

## Electronic Supplementary Material

**Article title:** Nicotine population pharmacokinetics in healthy smokers after intravenous, oral, buccal and transdermal administration

**Journal name:** Clinical Pharmacokinetics

**Authors:** Per O Olsson Gisleskog<sup>1</sup>, Juan José Perez Ruixo<sup>2</sup>, Åke Westin<sup>3</sup>, Anna C Hansson<sup>4</sup>, Paul A Soons<sup>5\*</sup>

### **Affiliation:**

<sup>1</sup>SGS Exprimo NV, Life Science Services, London, UK (currently at POG Pharmacometrics, London, UK)

<sup>2</sup>Janssen Research & Development, Quantitative Sciences, Beerse, Belgium

<sup>3</sup>McNeil AB, Global Medical Affairs and Clinical Research, Helsingborg, Sweden

<sup>4</sup>McNeil AB, Clinical Science, Helsingborg, Sweden

<sup>5</sup>Janssen Pharmaceutica NV, Alliance Management, Beerse, Belgium

**Email address corresponding author:** [psoons@its.inj.com](mailto:psoons@its.inj.com)

## Details on study designs, dosing regimens and sampling schedules

Study Name (EudraCT identifier, where available)	Route Formulation	Study description	Treatment arms	Number of subjects included in analysis	PK sampling schedule	Ethics Committee
96NNIV003	iv	Effect of Hepatic Impairment Parallel single dose	iv 0.028mg/kg /10min	8 <sup>a</sup>	-24, -20, -16, -12, predose, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24h after dosing	University of Lund, Lund, Sweden
96NNIV004	iv	Effect of Age Parallel single dose	iv 0.028mg/kg /10min	40	-20, -16, -12, predose, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 23h after dosing	University of Lund, Lund, Sweden
96NNIV005	iv	Effect of Renal Impairment Parallel single dose	iv 0.028mg/kg /10min	9 <sup>b</sup>	-24, -20, -16, -12, predose, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24h after dosing	University of Linköping, Linköping, Sweden
980CHC1050004	iv Buccal Chewing gum	Absolute bioavailability Cross-over single dose	iv 0.028mg/kg /10min Nicorette freshmint gum 4mg	23	predose, 0.033, 0.067, 0.1 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12h after dosing	University of Lund, Lund, Sweden
A6431108 (2006-006486-16)	Transdermal	Comparative PK Cross-over repeat dose	Nicorette Invisipatch 22.5cm2 (25mg/16h) applied 16/24h for 3 days  Nicorette Invisipatch 22.5cm2 (25mg/16h) applied 24/24h for 3 days	26	predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 24h after dosing on days 1 and 3.	University of Lund, Lund, Sweden
NICPAT9145003	Transdermal	Comparative PK Cross-over single dose	Nicorette patch10 cm2 (5mg/16h)  Nicorette patch 30 cm2 (15mg/16h)	17	predose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 17, 20, 22, 24, 26, 28h after dosing	University of Lund, Lund, Sweden

			Nicorette patch 50 cm2 (25mg/16h)				
			Nicorette Invisipatch 10 cm2 (10mg/16h)				
			Nicorette Invisipatch 22.5 cm2 (25mg/16h)				
			Nicorette Invisipatch 35 cm2 (37mg/16h)				
NICPAT9145004	Transdermal	Bioequivalence Cross-over single dose	Nicorette patch 50 cm2 (25mg/16h)	30	predose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 17, 20, 22, 24, 26, 28h after dosing	University of Lund, Sweden	Lund,
			Nicorette Invisipatch 22.5 cm2 (25mg/16h)				
92NNBT005	Oral Microtabs	Comparative PK Cross-over, 10 hourly doses	10 x 2mg sublingual tablet chewed and swallowed	20	Predose samples for doses 1-10; 10, 20, 30, 40, 50 and 60 min after last dose.	University of Lund, Sweden	Lund,
93NNBT007	Oral Microtabs	Single dose	3 x 2mg sublingual tablet swallowed	6	Predose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h after dosing.	University of Lund, Sweden	Lund,
A6431075	Buccal Chewing gum Lozenge	Comparative PK Single dose cross-over	Nicorette classic gum 4mg Nicorette freshmint gum 4mg NiQuitin lozenge 4mg	36	Predose, 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 75, 90, 105 min; 2, 3, 4, 6, 8, and 10 h after dosing	University of Lund, Sweden	Lund,
A6431076 (2004-003016-30)	Buccal Chewing gum	Comparative PK Single dose cross-over	Nicorette classic gum 2mg	19	Predose, 2, 4, 6, 8, 10, 13, 16, 20, 30, 45, 60 min; 1.25, 1.5, 2, 4, 6, and 8 h after dosing	University of Lund, Sweden	Lund,
A6431094 (2006-000160-81)	Buccal Chewing gum Mouth spray	Comparative PK Single dose cross-over	Nicorette classic gum 2mg Mouth Spray 2mg buccally Mouth spray 2mg sublingually	30	Predose, 2, 4, 6, 8, 10, 13, 16, 20, 30, 45, 60 min; 1.25, 1.5, 2, 4, 6, and 8 h after dosing	University of Lund, Sweden	Lund,

