Evaluation of Nicotine Pharmacokinetics and Subjective Effects following Use of a Novel Nicotine Aerosol System

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Introduction and Objectives

Alternative nicotine delivery systems as substitutes to cigarettes may constitute an approach to reduce the harm caused by tobacco smoking-related diseases.[1] For adult smokers willing to continue enjoy tobacco or nicotine, Philip Morris International is developing reduced risk products (RRPs*), including the novel nicotine aerosol system (P3L) which is based on the technology of generating an aerosol of a nicotine salt by combining vapors of nicotine and a weak acid as first described by Rose and co-workers.[2] The aerosol is characterized by a droplet size that is compatible with pulmonary absorption. In contrast to electronic cigarettes, P3L does not contain exogenous carrier compounds such as propylene glycol, used in e-liquids.

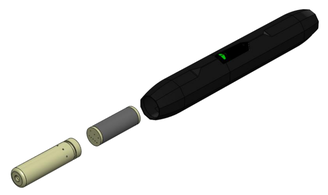
Product tolerability, acceptable taste and sensory characteristics, a nicotine delivery profile comparable to cigarettes and ritual characteristics similar to cigarette smoking are known to enhance the chances that smokers successfully transition from cigarettes to a RRP.

The objectives of this first-in-human study were to evaluate in healthy smokers the plasma pharmacokinetic (PK) profile of nicotine; subjective effects, as assessed by urge to smoke, craving relief and product evaluation; and the safety and tolerability of the P3L system at three dose levels in relation to the Nicorette® inhalator.

Methods

- Open-label ascending nicotine levels study
- 16 male and female, healthy, cigarette smoking subjects (Caucasian)
- Study consisting of a screening period, one day of admission including a product familiarization period, four separate days of on-site product use with 1-3 days in-between each product use and a seven-day safety follow-up period
- Product use regimen:
  - Nicorette® inhalator (15 mg): one inhalation every 15 seconds over approx. 20 minutes (total 80 puffs corresponding to ~2 mg nicotine)
  - P3L (50, 80 and 150 µg nicotine/puff, as determined on a smoking machine under Health Canada Intense smoking regimen): one inhalation every 30 seconds over 6 minutes (total 12 puffs corresponding to ~0.7 mg, ~1.0 mg and ~1.9 mg nicotine, respectively)
- Plasma nicotine PK analysis: 15 blood samples were collected: 3 samples from 45 minutes prior start of product use (t_0) and 12 samples after t_0. Nicotine concentration was determined in venous plasma by means of LC-MS/MS (LLOQ: 0.2 ng/ml)
- Subjective effects were assessed by means of the Visual Analog Scale (VAS) for craving[3], the brief version of the Questionnaire of Smoking Urges[4] and the modified Cigarette Evaluation Questionnaire (mCEQ)[5]
- Safety monitoring: adverse events (AEs), vital signs, physical examination, spirometry, ECG, clinical laboratory safety parameters and cough assessment
- The study was conducted in 2015 at Christchurch Clinical Studies Trust Ltd., New Zealand according to ICH GCP, approved by an Independent Ethics Committee and by the New Zealand Medicines and Medical Devices Safety Authority (MedSafe), and registered at www.clinicaltrials.gov (NCT02532374)

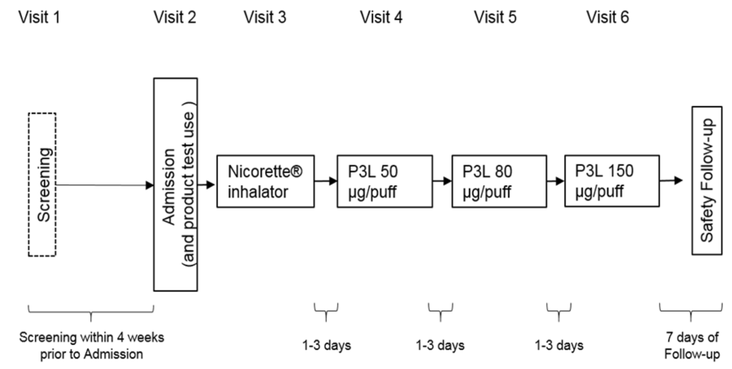
Investigational Product



P3L device

(The product depicted above is subject to ongoing development. The visual is therefore illustrative and does not necessarily represent the latest stage of product development.)

