Nicotine Pharmacokinetics and Subjective Effects Following Use of a Novel Nicotine-Containing Powder Product

M. Bosilkovska [1], S. Fredersdorf [1], J. Almodovar [1], N. Lama [1], B. Taranu [1], E. Pierri [1], M. Radicioni [2], J. Ancerewicz [1], C. Haziza [1], F. Lüdicke [1]

[1] PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000 Neuchâtel, Switzerland [2] CROSS Research, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland

Introduction and Objectives

Alternative nicotine delivery systems, delivering nicotine without smoke, are complementary to the strategy of tobacco harm reduction. For smokers who would otherwise continue smoking, Philip Morris International is developing these alternative products that have the potential to reduce individual risk and population harm. One of these products is P3P.

- Single-use product, appearance similar to a cigarette
- Consumable component comprises a capsule containing nicotine lactate
- Contains 1 or 2 mg of nicotine (variant dependent)
- Generates an inhalable aerosol when air is drawn through it with a flow close to cigarette smoking
- No electronics involved

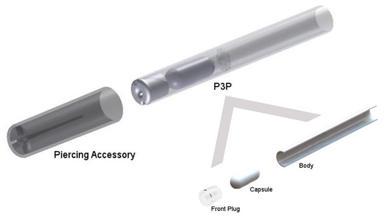
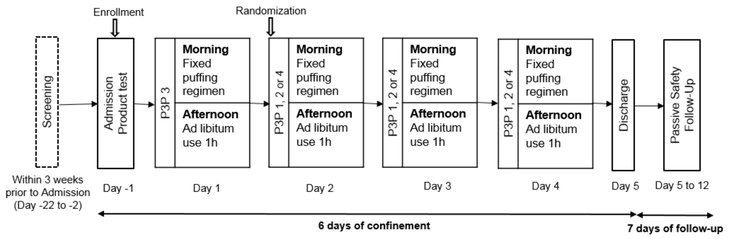


Figure 1: P3P product.

The objectives of this first in-human study were to evaluate the nicotine pharmacokinetic (PK) profile of four P3P variants following a fixed puffing regimen and 60 minutes *ad libitum* use as well as to assess product satisfaction, safety, and tolerability of P3P in healthy smokers.

Methods

- Open-label, randomized, crossover study
- Four product variants tested, differing in nicotine content (1 or 2 mg), nicotine-powder particle size, and presence/absence of mentholated flavor
- Product use regimens for each variant:
  - **Fixed puffing regimen** comprising 12 puffs in total at a rate of one inhalation every 30 seconds (± 5 seconds) in the morning
  - ***Ad libitum* use period** for 60 minutes (± 5 minutes) in the afternoon
- Wash-out period of at least 10 hours between each product use regimen



P3P 1 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; unflavored
P3P 2 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 3 characteristics: 1 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 4 characteristics: 2 mg nicotine; 1.8 µm nicotine powder particle size; flavored

Figure 2: Study design and variant characteristics.

- **Plasma nicotine measurement and PK analysis:** On each day, blood samples were collected for PK parameter estimation, 10 for fixed puffing and 8 for *ad libitum* use. Additional blood sampling was conducted on Day 5 (without product use) for estimation of individual terminal elimination half-life ($t_{1/2}$). Compartmental PK analysis was used to estimate $t_{1/2}$ for the purpose of baseline nicotine level correction, similar to previously described population PK model[1]. Nicotine concentration was determined in venous plasma using a LC-MS/MS method (LLOQ = 0.2 ng/mL).
- **Theoretical nicotine delivery:** Weighing of P3P before and after use, adjusted for nicotine content.
- **Human puffing topography (HPT):** Puffing topography device (SODIM® Instrumentation) was attached to each P3P during both fixed puffing and *ad libitum* use periods for the recording of HPT parameters (number of puffs, puff volume, puff duration, puff flow, etc.).
- **Product evaluation:** Adapted version of the modified cigarette evaluation questionnaire (mCEQ)[2].
- **Safety monitoring:** Adverse events (AE), vital signs, physical examination, spirometry, ECG, clinical laboratory safety parameters, and cough assessment.

The study was conducted at CROSS Research S.A., Phase I Unit, Switzerland, in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, approved by an Independent Ethics Committee, and registered at www.clinicaltrials.gov (NCT03369340).

