Nicotine Population Pharmacokinetics in Healthy Adult Smokers

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Introduction and Objectives

The Tobacco Heating System (THS) was developed to reduce or eliminate the formation of harmful and potentially harmful constituents (HPHCs) 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 (GUM). 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 [3].

A population PK analysis was performed to:

- Describe concentration-time profiles 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

Methods

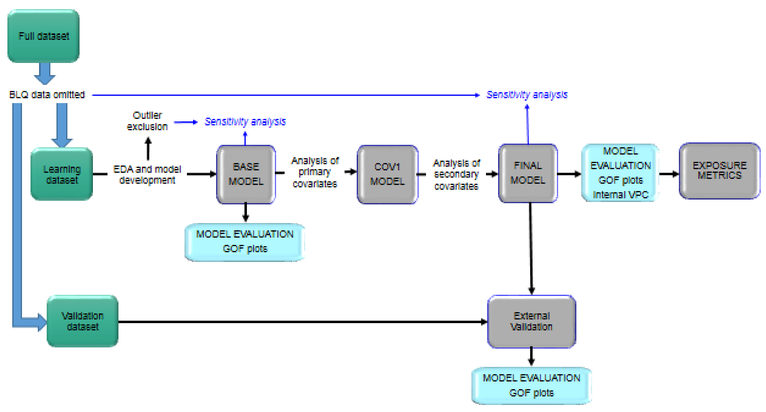
Dataset

- 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

Product	Brand Name	Nicotine Yield/Dose	Variant	Country	Learning Dataset	Validation Dataset
THS	IQOS and HEETS HeatSticks	0.5 mg	Regular or mentholated	US, EU, JP	Yes	Yes
CC	Subjects' preferred brand	0.1 to 1.5 mg	Regular or mentholated	US, EU, JP	Yes	Yes
NNS	Nicotrol® Nasal Spray 10 mg/mL	1 mg	Regular	US, EU	Yes	No
GUM	Nicorette® 2 mg gum	2 mg	Mentholated	JP	Yes	No

Analysis Flowchart

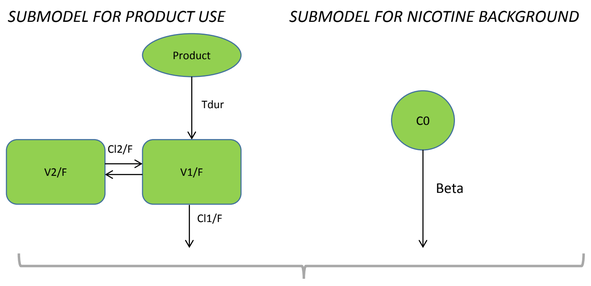


Covariate Hierarchy

- Primary
  Product, nicotine ISO yield, sex, weight, CYP2A6, creatinine clearance
- Secondary
  Age, height, BMI, race/ethnicity, ALT, AST, bilirubin, menthol, Fagerström scores , baseline daily cigarette consumption

Nicotine PK Model

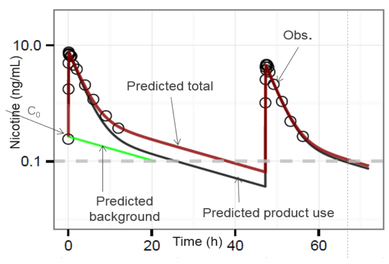
- The base model for nicotine included two components:



Total Nicotine = Product + Background

Base Model – Primary Parameters

- Cl1/F, Cl2/F: apparent clearance terms
- V1/F, V2/F: apparent volume terms
- Tdur: duration of zero-order input
- C0: background nicotine pre-exposure
- Frel: product-specific bioavailability relative to THS



- All products were included simultaneously in an integrated population PK model. Data from two consecutive single product use periods were analyzed jointly on a continuous time scale
- Non-linear mixed effect (NLME) modelling was conducted using Phoenix® NLME™ 1.3 and first-order conditional estimation with extended least squared estimation
- Final covariate selection: Stepwise forward selection ($p<0.05$) and backward elimination ($p<0.01$) procedure

