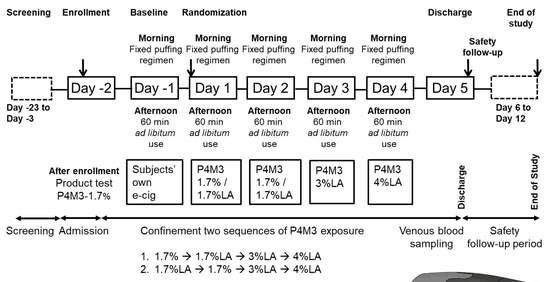


Figure 1: Study design.

Figure 2: P4M3.

**Product use regimen**

- **Fixed puffing regimen** comprising 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds)
- ***Ad libitum* use** 60 minutes (± 5 minutes)

For each session, start of product use ($T_0$) was at approximately the same time (± 30 minutes) for the fixed puffing regimen in the morning and for *ad libitum* use 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 $T_0$ 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 $T_0$ at 10, 20, 30, and 40 minutes and at 1, 2, and 4 hours.
- **Day 5.** Five venous blood samples: in relation to $T_0$ 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 to adjust for carry-over effects. The determination of nicotine in human plasma samples was carried out over a calibration range of 0.2 ng/mL to 25.0 ng/mL using a validated method (Celerion Lincoln, NE, USA). Nicotine exposure parameters were derived from background-corrected plasma nicotine concentrations versus time data by non-compartmental analysis principles using Phoenix® WinNonlin® version 7.0 (Certara USA, Inc., Princeton, NJ, USA).

**Human puffing topography**

- A portable puffing topography device (SODIM 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 volume, 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 Evaluation Questionnaire (mCEQ)).

**Safety**

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

## Results

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%.

Table 1: Demographics and smoking history.

| | | Sequence 1 | Sequence 2 | Overall |
|---|---|---|---|---|
| Sex | Female | 1 (12.5%) | 4 (57.1%) | 5 (33.3%) |
| | Male | 7 (87.5%) | 3 (42.9%) | 10 (66.7%) |
| Race | White | 8 (100%) | 7 (100%) | 15 (100%) |
| Ethnicity | Hispanic or Latino | 1 (12.5%) | 0 | 1 (6.7%) |
| | Not Hispanic or Latino | 7 (87.5%) | 7 (100%) | 14 (93.3%) |
| Age (yrs) | Mean | 38.3 | 42.0 | 40.0 |
| | SD | 13.09 | 13.61 | 12.99 |
| Preferred e-liquid flavor | BERRY | 2 (25.0%) | 0 | 2 (13.3%) |
| | CHERRY | 0 | 1 (14.3%) | 1 (6.7%) |
| | MENTHOL | 1 (12.5%) | 0 | 1 (6.7%) |
| | MINT | 1 (12.5%) | 2 (28.6%) | 3 (20.0%) |
| | NECTAR | 0 | 1 (14.3%) | 1 (6.7%) |
| | ORIGINAL | 2 (25.0%) | 1 (14.3%) | 3 (20.0%) |
| | REGULAR | 0 | 1 (14.3%) | 1 (6.7%) |
| | SUMMER FUSION | 0 | 1 (14.3%) | 1 (6.7%) |
| | TOBACCO | 2 (25.0%) | 0 | 2 (13.3%) |
| Preferred e-liquid nicotine (%) | Mean | 3.18 | 2.76 | 2.98 |
| | SD | 1.411 | 0.902 | 1.179 |

**Fixed puffing regimen**

Use of P4M3 variants resulted in an e-liquid nicotine concentration-related increase in plasma nicotine concentrations. Plasma nicotine concentrations following subject's own e-cigarette were comparable to P4M3-1.7% and -1.7%LA variants and higher for P4M3-3%LA and P4M3-4%LA.

VAS craving assessment scores decreased from baseline for all products, with the greatest decrease from baseline at 15 minutes for P4M3-1.7% (–32.5) and P4M3-1.7%LA (–30.4) and at 30 minutes for subject's own e-cigarettes (–34.5), P4M3-3%LA (–31.7), and P4M3-4%LA (–29.5), respectively.

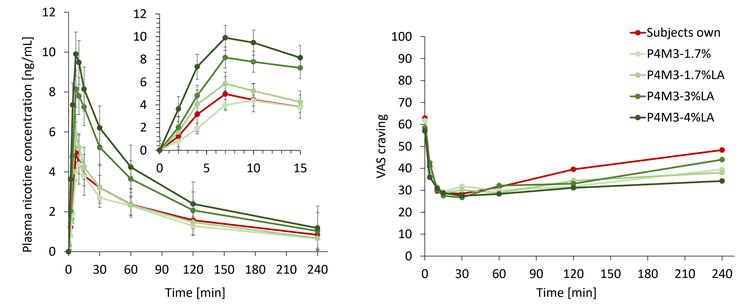


Figure 3: Geometric mean plasma nicotine concentrations and VAS craving assessment for fixed puffing regimen.