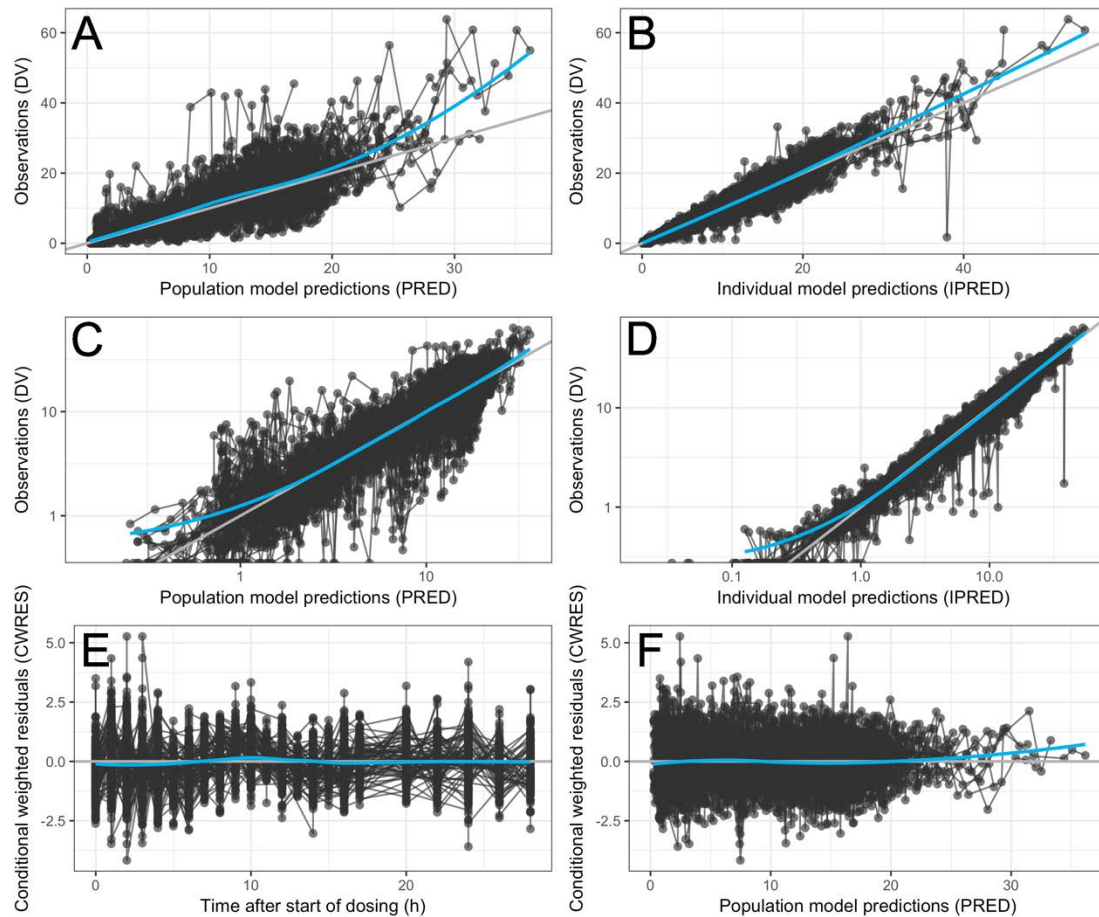
			Mouth spray 2mg normal administration				
A6431095 (2006-003335-75)	Buccal Chewing gum	Comparative PK Single dose cross-over	Nicorette classic gum 2mg Nicorette classic gum 4mg	36	Predose, 5, 10, 15, 20, 30, 45, 60, 75, 90 min; 2, 3, 4, 6, 8, 10 and 12 h after dosing	University of Lund, Sweden	Lund,
A6431096 (2006-000552-40)	Buccal Chewing gum	Comparative PK Cross-over, 12 hourly doses	12 x Nicorette classic gum 2mg 12 x Nicorette classic gum 4mg	35	Predose samples for doses 1-12. 10, 20, 30, 40, 50 and 60 min after last dose	University of Lund, Sweden	Lund,
NICSOS9132005	Buccal Chewing gum	Comparative PK Single and multiple dose (12 hourly doses) cross-over	Nicorette classic gum 4mg Nicorette freshmint gum 4mg 12 x Nicorette classic gum 2mg 12 x Nicorette freshmint gum 2mg	26	Single dose: pre-dose and at 5, 10, 15, 20, 30, 45 min; 1, 1.25, 1.5, 2, 3, 4, 6, 8 and 10 h after dosing. Repeat dose: Predose samples for doses 1-12; 10, 20, 30, 40, 50 and 60 min after last dose	University of Gothenburg, Gothenburg, Sweden	of
NICSOS9132006	Buccal Chewing gum	Comparative PK Single and multiple dose (12 doses) cross- over	Nicorette freshmint gum 4mg 12 x Nicorette freshmint gum 2mg	32	Single dose: predose and 5, 10, 15, 20, 30, 45 min; 1, 1.25, 1.5, 2, 3, 4, 6, 8 and 10 h after dosing Repeat dose: Predose samples for doses 1-12; 10, 20, 30, 40, 50 and 60 min after last dose	University of Lund, Sweden	Lund,
NICTDP1065 (2008-006280-36)	Buccal Chewing gum Mouth spray Lozenge	Comparative PK Single dose cross-over	Mouth spray 1mg Mouth spray 2mg Mouth spray 4mg Nicorette classic gum 4mg NiQuitin lozenge 4mg	45	Predose and 2, 4, 6, 8, 10, 15, 20, 30, 45, 60 min; 1.5, 2, 3, 4, 6, 8, 10, and 12 h after dosing	University of Lund, Sweden	Lund,
NICTDP1066 (2008-006279-65)	Buccal Chewing gum Mouth spray Lozenge	Comparative PK Cross-over, repeated dosing for 12h	Mouth spray 2mg every h for 12h Mouth spray 2mg every 30 min for 12h Nicorette classic gum 4mg every h for 12h	40	Predose at 0, 1, 2, 4, 6, 8, 9, 10, 11h. Every 5 minutes between 11 and 12h.	University of Lund, Sweden	Lund,