- **Model (Ordinary Differential) Equations**

Sub-model	Equations
Product use	if t ≤ Tdur, $dA1/dt = -Cl1/F \times C1 - Cl2/F \times (C1 - C2) + Dose/Tdur$ else: $dA1/dt = -Cl1/F \times C1 - Cl2/F \times (C1 - C2)$ $dA2/dt = Cl2/F \times (C1 - C2)$ $C1 = A1/(V1 / F)$ $C2 = A2/(V2 / F)$
Background	$k_{10} = Cl1/V1$, $k_{12} = Cl2/V1$, and $k_{21} = Cl2/V2$ $alpha = 0.5 \times \left(k_{12} + k_{21} + k_{10} + \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4 \times k_{21} \times k_{10}}\right)$ $beta = 0.5 \times \left(k_{12} + k_{21} + k_{10} - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4 \times k_{21} \times k_{10}}\right)$ $Background = C0 \times e^{-beta \times t}$
Total	$Total\ Nicotine\ Concentration = C1 + Background$

- A1, A2: nicotine in central and peripheral compartments
- C1, C2: nicotine concentration in central and peripheral components
- Dose: nicotine yield
- Dose/Tdur: absorption rate
- $t_{1/2}$(alpha) = ln2/alpha/60 (initial half life [h])
- $t_{1/2}$(beta) = ln2/beta/60 (terminal half-life [h])

Results

Demographics

Covariate	Unit	Learning (N=246) Mean ± SD	Validation (N=456) Mean ± SD
Age	year	33.5 ± 9.2	36.7 ± 10.9
Weight	kg	70.1 ± 13.9	68.6 ± 13.8
Height	m	1.69 ± 0.1	1.68 ± 0.1
BMI	kg/m²	24.3 ± 3.67	24.2 ± 3.6
ALT	U/L	18.3 ± 10.1	17.8 ± 8.9
AST	U/L	20.8 ± 16.4	18.3 ± 4.8
Bilirubin	µmol/L	0.66 ± 0.38	0.62 ± 0.25
Creatinine Clearance	mL/min	123 ± 25	124 ± 29.7
CYP2A6	%	31.5 ± 18.2	33.7 ± 17.1

Category	Learning (N=246)	Validation (N=456)
Sex – Female	45.5%	46.4%
Sex – Male	54.5%	53.6%
Ethnicity – Hispanic	0.4%	3.1%
Ethnicity – Not Hispanic	99.6%	96.9%
Country – USA	25.2%	21.7%
Country – EU	24.4%	26.3%
Country – Japan	50.4%	52.1%
Race – White	35.0%	40.3%
Race – Black	13.8%	5.7%
Race – Asian	50.8%	52.1%
Race – Other	0.4%	2.0%

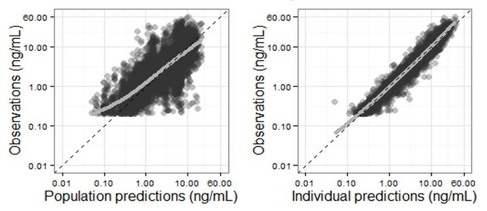
Final Population PK Parameters

Parameter (unit)	Estimate	RSE %	IIV%	Shrinkage (%)
V1/F (L)	70.0	2.8	80	1.9
CL1/F (L/min)	0.407	3.0	68	2.5
V2/F (L)	171	3.3	85	29.4
CL2/F (L/min)	0.171	3.5	139	14.3
Tdur (min)	5.30	1.2	38	12.4
C0 (ng/mL)	0.358	1.5	48	22.6
Frel – THS	1	fixed		
Frel – THS vs CC	0.0189(*)	1.6	70	5.2
Frel – THS vs NNS	-1.42(*)	1.5	70	5.2
Frel – THS vs GUM	-0.489(*)	1.6	70	5.2

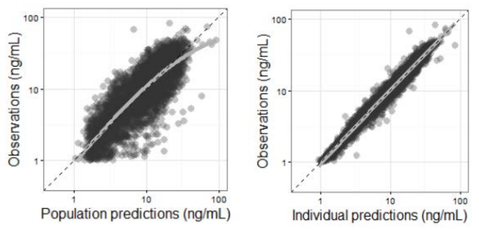
(*) Results expressed in the log scale.