Results

Nicotine PK for fixed puffing regimen

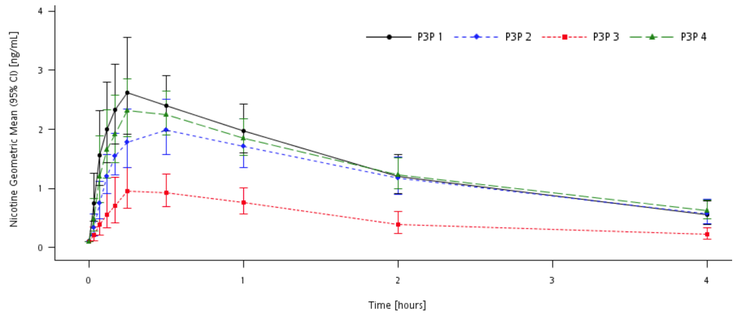


Figure 3: Background-corrected plasma nicotine concentration-time profiles for fixed puffing regimen.

Table 1: Nicotine PK parameters for fixed puffing.

Variant	Theoretical nicotine delivered (mg)	C_{max} (ng/mL)	T_{max} (min)	$AUC_{fix\ (0\text{-}4h)}$ (hr*ng/mL)
	Mean (SD)	Geo LS mean* (95%CI)	Median (range)	Geo LS mean* (95%CI)
P3P 3	0.45 (0.12)	1.14 (0.77, 1.68)	15.0 (4.0 – 60)	2.37 (1.67, 3.37)
P3P 1	0.78 (0.31)	3.08 (2.33, 4.06)	15.0 (4.0 – 60)	5.84 (4.56, 7.48)
P3P 2	0.86 (0.24)	2.13 (1.62, 2.81)	22.5 (4.0 – 62)	5.08 (3.97, 6.50)
P3P 4	0.89 (0.13)	2.79 (2.10, 3.71)	15.0 (4.0 – 70)	5.73 (4.45, 7.39)

*LS mean derived by mixed model with fixed effect terms for sequence, study day, product variant, and using subject within sequence as random effects.

Mean C_{max} ranged between 1.1 and 3.1 ng/mL for the different product variants during the fixed puffing regimen and were reached after 15–22.5 minutes (T_{max}).

Lowest nicotine exposure was observed for the 1 mg variant, while smaller nicotine powder particle size and the absence of flavor resulted in only slightly higher nicotine exposure during the fixed puffing regimen.

T_{max} was longer compared to data reported for cigarettes but shorter than the Nicorette® Inhaler, while C_{max} and $AUC_{0\text{-}4h}$ were lower compared to these products.[3,4] The PK profile may be indicative of a partial pulmonary and partial oro-mucosal absorption.

Nicotine PK for *ad libitum* use

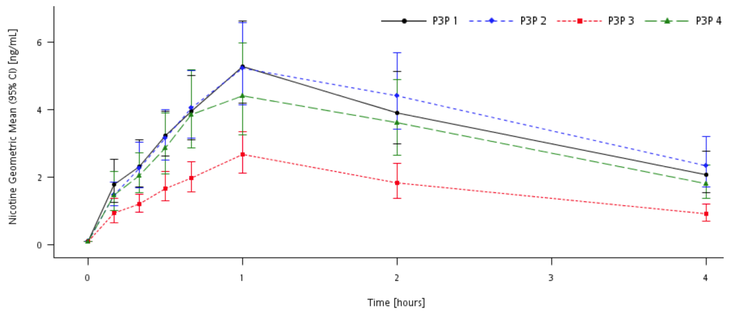


Figure 4: Background-corrected plasma nicotine concentration-time profiles for *ad libitum* use.

Table 2: Nicotine PK parameters for *ad libitum* use.

Variant	Number of products used	Theoretical total nicotine delivered (mg)	C_{peak} (ng/mL)	T_{peak} (min)	$AUC_{adlib(0\text{-}4h)}$ (hr*ng/mL)
	Mean (range)	Mean (SD)	geo LS mean (95%CI)	Median (range)	geo LS mean (95%CI)
P3P 3	2.84 (2 – 4)	1.45 (0.33)	2.63 (1.97, 3.52)	60 (30 – 120)	6.32 (4.73, 8.44)
P3P 1	2.44 (1 – 4)	2.02 (0.66)	5.38 (4.24, 6.84)	60 (40 – 120)	13.6 (10.7, 17.3)
P3P 2	2.67 (1 – 4)	2.75 (0.79)	5.41 (4.26, 6.88)	60 (20 – 240)	14.5 (11.4, 18.4)
P3P 4	2.56 (1 – 4)	2.46 (0.91)	4.67 (3.67, 5.95)	60 (30 – 120)	12.1 (9.54, 15.5)

During each *ad libitum* use session, subjects used between one and four products to reach maximal nicotine concentrations (C_{peak}) between 2.6 and 5.4 ng/mL at the end of the session (T_{peak} = 60 min).