Table 2: Geometric mean (Geo. CV%) plasma nicotine pharmacokinetics parameters for fixed puffing regimen; $t_{max}$ values as median (min, max).

| Pharmacokinetic Parameter | Subjects' Own E-cigarette | P4M3-1.7% | P4M3-1.7%LA | P4M3-3%LA | P4M3-4%LA |
|---|---|---|---|---|---|
| $C_{max}$ [ng/mL] | 5.40 (78.1) | 5.07 (77.6) | 6.74 (83.4) | 9.44 (63.1) | 11.99 (78.6) |
| $t_{max}$ [min] | 10.0 (4.0, 120.0) | 10.0 (4.0, 60.0) | 7.0 (4.0, 30.0) | 10.0 (4.0, 15.0) | 7.0 (2.0, 15.0) |
| $AUC_{(0-4h)}$ [ng*h/mL] | 7.80 (81.2) | 6.97 (50.2) | 7.68 (66.4) | 11.55 (56.0) | 13.57 (67.1) |

Table 3: Geometric mean (Geo. CV%) puffing topography parameters fixed puffing regimen.

| Puffing Topography Parameter | Subjects' Own E-cigarette | P4M3-1.7% | P4M3-1.7%LA | P4M3-3%LA | P4M3-4%LA |
|---|---|---|---|---|---|
| Puff Volume [mL] | 93 (64.6) | 91 (74.6) | 101 (66.0) | 92 (65.9) | 76 (64.3) |
| Average Flow [mL/s] | 25.1 (37.7) | 28.3 (43.9) | 27.6 (38.0) | 29.4 (57.6) | 27.9 (41.6) |
| Puff Duration [s] | 3.7 (48.86) | 3.2 (46.3) | 3.7 (52.5) | 3.1 (51.3) | 2.7 (51.3) |
| Total Puff Volume [mL] | 2055 (54.8) | 2752 (53.9) | 2946 (79.0) | 2601 (34.6) | 1935 (54.1) |

***Ad libitum* use**

Use of P4M3-1.7% and P4M3-1.7%LA resulted in nicotine exposure comparable to the subject's own e-cigarettes based on the plasma nicotine parameters $C_{peak}$ and $AUC_{(0-4h)}$, while P4M3-3%LA and P4M3-4%LA variants resulted in $C_{peak}$ and $AUC_{(0-4h)}$ values 56%–78% higher than those of the subject's own e-cigarettes.

Table 4: Nicotine pharmacokinetics parameters *ad libitum* use.

| Pharmacokinetic Parameter | Subjects' Own E-cigarette | P4M3-1.7% | P4M3-1.7%LA | P4M3-3%LA | P4M3-4%LA |
|---|---|---|---|---|---|
| $C_{peak}$ [ng/mL] | 14.9 (83.0) | 13.3 (55.6) | 13.1 (98.2) | 26.5 (63.7) | 26.6 (57.3) |
| $t_{peak}$ [min] | 60.0 (30.0, 65.0) | 60.0 (60.0, 122.0) | 60.0 (40.0, 60.0) | 60.0 (30.0, 60.0) | 60.0 (40.0, 65.0) |
| $AUC_{(0-4h)}$ [ng*h/mL] | 33.8 (86.9) | 33.0 (61.4) | 28.6 (96.9) | 60.2 (55.3) | 52.8 (50.2) |

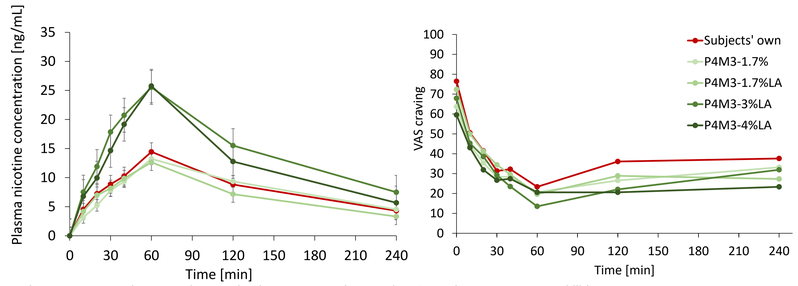


Figure 4: Geometric mean plasma nicotine concentrations and VAS craving assessment *ad libitum* use.

Table 5: Geometric mean (Geo. CV%) puffing topography parameters *ad libitum* use.

| Puffing Topography Parameter | Subject Own E-cigarette | P4M3-1.7% | P4M3-1.7%LA | P4M3-3%LA | P4M3-4%LA |
|---|---|---|---|---|---|
| Puff Volume [mL] | 71 (39.6) | 70 (62.2) | 81 (58.8) | 66 (54.9) | 63 (65.7) |
| Average Flow [mL/s] | 24.8 (34.6) | 25.4 (49.4) | 27.2 (63.9) | 25.1 (34.5) | 21.4 (39.1) |
| Puff Duration [s] | 2.9 (51.8) | 2.8 (58.0) | 3.0 (69.6) | 2.6 (57.4) | 2.9 (53.6) |
| Total Puff Volume [mL] | 2055 (54.8) | 2752 (53.9) | 2946 (79.0) | 2601 (34.6) | 1935 (54.1) |

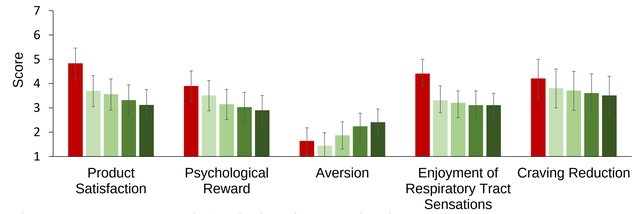


Figure 5: Least square mean (90% CI) adapted mCEQ subscale scores.

## Conclusions

During the **fixed puffing regimen**, increasing $C_{max}$ and $AUC_{(0-4h)}$ 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 ($t_{max}$) was between 7 and 10 minutes for all products.

Plasma nicotine concentration-time profiles from P4M3-3%LA and -4%LA appeared to be comparable, with peak plasma nicotine concentrations ($C_{peak}$) after **60 minutes *ad libitum* use** higher than those of the two 1.7%/LA variants and subject's own e-cigarette.

Use of 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 mCEQ subscale score for Aversion was higher for the P4M3 variants, while subscale scores for Product Satisfaction, Psychological Reward, Enjoyment of the Sensory Sensation, and Craving Reduction were lower following the use of the P4M3 variants compared to subjects' own e-cigarette.

There were no serious or severe adverse events (AEs) 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.

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