

The Population Pharmacokinetics of Active Metabolites of a prodrug PF-04171327, (Dissociated Agonist of Glucocorticoid Receptor), in Rheumatoid Arthritis subjects

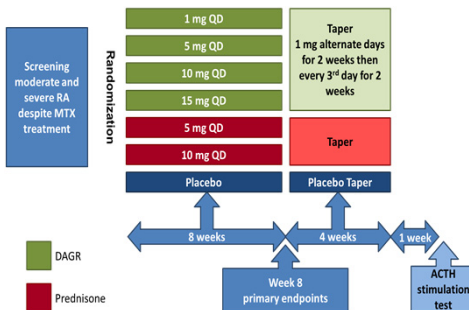
Authors: Barry Weatherley⁽¹⁾, Lynn McFadyen⁽¹⁾, Daniela Conrado⁽²⁾, Brinda Tammara⁽³⁾

⁽¹⁾ Pharmacometrics, Pfizer, Sandwich, UK ⁽²⁾ Clinical Pharmacology, Pfizer, Groton, USA ⁽³⁾ Clinical Pharmacology, Pfizer, Collegeville, USA

Background

- PF-04171327 is a phosphate ester prodrug of PF-00251802, a biologically active Dissociated Agonist of Glucocorticoid Receptors (DAGR).
- PF-00251802 is a high affinity, selective glucocorticoid receptor ligand with potent anti-inflammatory activity in nonclinical and preclinical models but has less adverse effects on bone and glucose metabolism.
- PF-04171327 is being developed as a treatment for the symptoms of active Rheumatoid Arthritis (RA).
- A9391010 was a phase 2, 8 week safety and efficacy dose ranging study of DAGR versus prednisone and placebo (on a methotrexate background) in Rheumatoid Arthritis (RA) patients (Figure 1).

Figure 1: A9391010 Study Design



PK Objectives

- To develop a PK model for PF-00251802 (parent) and its active metabolite PF-04015475 (metabolite) after oral administration of the prodrug, PF-04171327 to subjects with RA.
- Perform a limited evaluation of covariates for parent and metabolite in the study population.

Methods

Plasma sampling:

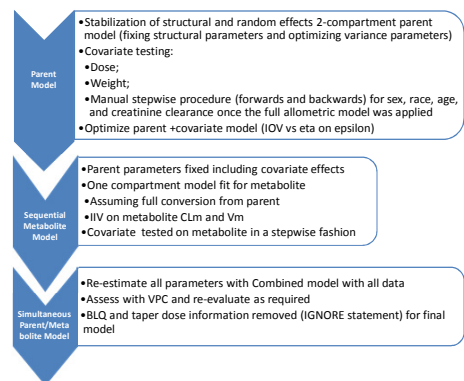
- Weeks 2, 4, 6, 10, 12 (±3 days) at time 0 hours (approximately 24 hours after dosing at weeks 2-6) and variable times at weeks 10 and 12 (taper period) (sparse samples).
- Week 8 (±3 days) at times 0 and at 1, 2, 3 and 4 hours after study medication taken in the clinic.

Concentration Analysis:

- The PK samples analyzed for PF-00251802 and PF-04015475 at WuXi App Tec (Shanghai China).
- A validated LC-MS/MS method was used; calibration range from 1.00-500 ng/mL for PF-00251802 and 0.5000 to 100 ng/mL for PF-04015475.

Population PK Modelling:

- NONMEM 7.2 was used to fit parent and metabolite data in ordinary space (1607 concentrations from 179 subjects).
- A 2-compartment disposition model with first order absorption was used for parent and a 1-compartment model for metabolite.
- Inter-individual variability (IIV) (CL, V2 and Ka for parent; CLm and metabolite central volume V3 for metabolite) were modeled exponentially.
- Peripheral V for parent was fixed but re-estimated periodically.
- Covariates were assessed on parent first prior to simultaneous modeling as describe in Fig 1.
- Visual predictive checks were performed for model assessment.
- Sensitivity checks to model for data with and without taper and BLQ values.



