Estimation by different techniques of steady-state achievement and accumulation for a compound with bi-phasic disposition and long terminal half-life

Xavier NICOLAS, Eric SULTAN, Céline OLLIER, Clemence RAUCH and David FABRE
Drug Disposition Domain, Disposition, Safety and Animal Research, Sanofi R&D Montpellier, France

Objectives

Understand the differences observed in the pharmacokinetic analysis (steady state and accumulation assessments) of a repeated dose administration of a compound with bi-phasic disposition and long terminal $t_{1/2}$ in a pool of healthy young and elderly subjects using NCA (Non Compartmental Analysis) , PopPK analysis approaches and effective half-life computed using Boxenbaum's and Gabrielson's formula.

Evaluate NCA limitation for estimation of both steady state achievement and accumulation.

Data Description

The data from two clinical studies were involved in this analysis.

- The first study was a three-part, first-time-in-human (FTIH) study with ascending single and multiple oral doses given to healthy male and female subjects. The study was performed as a randomized, double-blind, placebo-controlled (Part A and Part C) study with an open-label, cross-over part (Part B, food effect).

Subject's demographic characteristics	
	Mean (SD) or n (%)
Age (years) for total dataset	40.21 (18.5)
Age (years) for elderly subjects	73 (5.63)
Males n (% of Total)	46 (88.5%)
Females n (% of Total)	8 (11.5%)
Single dose: Study 1, Part A and Part B – Fasted or Fed (High fat meal)	
Dose 20 mg	8 (15.4%)
Dose 60 mg	6 (11.5%)
Dose 120 mg	6 (11.5%)
Dose 240 mg	6 (11.5%)
Dose 480 mg	6 (11.5%)
Repeated doses: Study 1, Part C – Fed (standard meal)	
Dose 240 mg OD	6 (11.5%)
Dose 240 mg BID	6 (11.5%)
Repeated doses: Study 2 (Elderly subjects) - Fed (standard meal)	
Dose 240 mg BID	8 (15.4%)
Total number of subjects	52

  - In part A: ascending doses were administrated from 20 mg up to 480 mg . Blood samples for PK assessment were collected before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 24, 36, 48, 72, 96, 168, 336 and 672 hours post-dose.
  - In part B: a food effect was investigated. Subjects, who participated in the first dose level cohort of Part A, received the same dose after a high-fat breakfast (under fed conditions).
  - In part C: repeated administrations in fed conditions (standard meal) were investigated. Six subjects were dosed with 240 mg once daily for 14 consecutive days and six subjects were dosed with 240 mg twice daily for 14 consecutive days . Pre-defined time points on Day 1 and Day 14 were: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16 and 24 hours post-dose.

  → 44 subjects of part A and B were included in the Population analysis

- The second study was a randomized, double-blind, placebo-controlled study to assess the tolerability and pharmacokinetics of a 14-day repeated oral dosing in healthy elderly male and female subjects.
  - Eight subjects were dosed with 240 mg BID for 14 consecutive days. Pre-defined time points on Day 1 and Day 14 were: pre-morning dose, 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours.

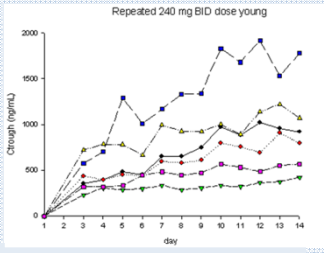
The administration form for 240 and 480 mg single doses was granule, while for other doses, the administration form was capsule.