Study Design



Study flow chart

Results

Demographics

Characteristics	PK Population (N=15)
Males - n(%)	8 (53.3)
Age (years) – Mean (SD)	39.8 (13.8)
Daily CC consumption - n(%)	
10-19 cig/day	9 (60.0)
>19 cig/day	6 (40.0)
E-cigarettes usage over the last year - n(%)	
No	8 (53.3)
Yes	7 (46.7)
Fagerström Test for Nicotine Dependence (FTND) Total Score - n(%)	
Mild (0-3)	2 (13.3)
Moderate (4-6)	7 (46.7)
Severe (7-10)	6 (40.0)

Safety

There were no serious adverse events (SAE) or adverse events (AE) leading to product discontinuation in this study.

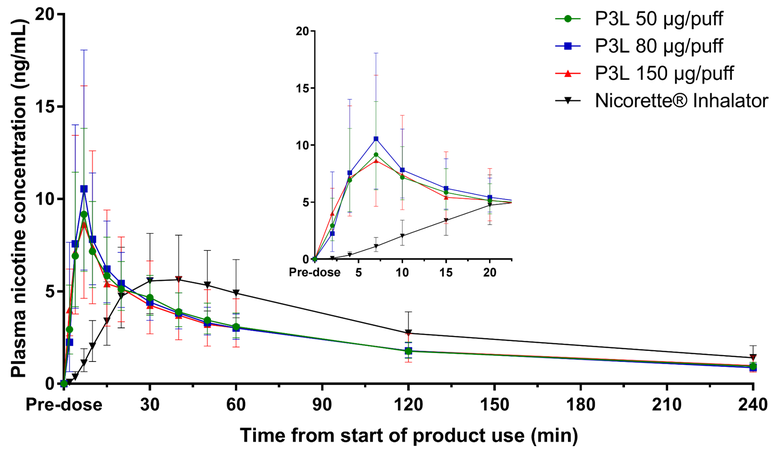
There were no specific patterns in AEs related to study procedures or related to the Nicorette® inhalator.

In total, sixteen AEs related to P3L (8 subjects) were detected, the majority were mild in severity, the most common one being dizziness.

One single product-related severe AE of syncope occurred (during P3L 80 µg/puff product use) and resolved within the course of the visit day without treatment.

One subject reported a regular need to cough during the exposure periods (Nicorette® inhalator and P3L 80 µg/puff and 150 µg/puff) with intensity rated as very mild.

Plasma Nicotine Pharmacokinetics



Geometric means and 95% confidence intervals of the baseline corrected plasma nicotine concentrations over time per product used.

The plasma nicotine concentration-time curves following use of P3L were characterized by a rapid absorption phase, with median time from product use start to reach the maximum nicotine plasma concentration (t_{max}) at 7 minutes, while median t_{max} following use of Nicorette® inhalator occurred at 30 minutes.

The maximum nicotine plasma concentration (C_{max}) was similar between the three nicotine delivery levels of P3L and almost double compared to Nicorette® inhalator.

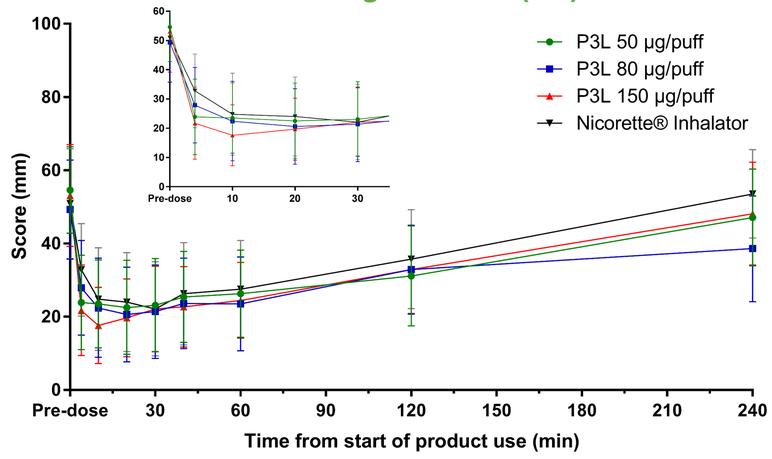
C_{max} and t_{max} values with Nicorette® inhalator were consistent with published data[6], and P3L with published data on cigarettes.[7]

