Characterization of Nicotine Pharmacokinetics from Use of Reduced Nicotine Content Cigarette Prototypes in Adult Smokers

ABSTRACT

In March 2019, FDA issued an advance notice of proposed rulemaking (ANPRM) on a nicotine standard for conventional cigarettes to make them minimally- or non-addictive. Currently, there are limited data available on the relationship between the nicotine content in tobacco and human nicotine pharmacokinetics (PK).

METHODS: We developed five prototype reduced nicotine cigarettes (RNCs) with nicotine levels between 1.3 to 1.5 mg per gram tobacco and one prototype conventional nicotine cigarette (CNC). Using these prototypes, we conducted a randomized 2×4 crossover clinical study in 21 healthy adult cigarette smokers following controlled use of a single cigarette (10 puffs taken at 30 intervals). The study also examined product parameters and increased in broad carbonyl/hemoglobin saturation (CO) levels during 30 minutes of ad libitum use product use. RESULTS: Both maximum plasma nicotine concentration (Cmax) and area under the nicotine concentration curve (AUC) following the use of the RNC prototypes (1.4-1.7 mg/ml and 1.7-2.0 mg/ml, respectively) were lower than with the CNC prototype (9.33 mg/ml and 10.39 mg/ml, respectively). Overall, the average number of puffs, puff duration, and number of cigarettes smoked during the first 15 ad libitum product use conditions, and cigarette butts length, were similar between the RNC and CNC prototypes. There were no significant differences in concomitant use of the study cigarettes. CONCLUSION: Cigarette exposure is closely related to the nicotine content of the study cigarettes. We found no significant differences in use parameters in concomitant use conditions when participants used the study cigarettes with different nicotine levels during 30 minutes of ad libitum use conditions. The lowest nicotine content (1.3 mg/g) tested in the study was higher than the level of nicotine content reference cigarette.

RESULTS

This study utilized a single-blind, randomized, 2×4 crossover design to evaluate PK, and product use behavior, association with study prototypes including five RNCs and one CNC with nicotine content between 1.3 to 1.5 mg/g filter among healthy adult cigarette smokers of 21-45 years of age. All subjects were cigarette smokers and products manufactured non-microbe combustion cigarettes having an average consumption of 5-10 cigarettes per day (CPD) for at least 12 months and did not have other tobacco or nicotine-containing products use in the 30 days prior to Check-in. Subjects who met all inclusion and none of the exclusion criteria during screening checked into the clinic on Day -1 and abstained from use of any tobacco- or nicotine-containing products until the first product use study day. On each study day (Days 1-4), subjects received one of the 6 study products (A-F) according to the randomization schedule and administered to each subject at the end of the 30 minutes of cigarette use episode. Carboxyhemoglobin (COHb) blood samples were taken at approximately 5 minutes prior to and 2, 4, 6, 8, 10, 15, 30, 60, 120 and 180 minutes following the start of the 1st product use episode. Corbinohemoglobin (COHb) blood samples were taken at approximately 5 minutes prior to and at approximately 5 and 30 minutes following the start of the 2nd product use episode. Number of puffs, duration of each puff (first cigarette only), number of cigarettes smoked, and cigarette butts were recorded by site staff for the 2nd product use episode.

The mean number of puffs per cigarette was slightly greater, whereas the mean puff duration was slightly shorter, for the 1st cigarette during ad libitum use compared to those during controlled use across all products. The mean number of cigarettes smoked and cigarette butt length during all ad libitum use were similar across all products.

CO Boost

Study Products

- Product A
- Product B
- Product C
- Product D
- Product E
- Product F

Pharmacokinetic Measures

- Baseline-Adjusted Plasma Nicotine Parameters

<table>
<thead>
<tr>
<th>Product</th>
<th>Cmax (µg/ml)</th>
<th>AUC (µg·hr/ml)</th>
<th>T25% (min)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>2.6 ± 0.7</td>
<td>3.3 ± 0.9</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>B</td>
<td>3.8 ± 1.2</td>
<td>4.5 ± 1.5</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>C</td>
<td>5.2 ± 1.9</td>
<td>6.3 ± 2.2</td>
<td>3.6 ± 1.0</td>
</tr>
<tr>
<td>D</td>
<td>7.0 ± 2.8</td>
<td>8.3 ± 3.2</td>
<td>4.4 ± 1.5</td>
</tr>
<tr>
<td>E</td>
<td>9.1 ± 3.5</td>
<td>10.6 ± 4.0</td>
<td>5.2 ± 1.9</td>
</tr>
<tr>
<td>F</td>
<td>11.2 ± 4.2</td>
<td>12.9 ± 5.1</td>
<td>6.0 ± 2.3</td>
</tr>
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REFERENCES


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