Non Compartmental Analysis

- A Long terminal $t_{1/2}$ of 250-260 h (10-11 days) for single doses was observed
- The predicted steady state accumulation ratio for 240 mg OD regimen based on single dose data would be around 3.3-fold
- For repeated administration, despite the long $t_{1/2}$ of 300-370 h (13-15 days) the accumulation was limited: 2.3-fold for 240 mg OD and 2.9-fold for 240 mg BID
- Steady state (based on individual Ct_{rough}) appeared to be reached graphically on average by Day 10-12
- Visual inspection of mean data suggested steady state was achieved by Day 12
- For elderly, a limited increase in steady state exposure (1.3-fold) versus young volunteers let suggest that steady state reached within 2 weeks

Summary of Plasma Pharmacokinetic Parameters by Treatment: Part A and Part B

Treatment	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}last}$ (h*ng/mL)	$AUC_{0\text{-}last,ss}$ (h*ng/mL)*	$AUC_{0\text{-}24}$ (h*ng/mL)	$t_{1/2}$ (h)	t_{last} (h)
	Median (Range)	GeoMean (CV%)	GeoMean (CV%)	GeoMean (CV%)	GeoMean (CV%)	GeoMean (CV%)	Median (Range)
240 mg (n=6)	2.26 (1.50-2.52)	247 (15.1)	6580 (21.6)	5849 (19.0)	2025 (22.5)	265 (25.1)	672 (671-751)
480 mg (n=6)	2.50 (1.02-3.02)	378 (36.8)	10869 (42.5)	9468 (35.6)	3257 (29.7)	252 (32.3)	672 (335-675)



Summary of Plasma Pharmacoknetic Parameters: Part C

Parameter	240 mg once daily (n=6)	240 mg twice daily (n=6)
DAY 1		
t_{max} (h) median (range)	3.00 (2.98-3.10)	3.03 (2.50-5.08)
C_{max} (ng/mL) Geomean(CV%)	726 (24.5)	541 (24.9)
$AUC_{0\text{-}tau}$ (ng.h/mL) Geomean(CV%)	6027 (32.6)	3846 (25.4)
DAY 14		
t_{maxSS} (h) median (range)	2.94 (2.92-5.03)	2.92 (2.48-4.00)
C_{maxSS} (ng/mL) Geomean(CV%)	1119 (26.7)	1291 (36.0)
C_{minss} (ng/mL) Geomean(CV%)	344 (41.9)	674 (44.2)
$AUC_{0\text{-}tau}$ ss (ng.h/mL) Geomean(CV%)	13678 (36.5)	11270 (38.1)
$AUC_{0\text{-}24}$ ss (ng.h/mL) Geomean(CV%)	13678 (36.5)	21609 (43.8)
$t_{1/2}$z (h) Geomean(CV%)	365 (33.9)	289 (10.4)
Rac (based on $AUC_{0\text{-}tau}$ ss) Geomean(CV%)	2.27 (12.4)	2.93 (18.9)

	C_{max} (ng/mL)			$AUC_{0\text{-}12}$ (ng.h/mL)			t_{max} (h)		$t_{1/2z}$ (h)
	Day 1	Day 14	Rac[a]	Day 1	Day 14	Rac[a]	Day 1	Day 14	Day 14
Elderly Subjects	932 (25)	1650 (22)	1.77	5820 (25)	14400 (18)	2.51	4.00 [3.00-5.00]	4.00 [2.50-5.00]	903 (76)

Derived exposure variables

The exposure variables observed in the population PK study were in the same order of magnitude than those obtained by the non compartmental analysis study.

Mean, CV of individual PK parameters at 240 mg BID		
Parameter	Young	Elderly
	Mean (CV%)	Mean (CV%)
$AUC_{0\text{-}tau}$ (ng.h/mL)	3700 (24.7)	6160 (23.4)
$AUC_{0\text{-}tau,ss}$ (ng.h/mL)	16400 (45.3)	32800 (31.1)
RacAUC	4.29 (26.1)	5.39 (25.8)
C_{max} (ng/L)	409 (21.8)	671 (25.1)
t_{maxSS} (h)	3.39 (13.1)	3.86 (7.41)
C_{maxSS} (ng/L)	1490 (42.4)	2920 (29.7)
C_{min} (ng/L)	1190 (49.6)	2460 (33.5)
$t_{1/2alpha}$ (h)	1.69 (32.6)	2.87 (18.6)
$t_{1/2beta}$ (h)	273 (16.0)	609 (36.1)
$t_{1/2eff}$ (h)	31.3 (29.9)	40.5 (28.7)

The exposure parameters were 6120 and 5820 ng.h/mL for $AUC_{0\text{-}12}$ on Day 1, 671 and 932 h for C_{max}, 609 h (25 days) for $t_{1/2\beta}$ and 903 h (36 days) for $t_{1/2z}$ respectively for these two studies.

