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

PMI SCIENCE
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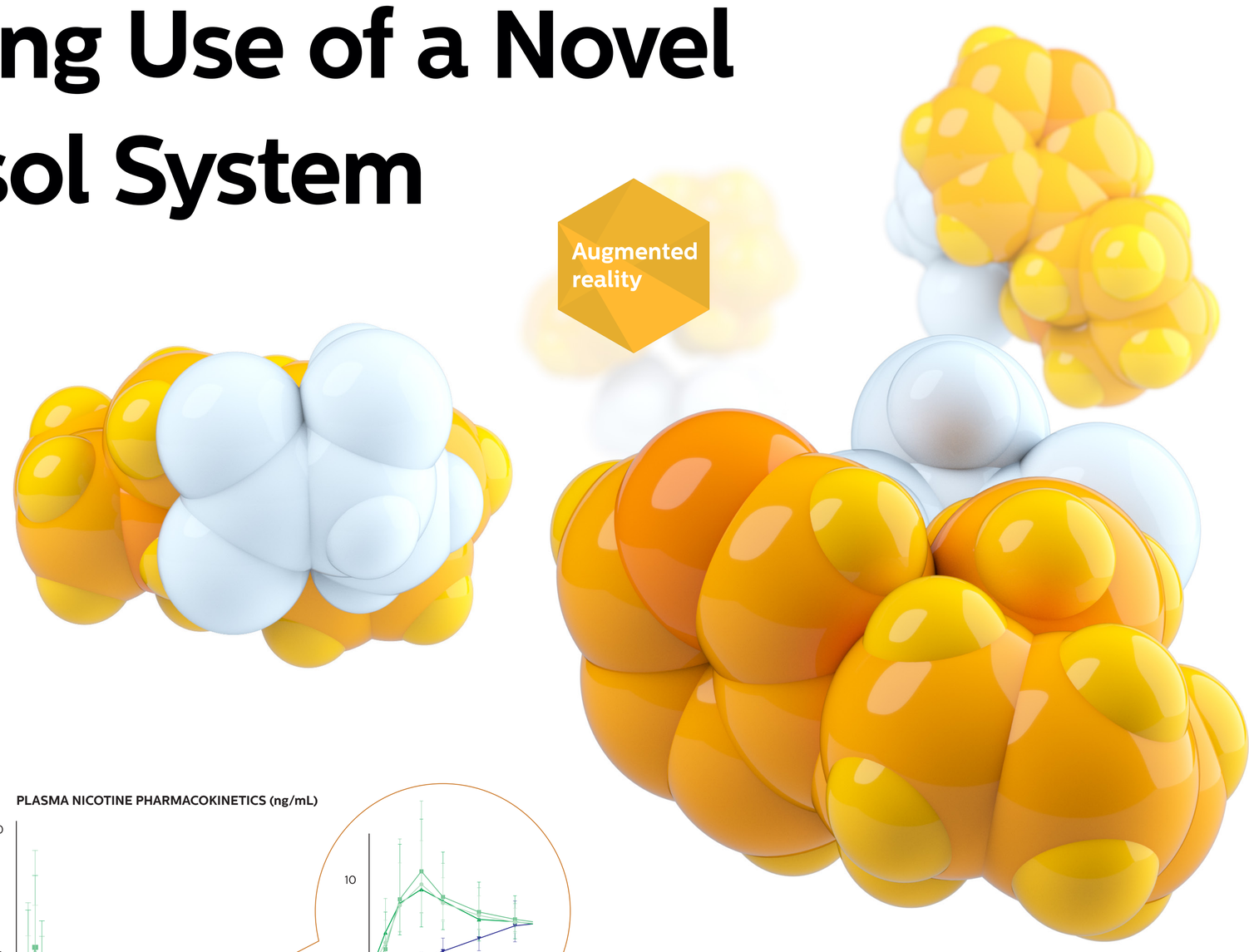
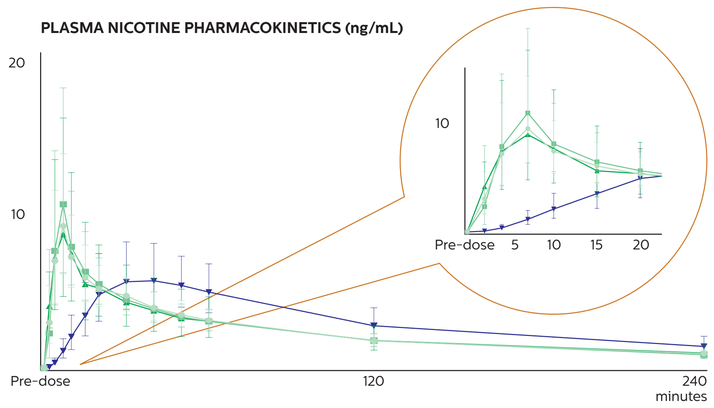


Intro

Novel nicotine aerosol systems represent an evolving part of the tobacco harm reduction strategy. We present the first in human data from the clinical assessment of a novel nicotine aerosol system (P3L) based on the in situ formation of an aerosol of submicron airborne particles consisting of a nicotine salt delivered to the lungs through inhalation. The nicotine salt aerosol is generated by combining vapors of nicotine and a weak acid (lactate). Unlike electronic cigarettes, P3L does not contain exogenous carrier compounds such as propylene glycol, widely used in e-liquids.

This open-label, ascending nicotine levels study, conducted in 16 healthy smokers, investigated the plasma nicotine pharmacokinetic profile, subjective effects, and the safety and tolerability of P3L in relation to the Nicorette® inhalator.