Modeling Assumptions

- 2-compartment disposition (based on previous analyses)
- 100% of prodrug converted to PF-00251802
- 100% PF-00251802 converted to metabolite PF-04015475
- Weight effects on parent CL and V scale allometrically (tested)

Results

Table 1 shows the demographics for males and females.

Table 2 gives the results from parent covariate testing (all parent data only)

Table 3 gives estimates for the final simultaneous parent and metabolite model using the full dataset and then 3 data subsets. Figure 2 show VPC plots for the full dataset model (A) and the final reduced data set (B).

- Although the simulated and observed 5th and 50th percentiles overlap the 95th simulated percentile shows the model overestimates variability for parent and metabolite, at time points within the 24 hour dose interval.
 - B shows the removal of BLQ and taper concentrations (overlapping subsets)(n=700) improves the VPC.
- The major effects with data reduction are:
- Reduction in parent IOV from 51 to 24%
 - Moderate reductions in IIV of parent CL from 43-33% and of metabolite CLm from 32 to 26%
 - Decrease in reference CL from 8.13 to 7.29 L/h for parent and in reference CLm for metabolite from 18.9 to 17.2 L/h.
 - None of the covariate effects changed substantially with the data reduction

Table 1. Demographics

	Males (n=43) 24%		Females (n=136) 76%	
	Mean	Median (range)	Mean	Median (range)
Age (years)	53.47	55 (25-73)	53.16	55 (18-84)
Weight (kg)	80.42	80.5 (50.5-128)	72.9	69.15 (36.6-144)

Table 2. Parent covariate testing (values are changes in NONMEM Objective Function Value)

Base Model	Base model 2	Round 1 Allometric Base	Round 2 + Sex on CL	Round 3 + Age on CL	Backwards deletion
Allometric	-41.934 ✓	In model	In model	In model	In model
+Dose on Ka	-	-2.439	-	-	-
+Age on CL	-	-7.052	-7.877 ✓	In model	+7.877 x
+CRL on CL	-	-0.020	-	-	-
+Sex on CL	-	-21.695 ✓	In model	In model	+22.520 x
+Race on CL	-	-1.731	-	-	-
+Sex on V2	-	-3.890	-3.554	-3.671	-

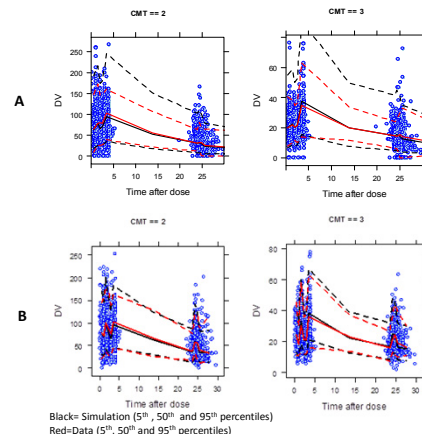
✓ = include x = do not exclude

Table 3. Final Simultaneous Model parameters with: all data with BLQ set to 0; exclusion of BLQ observations; exclusion of taper observations and exclusion of both (final model).