Effective Half-life

- Effective half-life, $t_{1/2eff}$ estimated to evaluate the relative importance of the distribution and elimination phases, computed as

$$t_{1/2eff} = \frac{Ln2}{k_{eff}} \quad \text{,with } k_{eff} = \frac{-Ln\left(1-\frac{1}{Rac}\right)}{\tau}$$,τbeing the dosing interval (12 hours).

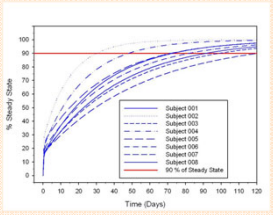
- Effective half-life computed with Boxenbaum's[1] formula provide results around 30 h for young and 40 h for elderly subjects at 240 mg BID
  - Appeared consistent with a steady state achievement by NCA around 10-12 days
  - R_{ac} AUC obtained with NCA and PopPK show inconsistencies

$$t_{1/2eff} = t_{1/2\alpha} \cdot \frac{AUC_{\alpha}}{AUC} + t_{1/2\beta} \cdot \frac{AUC_{\beta}}{AUC} \quad \text{with } AUC_{\alpha} = \frac{A}{\alpha} \quad \text{and} \quad AUC_{\beta} = \frac{B}{\beta}$$

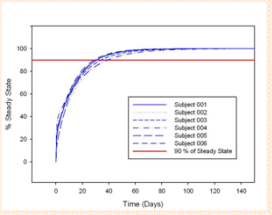
- Effective half-life computed with Gabrielson's[2] formula provide results around 7.5 days for young and 19 days for elderly subjects at 240 mg BID
  - 57-76 days to reach 90% of SS for elderly subjects
  - 23-30 days to reach 90% of SS for young subjects
  - Appeared consistent with 90% of steady state achievement obtained by Simulation

Simulation for Steady State achievement

Elderly Subjects
% of steady state vs time



Young Subjects
% of steady state vs time



- Steady state achievement obtained by simulation appears reached on Day 77 for elderly subjects.
- For young subjects, 90% of SS appears reached on Day 33.

Population Pharmacokinetics

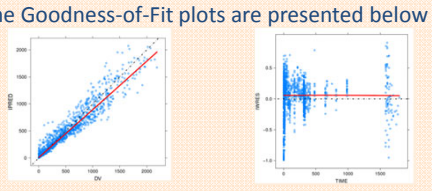
- The analysis was performed using **NONMEM** version 7.1.2
- A Bi-compartmental model with 1st order absorption and lag-time, inter-individual variability modeled assuming a log normal distribution, residual variability described with a proportional error model

  The PopPK parameters obtained in the Model Building Data Set before and after covariates inclusion are given in the table below:

