

MEMO

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Date: 25/Nov/2014

From: Hossack, Stuart

To: Croasdale, Paul

Copy to: Mulholland, Sarah; Hope, Paul; Russum, Kilda; Gaw, Nina; Wilkinson, Alexander

Re: CCRU Study number: 1001000-8278005 (ZRHM-PK-05-JP), date: 25/Nov/2014, PK handover Memo Version 4

Version 4 PK handover created to remove the double strike-through text on Page 4 to indicate that selected parameters should be listed.

The following files are available for use:-

Directory of P:\1001000\8278005\Pharmacometrics\PK\Parameters

24/Jun/2014 18:45	364,320 ENT\Shossack	fso.xpt
18/Aug/2014 13:48	164,240 ENT\Shossack	fso12.xpt
29/May/2014 22:50	894,080 ENT\Shossack	pki.xpt
29/May/2014 22:51	839,200 ENT\Shossack	pki12.xpt
27/Jun/2014 16:28	478,640 ENT\Shossack	sso.xpt
18/Aug/2014 13:49	464,080 ENT\Shossack	sso12.xpt
6 File(s)		3,204,560 bytes

Key

pki.xpt	PK input data for nicotine
pki12.xpt	PK input data for nicotine (0-12 hours post exposure)
fso.xpt	PK output parameters for nicotine
fso12.xpt	Half-life output parameters for nicotine (0-12 hours post exposure)
sso.xpt	Regression selections (for individual conc-time figures).
sso12.xpt	Regression selections over 0-12 hours post exposure (for individual conc-time figures).

WinNonlin/SAS transport file: SAP/TFL naming conventions and definitions

fso.XPT PK parameters

WinNonlin/SAS transport file name	SAP/TFL Parameter	Definition
AUClast	$AUC_{(0-last)}$	Area under the plasma concentration-time curve from start of product use to the time of the last quantifiable concentration.
AUC0_t	$AUC_{(0-t')}$	Area under the plasma concentration-time curve from start of product use to the subject-specific time (t') of maximum nicotine concentration following single use of the CC or NRT gum product, between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum.
AUCINF_obs	$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from start of product use extrapolated to infinite time.
AUC_%Extrap_obs	%AUC _{extrap}	Percentage of AUC that is extrapolated from t _{last} to infinity.
Cmax	C _{max}	Maximum observed plasma concentration.
Clast	C _{last}	Last quantifiable concentration.
Tlast	t _{last}	Time of the last quantifiable concentration.
Tmax	t _{max}	Time of maximum observed plasma concentration.
Lambda_z	λ_z	Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data.
HL_Lambda_z	t _{1/2}	Terminal elimination half-life.
Rsq_adjusted		
No_points_lambda_z		
Lambda_z_lower		
Lambda_z_upper		
Pct_Cmax		Percentage of T ₀ relative to Cmax
Flag_PctCmax		Flag where T ₀ > 5% of Cmax
Flag_missingT0		Flag where T ₀ is missing (no instances in this study)
HL_flag		Flag where t _{1/2} calculated over period less than 2x t _{1/2}
HL_flagexc		Flag where t _{1/2} calculated over period less than 1.5x t _{1/2}
AUCextflag		Flag where %AUC _{extrap} > 20%

WinNonlin/SAS transport file: SAP/TFL naming conventions and definitions

fso12.XPT PK parameters

WinNonlin/SAS transport file name	SAP/TFL Parameter	Definition
Lambda_z_12	$\lambda_{z(0-12)}$	Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data.
HL_Lambda_z_12	$t_{1/2(0-12)}$	Half-life estimated up to 12 hours post exposure
Rsq_adjusted_12		
No_points_lambda_z_12		
Lambda_z_lower_12		
Lambda_z_upper_12		
HL_flag12		Flag where $t_{1/2}$ calculated over period less than $2 \times t_{1/2(0-12)}$
HL_flagexc12		Flag where $t_{1/2}$ calculated over period less than $1.5 \times t_{1/2(0-12)}$
AUC0_12	$AUC_{(0-12)}$	Area under the plasma concentration-time curve from start of product use to 12 hours. Additional parameter calculated in case needed at later stage – include in PP and ADPP

The disposition of nicotine appears to be generally bi-phasic, with a longer apparent terminal elimination phase observed in some subjects. In consideration that there was no PK blood sampling between 12 and 24 hours post-exposure and approximately half of subjects showed quantifiable nicotine concentrations at 24 hours post-exposure, additional half-life estimates were derived over 0 to 12 hour post-exposure time period. The parameters within fso12.XPT should be included in the PP and ADPP datasets, as these may be reported at a later time.

Additional Comments for PK data:

Subject 129, THS 2.2 Menthol, AUC₀₋₁₂ could not be calculated as this area could not be extrapolated from C_{last} due to λ_z not being calculable (Rs_q_adjusted <0.7). Please assign AUC₀₋₁₂ for this subject as not calculable (NC) and flag in listing with footnote as 'Not calculated; Rs_q_adjusted <0.7'

- The following subject has an incomplete PK profile due to being withdrawn from study:

SUBJID	APERIOD	TRTA	PK data available
0107	1	THS	Up to 6h

Report C_{max} and t_{max} and AUC_(0-t) in listings and exclude these from summary statistics. This subject is excluded from PK population as they did not complete at least one of the single use days.

For all other PK parameters present these are not calculated (NC) in listings, include a flag with a footnote as:

'Partial concentration versus time profile due to subject withdrawal; derived parameters not calculated'

- Where HL_flagexc = 1 do not report the following in TFLs:

AUC_(0-∞)
%AUC_{extrap}
 λ_z
Rs_q_adjusted
No_points_lambda_z
Lambda_z_lower
Lambda_z_upper

(note this will also apply to applicable parameters calculated over 0 to 12 hours)

- The percentage of C_{max} represented by the concentration at T₀ is calculated (Pct_Cmax)
- The flag for T₀>5% C_{max} is included (Flag_PctCmax)
- A flag for T₀ concentration missing is included – flag is only applicable where Flag_missingT₀ = TRUE. Ignore FALSE records. There are no instances of missing T₀ in this study.
- All BLQs occurring after T₀, but before the last quantifiable concentration have been imputed with ½ LLOQ for PK analysis.
- Where No_points_lambda_z = 0 is blank the following parameters should be flagged in listing with footnote as 'Not calculated; Rs_q_adjusted <0.7':

AUC_(0-∞)
%AUC_{extrap}
λ_z
t_{1/2}
Rsq_{adjusted}

Lambda_z_lower
Lambda_z_upper

(note this will also apply to applicable parameters calculated over 0 to 12 hours)

The following nicotine sample results were queried with bioanalytical lab following review by Pharmacokineticist:

Subject	Day	Time (h)	Concentration (ng/mL)	Reason
27	1	24	2.92	Increased conc from preceding time
60	3	24	0.497	Increased conc from preceding time
84	1	12	10.6	Approx 10-fold higher than expected
90	3	9	BLQ	Embedded BLQ
90	3	12	0.202	Conc follows BLQ
113	1	24	0.338	Increased conc from preceding time
129	3	0.25 to 6 h	all concentrations	Low concentrations and multiple peaks
134	1	12	5.76	Increased conc from preceding time

The bioanalytical lab confirmed that there were no analytical issues.

Additional Comments for Medical Writer:

- Phoenix WinNonlin Version 6.2.1 used for PK analysis.

Compiled by: 

Date: 25 NOV 2014

Checked by: 

Date: 25 Nov 2014