			NiQuitin Lozenge 4mg every h for 12h			
NICTDP1070 (2008-006279-65)	Buccal Chewing gum	Comparative PK Single dose cross-over	Nicorette freshfruit 2mg Nicorette freshfruit 4mg Nicorette freshfruit 6mg	24	Predose and 5, 10, 15, 20, 30, 45, 60 min; 1.25, 1.5, 2, 3, 4, 6, 8 and 10 h after dosing.	University of Lund, Lund, Sweden
NICTDP1071 (2008-003358-14)	Buccal Chewing gum	Bioequivalence Single dose cross-over	Nicorette classic 2mg Nicorette classic 4mg	85	Predose and 5, 10, 15, 20, 30, 45, 60 min; 1.25, 1.5, 2, 3, 4, 6, 8 and 10 h after dosing.	University of Linköping, Linköping, Sweden
NICTDP1080 (2010-021087-15)	Buccal Chewing gum Lozenge	Comparative PK Single dose cross-over	Nicorette freshfruit 2mg Nicorette freshfruit 4mg Nicorette freshfruit 6mg NiQuitin Lozenge 4mg	44	Predose and 2, 4, 6, 8, 10, 15, 20, 30, 45, 60 min; 1.5, 2, 4, 6, 8, 10, and 12 h after dosing.	University of Lund, Lund, Sweden
NICTDP1081 (2010-023026-20)	Buccal Chewing gum Lozenge	Comparative PK Cross-over, repeated dosing for 12h	Nicorette freshfruit 4mg/h Nicorette freshfruit 4mg/1.5h Nicorette freshfruit 6mg/h Nicorette freshfruit 6mg/1.5h NiQuitin lozenge 4mg/h	50	Dosing every h: predose at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 h; 5, 10, 15, 20, 30, 40, 50, and 60 min after the last dose. Dosing every 1.5h: predose at 0, 1.5, 3, 4.5, 6, 7.5, 9, 10.5 h; 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 min after the last dose.	University of Lund, Lund, Sweden
NICTDP1076 (2009-012407-26)	Buccal Lozenge	Bioequivalence Single dose cross-over	Nicotine Strongmint Lozenge 2mg Nicorette Strongmint Lozenge 4mg NiQuitin lozenge 2mg NiQuitin lozenge 4mg	104	Predose, 7.5, 15, 20, 30, 40, 50, 60 min; 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after dosing.	University of Lund, Lund, Sweden
A6431107 (2006-004904-37)	Buccal Mouth spray	Comparative PK Single dose cross-over	Mouth spray 1mg Mouth spray 2mg Mouth spray 3mg Mouth spray 4mg	24	Predose and 2, 4, 6, 8, 10, 13, 16, 20, 30, 45, 60 min; 1.25, 1.5, 2, 4, 6, and 8 h after dosing.	University of Lund, Lund, Sweden
NICTDP0003 (2011-004696-37)	Buccal Mouth spray	Comparative PK	Mouth spray 2mg	33	Predose and 2, 4, 6, 8, 10, 13, 16, 20, 30, 45,	University of Lund, Lund, Sweden

