The Tobacco Heating System (THS) was developed to reduce or eliminate the formation of harmful and potentially harmful constituents (PHHCs) in the aerosol through heating and not burning tobacco, while preserving as much as possible taste, sensory experience, nicotine delivery profile and ritual characteristics of cigarettes (CC).

Clinical studies have been conducted in various populations of healthy adult smokers to compare the pharmacokinetics (PK) of nicotine following exposure to aerosol generated by THS with that from CC, as well as nicotine nasal spray (NNS) and oral nicotine gum (QUM). The duration of the washout periods was designed assuming that plasma nicotine terminal half-life ($t_{1/2}$) was approximately 2h (1.2). However, in our clinical studies, pre-dose nicotine plasma concentrations were often measurable, resulting in carry-over effects.

A population PK analysis was performed to:
- Describe concentration-time profile of plasma nicotine based on data of various nicotine delivery systems collected in the assessment program of THS, distinguishing between the nicotine exposure due to product use and background exposure
- Assess sources of variability in nicotine PK parameters
- Assess the predictive performance of the model

### Introduction and Objectives

The aim of this study was to understand the nicotine PK after single product use and after 4 days of ad libitum use of THS, and to identify the source of variability in the PK parameters.

### Methods

#### Dataset
- Data from 4 single product use (PK) studies (4) were pooled in a learning dataset (n=246) to develop a population PK model, perform the covariate analysis, derive exposure parameters, and to perform internal model evaluation
- Data from 4 separate ad libitum use studies (5) were pooled in a validation dataset (n=456) and were used for external model validation

#### Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>Nicotine Yield/Dose</th>
<th>Variant</th>
<th>Country</th>
<th>Learning Dataset</th>
<th>Validation Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>THS</td>
<td></td>
<td></td>
<td></td>
<td>US, EU</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CC</td>
<td>Subjects’ preferred brand</td>
<td>0.1 to 1.5 mg</td>
<td>Regular or modified</td>
<td>US, EU</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NNS</td>
<td>Nicorette® Nasal Spray</td>
<td>10 mg/mL</td>
<td>1 mg</td>
<td>US, EU</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>QUM</td>
<td>Nicorette® 2 mg gum</td>
<td>2 mg</td>
<td>Mentholated</td>
<td>JP</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Analysis Flowchart

- Nicotine PK Model
  - The base model for nicotine included two components:
    - Primary: Product, nicotine KYG (yield/dose), sex, weight, CC, CYP2A6, CYP2B6, menthol, fentanyl score, baseline daily cigarette consumption
    - Secondary: Age, height, BMI, race, ethnicity, ALT, AST, Bilirubin, sex, race, smoking status (current, former, never), age (years), height (cm), weight (kg), race (Asian, African-American, Other), smoking status (current, former, never), age (years), height (cm), weight (kg), race (Asian, African-American, Other)

- All products were included simultaneously in an integrated population PK model. Data from two consecutive single product use studies were pooled in a validation dataset (n=246) and were used for external model validation.

#### Base Model – Primary Parameters

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Estimate</th>
<th>RSE</th>
<th>% IIV</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (alpha)</td>
<td>1.72</td>
<td>0.001</td>
<td>0.058</td>
<td>0.008</td>
</tr>
<tr>
<td>$t_{1/2}$ (beta)</td>
<td>17.0</td>
<td>0.000678</td>
<td>0.00858</td>
<td>0.00085</td>
</tr>
<tr>
<td>Dose</td>
<td>4.0</td>
<td>0.001</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>CL1/F, CL2/F: apparent clearance terms</td>
<td>24.4</td>
<td>0.001</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>V1/F – Menthol vs Regular</td>
<td>31.5</td>
<td>0.001</td>
<td>0.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Model (Ordinary Differential) Equations

\[ \begin{align*}
\frac{dC}{dt} &= \frac{Dose}{Tdur} \times \frac{C}{V1/F} + \frac{C}{CL1/F} + \frac{C}{CL2/F} - \frac{C}{Tdur} \\
\frac{dC1}{dt} &= \frac{C1}{CL1/F} + \frac{C1}{CL2/F} \times \frac{C}{Tdur} - \frac{C1}{CL1/F} - \frac{C1}{CL2/F} \\
\frac{dC2}{dt} &= \frac{C2}{CL1/F} + \frac{C2}{CL2/F} \times \frac{C}{Tdur} - \frac{C2}{CL1/F} - \frac{C2}{CL2/F} \\
\end{align*} \]

#### Conclusions

The population PK model was able to describe the nicotine PK after single product use and after 4 days of ad libitum use with products and various routes of administration (inhaled, oral) in different populations (Americans, Japanese, and Europeans) and to identify the source of variability in the PK parameters.

### Bibliography