PopPK parameters before (PSM) and after covariates inclusion

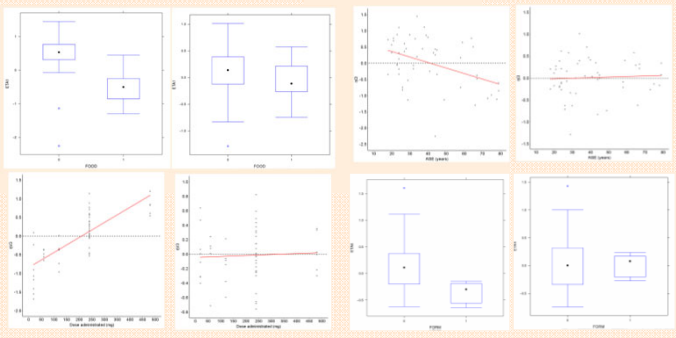
	PSM		Final model with covariates		
Parameter	Estimate	% RSE	Estimate	% RSE	[95%CI]
Typical value of CL/F (θ1, L/h)	18.5	11.2	34.2	8.37	[28.5; 40.0]
Effect of Food on CL/F (θ7)	NA	NA	-13.0	13.6	[-16.5; -9.45]
Effect of Age on CL/F (θ10)	NA	NA	-6.20	17.9	[-8.43; -3.98]
Typical value of V2/F (θ2, L)	117	9.68	112	10.9	[87.8; 137]
Q/F (θ3, L/h)	35.9	11.0	34.4	11.4	[26.5; 42.3]
V3/F (θ4, L)	3481	10.5	669	26.2	[319; 1020]
Effect of Dose on V3/F (θ8)	NA	NA	15.9	10.4	[12.6; 19.2]
Ka (θ5, h^{-1})	0.187	7.92	0.210	9.19	[0.171; 0.249]
Effect of Form on Ka (θ9)	NA	NA	-0.091	17.9	[-0.126; -0.056]
LAG (θ6, h)	0.172	NA	0.172	NA	NA
Inter-individual variability					
Parameter	Estimate (CV%)	% RSE	Estimate (CV%)	% RSE	[95%CI] – (Shrinkage %)
ω^2CL/F	0.602 (77.6%)	23.6	0.197 (44.3%)	24.9	[0.099;0.295] – 2.54
ω^2Q/F	0.508 (71.2%)	17.4	0.489 (69.9%)	20.2	[0.291; 0.687] - 1.43
ω^2V3/F	0.501 (70.7%)	23.3	0.159 (0.399%)	21	[0.092; 0.226] - 9.96
ω^2Ka	0.226 (47.5%)	27.3	0.180 (42.4%)	28.2	[0.078; 0.281] – 3.83
Residual variability					
Parameter	Estimate (CV%)	% RSE	Estimate (CV%)	% RSE	[95%CI] – (Shrinkage %)
σ^2	0.109 (33.0%)	9.54	0.103 (32.1%)	8	[0.087; 0.120] – 4.95

  Some Goodness-of-Fit plots are presented below



Final model

- Feeding status on CL/F $CL/F = \theta_{..} + \theta_{..} \times FOOD + \theta_{10} \times (AGE/34)$
- Dose on V/F $V3/F = \theta_4 + \theta_8 \times DOSE$
- Formulation on Ka $Ka = \theta_5 + \theta_9 \times FORM$



  The plots of η values vs. covariates confirmed the relationships between CL/F and feeding status, V3/F and dose and the impact of administration form on the absorption constant. Age was also added in the model with an impact CL/F.

  For a typical subject (34-year old, Fed conditions) the CL/F was equal to 15 L/h. CL/F increased up to 17.9 L/h for a younger subject (18-year old, Fed conditions) and reached a minimal value of 4.79 L/h for a 90-year old subject on Fed conditions. V3/F increased from about 987 L/h with a 20 mg single dose up to 8301 L/h with a 480 mg single dose. Administration form impacted significantly the absorption, with a 2-fold decrease in Ka from 0.210 h^{-1} with the capsule form to 0.119 h^{-1} with the granule form.

Conclusion

NCA and statistics associated with either C_{trough} or dosing interval PK parameters have limited value for SS characterization.
C_{trough} is not very sensitive to characterize steady state (SS), especially for compounds that attained steady state slowly. The characterization of the terminal $t_{1/2}$ during the washout period provides a superior prediction of the time to reach steady state.

For poly-exponential PK (most common case), there is limited meaning of an effective half-life. Equations used for 1-compartment IV models are inaccurate when applied to poly-exponential situation by PO route. PopPK provides a better description of the time to reach steady state and extent of accumulation for molecules that slowly attained steady state.

Modeling of the entire data is the optimal tool, and documenting the PK profile after treatment cessation offers the best estimate of terminal half-life, especially for long half-life compounds. Observed data obtained soon after long term repeated administration are expected to assess these conclusions.

References:
1 Boxenbaum & Battle 1995, Effective half-life in clinical pharmacology, J.Clin.Pharmacol, 35, 763
2 Gabrielsson J; Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, Fourth Edition, 2006, 70-71.