		Single dose cross-over			60 min; 1.25, 1.5, 2, 4, 6, and 8 h after dosing.		
NICTDP1078 (2006-006486-16)	Buccal Mouth spray	Comparative PK Single dose cross-over	Mouth spray 2mg	30	Predose and 2, 4, 5, 8, 10, 15, 20, 30, 45, 60 min; 1.5, 2, 4, 6, and 8 h after dosing.	University of Lund, Sweden	Lund,
95NNIN014	Buccal Inhaler	Bioequivalence Cross-over, 12 hourly doses	Nicorette inhaler 10mg replaced every hour Nicorette inhaler 15mg replaced every 2h	19	Predose at 0, 1, 2, 3, 4, 6, 8, 9, 10, 11 h; 10, 20, 30, 40, 50 60 min after the last dose .	University of Lund, Sweden	Lund,
97NNIN025	Buccal Inhaler	Bioequivalence Cross-over, 12 hourly doses	Nicorette inhaler 10mg replaced every 2h Nicorette inhaler 15mg replaced every 4h	21	Predose at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 h; 10, 20, 30, 40, 50 60 min after the last dose .	University of Lund, Sweden	Lund,
A6431002	Buccal Inhaler	Bioequivalence Single dose cross-over	Nicorette inhaler 10mg	18	Predose and 5, 10, 15, 20, 25, 30, 45 min; 1, 1.5, 2, 3, 4, 5, 6, 7, 8 h after dosing.	University of Lund, Sweden	Lund,