PLASMA NICOTINE PHARMACOKINETICS (ng/mL)



P3L DEVICE

The final design of the product is under development

Study Design

1. Open-label ascending nicotine level study

2. Subjects: 16 male and female, healthy, cigarette smokers (Caucasian)

3. 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)

4. 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 up to 240 minutes. Nicotine concentration was determined in venous plasma by means of LC-MS/MS (LLOQ: 0.2 ng/ml)

5. Subjective effects were assessed on the Visual Analog Scale (VAS) for craving, the brief version of the Questionnaire of Smoking Urges and the modified Cigarette Evaluation Questionnaire (mCEQ)

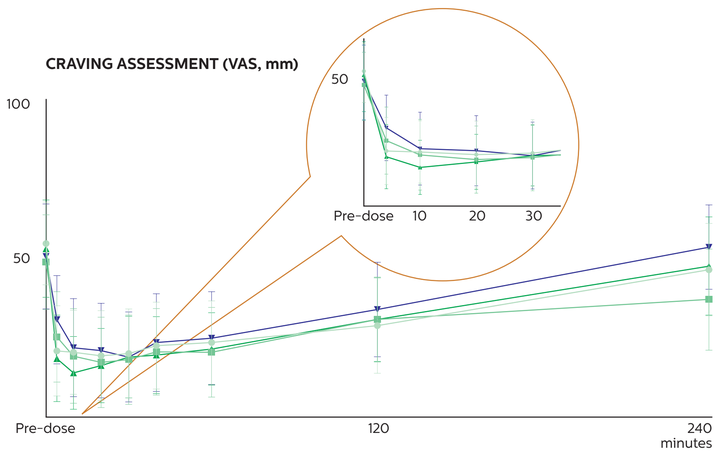
A supplementary leaflet contains references and information on safety monitoring procedures.

TABLE 2. NICOTINE PHARMACOKINETIC PARAMETERS

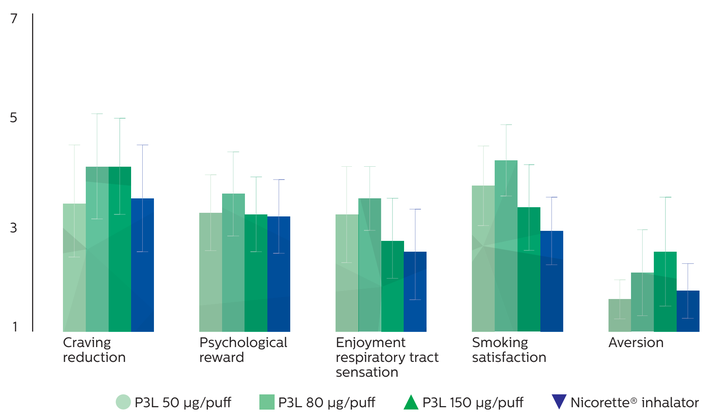
Product	N	C_{max} [ng/mL] (95% CI)[a]	Median t_{max} [min] (min, max)	$AUC_{0\text{-}30'}$ [h*ng/mL] (95% CI)[a]	$AUC_{0\text{-}last}$ [h*ng/mL] (95% CI)[a]
P3L (50 µg/puff)	15	9.7 (6.7, 13.9)	7.0 (4.0, 30.0)	1.0 (0.6, 1.7)	9.9 (7.5, 13.2)
P3L (80 µg/puff)	14	11.1 (7.7, 16.1)	7.0 (4.0, 20.0)	1.2 (0.7, 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

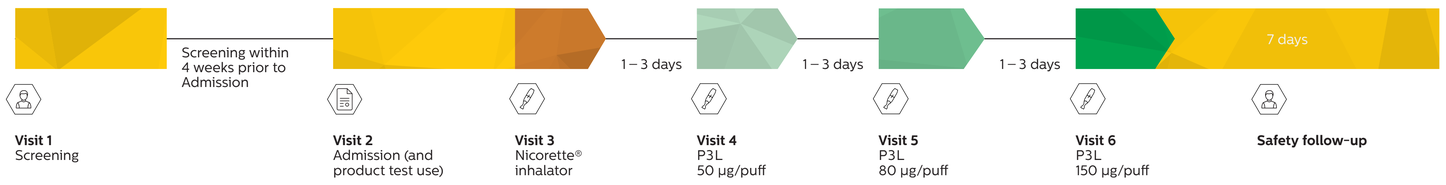
CRAVING ASSESSMENT (VAS, mm)



PRODUCT EVALUATION (MCEQ)



STUDY DESIGN



Results

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

P3L's three nicotine delivery levels showed similar maximum nicotine plasma concentrations (C_{max}), over 50% higher than the Nicorette® inhalator C_{max}. The Nicorette® inhalator's C_{max} and t_{max} values were consistent with published data, and P3L with published data on cigarettes.

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

Product evaluations using mCEQ sub-scales for craving reduction and psychological reward were similar across all P3L 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 P3L 150 µg/puff and the Nicorette® inhalator. There was a trend of increase in the aversion sub-scale score as P3L nicotine level increased.

For references, demographics and safety data please see the supplementary leaflet.

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 than 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 all P3L nicotine delivery levels than the Nicorette® inhalator, with an earlier onset. With the exception of "Aversion", product evaluations for P3L and the inhalator were at least equivalent, with an apparent preference for the P3L 80 µg/puff variant. P3L was generally well tolerated.

For the references and the competing financial interest see the supplementary brochure

Global Forum on Nicotine June 15 – 17, Warsaw, Poland