Parameter (unit)	Estimate (*)	RSE %
Tdur – GUM vs THS ,CC, NNS	2.14	1.2
Tdur – Menthol vs Regular	0.053	1.6
C0 – CYP2A6 effect	-0.401	1.6
C0 – Black vs non Black	0.408	1.6
CL1/F – Female vs Male	0.235	1.6
CL1/F – CYP2A6 effect	0.322	1.6
V1/F – Menthol vs Regular	0.091	1.6
Frel – ISO Yield effect	-0.573	1.6
Frel – Weight effect	-0.715	1.6
Residual	0.289	0.9

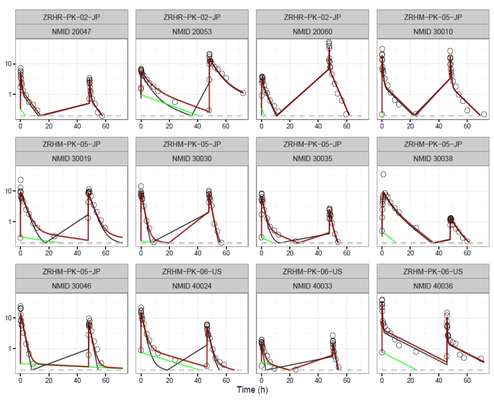
GOF Plots - Learning Dataset



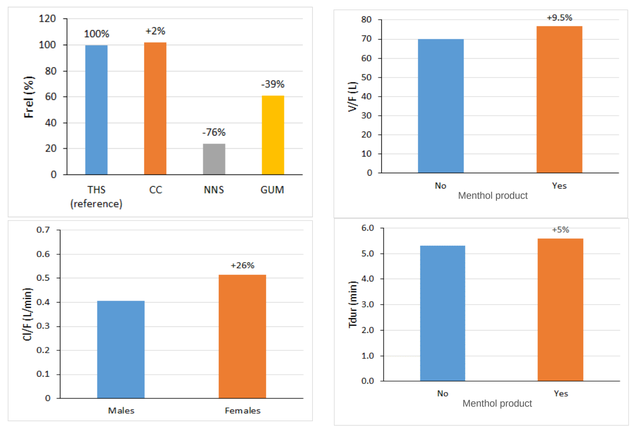
GOF Plots - Validation Dataset



Individual Fits Plots



Secondary Parameter (unit)	Estimate
Alpha (1/min)	0.00858
Initial half-life (h)	1.35
Beta (1/min)	0.000678
Terminal half-life (h)	17.0



- Two-compartment linear disposition combined with zero-order absorption were adequate to describe nicotine PK and a mono-exponentially decreasing background component to account for nicotine carry-over effects
- Bioavailability was product-specific and absorption duration was prolonged with nicotine gum in relation to a prescribed chewing duration of 35 +/- 5 min
- The presence of menthol did not impact Frel but only V1/F (inversely related to C_{max}) and Tdur (directly related to t_{max})
- The derived typical initial and terminal half-lives were 1.35 and 17 hours, respectively. Some uncertainty remains with regard to terminal half-life due to challenges in accounting for BLQ concentrations (0.2 ng/mL for the single use studies and 1 ng/mL for the *ad libitum* studies)

Conclusions

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

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4) ClinicalTrials.gov id of single use PK studies: NCT01967732, NCT01959607, NCT01967706, NCT01967719
5) ClinicalTrials.gov id of ad-libitum use studies: NCT01959932, NCT01970982, NCT01970995, NCT01989156

Abbreviation

ALT: alanine transaminase; AST: aspartate transaminase; Beta: terminal rate constant; BMI: body mass index, BLQ: below the lower limit of quantification; C_{max}: maximum concentration; C0: pre-dose nicotine concentration; CL1/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; CYP2A6: cytochrome P450 2A6 isoform; EDA: exploratory data analysis; Frel: product-specific bioavailability relative to THS; GOF: goodness-of-fit; ISO: International Standard Organization; IIV: inter-individual variability; NLME: nonlinear mixed effect; PK: Pharmacokinetic; RSE: relative standard error; V1/F, V2/F: apparent central/peripheral volumes of distribution; t_{max}: time to maximum concentration; Tdur: duration of nicotine absorption

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Competing Financial Interest

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