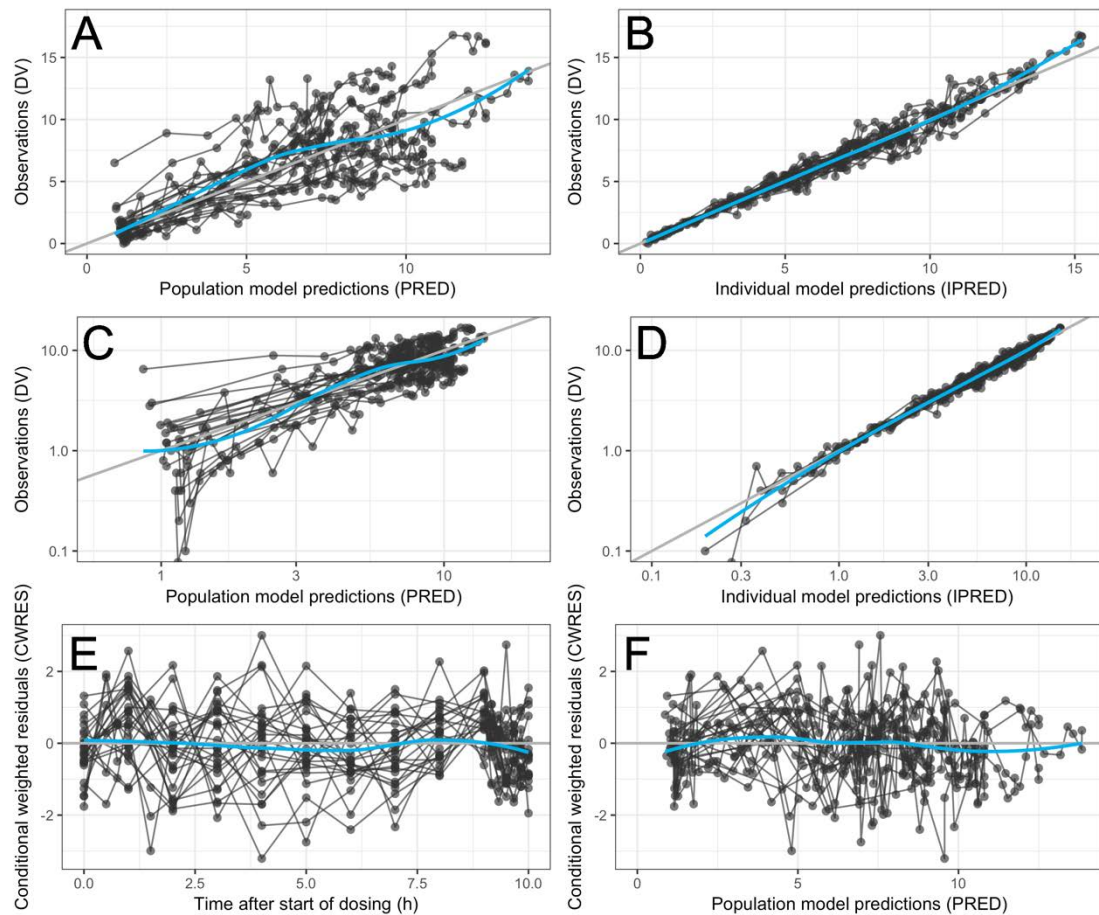
<sup>a</sup>Only subjects with normal liver function included. <sup>b</sup>Only subjects with normal renal function included.