Lowest nicotine exposure was observed for the 1 mg variant, while the presence/absence of flavor and nicotine powder particle size did not influence the PK parameters.

Demographics

Characteristics	N = 19
Females – n (%)	10 (52.6)
Age (years) – Mean ± SD	35.4 ± 9.0
BMI (kg/m²) – Mean ± SD	24.6 ± 2.7
Daily cigarette consumption – Mean ± SD	16.4 ± 4.6
Fagerström Test for Nicotine Dependence (FTND) score	
Mean ± SD	3.74 ± 1.94
Mild (0-3) – n (%)	8 (42.1)
Moderate (4-6) – n (%)	9 (47.4)
Severe (7-10) – n (%)	2 (10.5)

Nineteen healthy Caucasian smokers who had been smoking for at least the past three years were enrolled, and 18 were randomized and completed the study.

Puffing Topography

The four P3P variants showed similarities with respect to puffing topography parameters. The average puff duration during the *ad libitum* session ranged between 1.4 and 1.8 seconds, and the average puff flow ranged between 38.0 and 40.6 mL/s. The average flow was only slightly higher compared to the flow reported during cigarette smoking, while the puff duration was similar.[5,6]

Product Evaluation

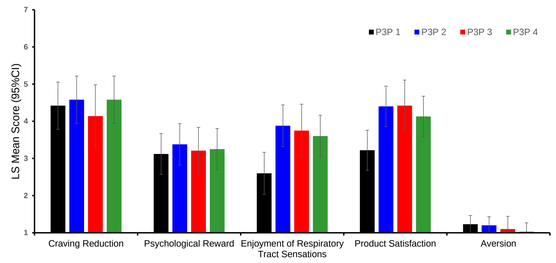


Figure 5: Adapted mCEQ domain scores profiles for each product variant.

Product satisfaction was similar across variants, with slightly lower scores for the unflavored variant, and was also similar to previously reported scores for cigarettes.[2]

Safety

No serious AEs were reported, and no subject was discontinued from the study due to an AE.
Overall, 23 AEs occurred in 10 of 19 subjects (52.6%), the majority of which were mild. Sixteen AEs were considered related to the P3P, including dizziness (eight AEs), nausea (five AEs), vomiting (two AEs), and dyspepsia (one AE). There were no clinically relevant changes in vital signs, ECG, spirometry assessment, physical examination, or safety laboratory parameters during the study.

Conclusions

The plasma nicotine concentration-time profiles suggest that the nicotine dose is delivered both via a faster pulmonary route and via an oro-mucosal route, situating this product between cigarettes and the Nicorette® inhaler in terms of rapidity of nicotine delivery.

Despite lower nicotine exposure, product satisfaction and acceptance were comparable with data reported for cigarettes.[2]

This novel nicotine-containing product shows potential as an alternative to cigarettes for smokers, in terms of product satisfaction and acceptance, without the involvement of electronics.

References

1. Marchand M, et al. Nicotine Population Pharmacokinetics in Healthy Adult Smokers: A Retrospective Analysis *Eur J Drug Metab Pharmacokinet.* 2017;42(6):943-954
2. Cappelleri JC, et al. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addict Behav.* 2007;32(5):912–923.
3. Hukkanen J, et al. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev.* 2005;57(1):79-115
4. Schneider NG, et al. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet.* 2001;40(9):661-684
5. Ross KC, et al. The influence of puff characteristics, nicotine dependence, and rate of nicotine metabolism on daily nicotine exposure in African American smokers. *Cancer Epidemiol Biomarkers Prev.* 2016;25(6):936-43.
6. Haziza C, et al. Evaluation of the Tobacco Heating System 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. *Regul Toxicol Pharmacol.* 2016;81 Suppl2:S139-S150.

SRNT 25th Annual Meeting, San Francisco, CA, USA, February 20–23, 2019

Competing Financial Interest – The research described in this poster was sponsored by Philip Morris International.