Nicotine Pharmacokinetic Parameters

Product	N	C_{max} [ng/mL] (95% CI)[a]	Median t_{max} [min] (min, max)	$AUC_{0-10'}$ [h×ng/mL] (95% CI)[a]	AUC_{0-last} [h×ng/mL] (95% CI)[a]
P3L (50 µg/puff)	15	9.7 (6.7, 13.9)	7.0 (4.0, 30.0)	1.0 (0.6, 1.7)	9.9 (7.5, 13.2)
P3L (80 µg/puff)	14	11.1 (7.7, 16.1)	7.0 (4.0, 20.0)	1.2 (0.7, 1.9)	10.3 (7.6, 13.8)
P3L (150 µg/puff)	14	9.8 (6.8, 14.2)	7.0 (2.0, 20.0)	1.0 (0.6, 1.7)	10.0 (7.4, 13.4)
Nicorette® Inhalator	15	6.1 (4.2, 8.8)	30.0 (20.0, 60.0)	0.1 (0.1, 0.2)	12.3 (9.3, 16.4)

[a] *Geometric LS mean*

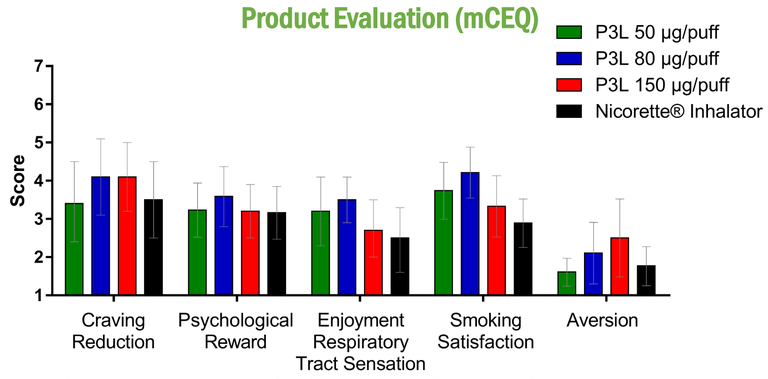
Craving Assessment (VAS)



Arithmetic mean and 95% confidence of the VAS-craving scores over time per product used .

The overall profile of the VAS-Craving over time curves was similar following use of the P3L system and Nicorette® inhalator. The maximum craving reduction following the start of product use was higher with P3L at all nicotine delivery levels than with the Nicorette® inhalator. The maximum reduction in craving was reached earlier with P3L use (10 minutes for P3L with 150 µg/puff, 20 minutes for P3L 50 µg/puff and P3L 80 µg/puff) than for Nicorette® inhalator (at 30 minutes).

Product Evaluation (mCEQ)



MCEQ domain scores profiles (arithmetic mean and 95%CI) per product used.

Product evaluation using mCEQ sub-scales for craving reduction and psychological reward were similar for P3L at all nicotine delivery levels and Nicorette® inhalator. Enjoyment of respiratory tract sensations, and smoking satisfaction for P3L 50 µg/puff and 80 µg/puff were higher than for P3L 150 µg/puff and Nicorette® inhalator. There was a trend of increase in aversion sub-scale score with increasing P3L nicotine level.

Conclusions

At all three nicotine levels tested, inhalation of the nicotine lactate aerosol delivered with the P3L system provided higher and faster plasma nicotine concentrations compared to the Nicorette® inhalator. The plasma nicotine concentration-time profile supports a pulmonary route of absorption for P3L rather than the oromucosal absorption associated with the inhalator. The maximum craving reduction following start of product use, as assessed by VAS, was higher for P3L at all nicotine delivery levels compared to the Nicorette® inhalator, with an earlier onset reached with P3L. With the exception of "Aversion", the product evaluation appeared to be at least as good for P3L as for the inhalator with an apparent preference for the P3L 80 µg/puff variant. P3L was generally well tolerated.[8]

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*Reduced-Risk Products ("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 these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment and commercialization. Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

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