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


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 to enjoy tobacco or nicotine, Philip Morris International is developing reduced risk products (RiP®), including the novel nicotine aerosol system (P3L) which is based on the technology of generating an aerosol of a nicotine salt by combining waxes of nicotine and a weak acid as first described by Desforges 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 RiP. 

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 regime): one inhalation every 30 seconds over 6 minutes (total 120 puffs corresponding to ~0.7 mg, ~1.5 mg and ~2.5 mg nicotine, respectively)
• Plasma nicotine PK analysis: 15 blood samples were collected: 3 samples from 45 minutes prior start of product use (t0) and 12 samples after.
• Nicotine concentration was determined in venous plasma by means of LC/MS/MS (LOQ: 0.2 µg/ml)

• Subjective effects were assessed by means of the Visual Analog Scale (VAS) for craving3, the brief version of the Questionnaire of Smoking Urgo® and the modified Cigarette Evaluation Questionnaire (mCEQ)4
• Safety monitoring: adverse events (AEs), vital signs, physical examination, ophthalmic, ECG, clinical laboratory safety parameters and cough assessment
• The study was conducted in 2015 at Christchurch Clinical Trials Trust Ltd., New Zealand according to ICH GCP, approved by an Independent Ethics Committee and to the New Zealand Nicotine and Medical Devices Safety Authority (MedSafety), and registered at www.clinicaltrials.gov (NCT02523274)

Results

Safety

There were no serious adverse events (SAEs) or adverse events (AEs) 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, isolation AEs related to P3L (8 subjects) were detected, the majority were mild in severity, the most common one was rhinitis. One single product-related severe AE of syncope occurred (during P3L 80 µg/puff product use) and resolved within the course of the 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.

Nicotine Pharmacokinetic Parameters

The plasma nicotine concentration-time courses following use of P3L were characterized by a rapid absorption phase, with medium time from product start to reach the maximum nicotine plasma concentration Cmax at 7 minutes, while medium tmax following use of Nicorette® Inhalator occurred at 30 minutes.

The maximum nicotine plasma concentration Cmax was similar between the nicotine delivery levels of P3L and almost double compared to Nicorette® inhalator. Cmax and tmax values with Nicorette® inhalator were consistent with published data4, and P3L with published data for cigarettes.5

Compared to Nicorette® inhalator, the nicotine concentration-time profile of nicotine delivered by P3L was characterized by a rapid absorption phase, with medium time from product start to reach the maximum nicotine plasma concentration Cmax at 7 minutes, while medium tmax following use of Nicorette® Inhalator occurred at 30 minutes.

Nicotine Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Product</th>
<th>N</th>
<th>Cmax (µg/ml)</th>
<th>Median Tmax (min)</th>
<th>AUC0-90 (mg*h/ml)</th>
<th>AUC0-inf (mg*h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3L (50 µg/puff)</td>
<td>15</td>
<td>7.9</td>
<td>7.0</td>
<td>1.0</td>
<td>9.9</td>
</tr>
<tr>
<td>P3L (80 µg/puff)</td>
<td>14</td>
<td>11.4</td>
<td>8.7</td>
<td>1.7</td>
<td>11.5</td>
</tr>
<tr>
<td>P3L (150µg/puff)</td>
<td>16</td>
<td>9.4</td>
<td>7.0</td>
<td>1.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Nicorette® Inhalator</td>
<td>15</td>
<td>6.1</td>
<td>3.9</td>
<td>0.1</td>
<td>12.3</td>
</tr>
</tbody>
</table>

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REFERENCES


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 oral mucosal 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 "Theoren", the product evaluation appeared to be as good as for P3L on the inhalator with an apparent preference for the P3L 80 µg/puff inhalator. P3L was generally well tolerated.

Comparing Financial Interest

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