## Goodness of Fit plots for all models



### Supplementary figure 1: Goodness of fit for the transdermal model .

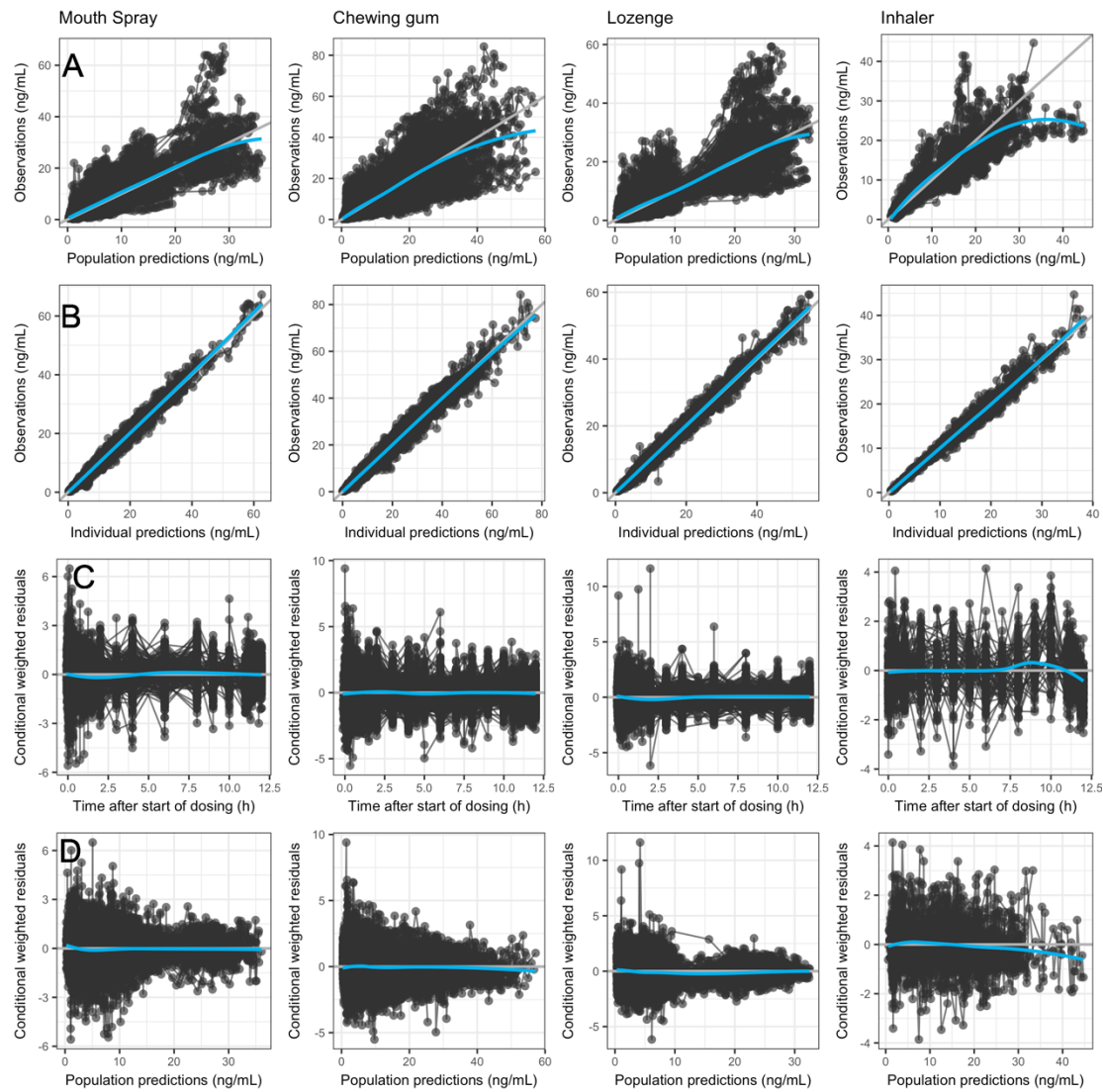
A) Observed vs predicted concentrations, linear scale. B) Observed vs individually predicted concentrations, linear scale. C) Observed vs predicted concentrations, log-log scale. D) Observed vs individually predicted concentrations, log-log scale. E) Conditional weighted residuals vs Time. F) Conditional weighted residuals vs population predictions. Grey line is the line of identity or the zero line, the blue line a smoother. Observations and predictions are in ng/mL.



**Supplementary figure 1: Goodness of fit for the oral model**

A) Observed vs population predicted concentrations, linear scale. B) Observed vs individual predicted concentrations, linear scale. C) Observed vs population predicted concentrations, log scale. D) Observed vs individual predicted concentrations, log- scale. E) Conditional weighted residuals vs Time. F) Conditional weighted residuals vs population predictions. Grey line is the line of identity, blue line a smooth. Observations and predictions are in ng/mL.





**Supplementary figure 3: Goodness of fit for the buccal models.**

From left to right: Mouth spray, chewing gum, lozenge, inhaler. A) Observed vs population predicted concentrations. B) Observed vs individual predicted concentrations. C) Conditional weighted residuals vs Time. D) Conditional weighted residuals vs population predictions. Grey line is the line of identity, blue line a smooth.