Parameter	All Data (%SE)	Without BLQ (%SE) ¹	Without Taper (%SE) ¹	Without BLQ or Taper (%SE)
Parent Drug ³				
F1, fraction of dose absorbed, θ_1	1 FIXED	1 FIXED	1 FIXED	1 FIXED
CL, parent clearance (L/h), 70 kg male, 40 y, θ_2	8.13 (3.0)	6.70 (-)	8.24 (-)	7.29 (7.5)
Female on CL, % change, θ_{10}	-32.9 (12)	-25.2 (-)	-31.2 (-)	-26.8 (19)
Age on CL, change in L/h every year above 40, θ_{11}	-0.00627 (30)	-0.00589 (-)	-0.00675 (-)	-0.00633 (30)
V2, parent central volume (L), 70 kg, θ_3	98.7 (7.7)	92.3 (-)	98.4 (-)	85.9 (19)
KA (K12), parent absorption rate constant (1/h), θ_4	0.489 (3.2)	0.424 (-)	0.531 (-)	0.377 (24)
ALAG1, parent absorption lag time (h), θ_5	0 FIXED	0 FIXED	0 FIXED	0 FIXED
Q, parent inter-compartmental clearance (L/h), θ_6	14.3 (14)	13.7 (-)	11.6 (-)	11.6 (51)
V3, parent peripheral volume (L), θ_7	209 FIXED	209 FIXED	209 FIXED	209 FIXED
IIV				
On parent CL (%), ω_2	43 (18)	32 (-)	42 (-)	33 (8.6)
On parent KA (K12) (%), ω_4	208 (9.0)	233 (-)	229 (-)	249 (10)
On Parent V2 (%), ω_3	0 FIXED	0 FIXED	0 FIXED	0 FIXED
IOV				
On Parent F1 (%), $\omega_1 - \omega_{15}$	51 (13)	33.5 (-)	39.9 (-)	23.8 (9.8)
Residual Error Parameters				
Parent Proportional (%), θ_8	18.5 (4.6)	21.0 (-)	18.4 (-)	19.9 (5.1)
Parent Additive (ng/mL), θ_9	0.54 (11)	0.00014 (-)	0.805 (-)	0.305 (172)
Metabolite				
Fm, fraction of parent converted to metabolite, θ_{12}	1 FIXED	1 FIXED	1 FIXED	1 FIXED
Vm, metabolite volume of distribution (L), θ_{13}	61.2 (7.3)	56.9 (-)	62.4 (-)	62.8 (21)
CLm, metabolite clearance (L/h), 70 kg male, θ_{14}	18.9 (4.8)	16.1 (-)	19.0 (-)	17.2 (6.0)
BWT power on CLm, θ_{17}	0.421 (17)	0.388 (-)	0.528 (-)	0.450 (30)
Female on CLm, % change, θ_{18}	-39.5 (4.3)	-33.7 (-)	-37.7 (-)	-34.1 (9.6)
IIV				
On metabolite Vm (%), ω_{16}	41 (15)	38 (-)	41 (-)	44 (14)
On metabolite CLm (%), ω_{17}	32 (19)	25 (-)	34 (-)	26 (7.0)
Residual Error Parameters				
Metabolite Proportional (%), θ_{15}	7.6 (5.5)	7.7 (-)	7.6 (-)	7.8 (6.0)
Metabolite Additive (ng/mL), θ_{16}	0.29 (8.3)	0.11 (-)	0.34 (-)	0.10 (0.0008) ²

¹ No SE as NONMEM SCOV step failed with "R MATRIX ALGORITHMICALLY SINGULAR AND ALGORITHMICALLY NON-POSITIVE SEMIDEFINITE"
² Lower bound of 0.1 reached, if boundary reduced, SCOV step failed
³ Allometric model (Fixed BWT power 0.75 on CL and Q and Fixed BWT power 1 on V2 and V3)

Figure 2. Prediction corrected VPC of Simultaneous parent and metabolite Model (A=Full data set, B=Dataset without BLQ and without taper data, CMT=2=parent and CMT=3=metabolite)

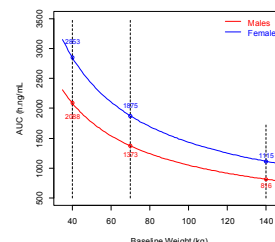


Discussion

The most important covariate, sex, showed that compared to a reference male of age 40 and weight 70 kg (CL=7.29 and CLm =17.2 L/h), the reference female of this age and weight had a 27% drop in parent clearance (CL= 5.4 L/h) and a 34% drop in metabolite clearance (CLm=11.4 L/h); this resulted in a very small gender difference in metabolite/parent AUC ratios.

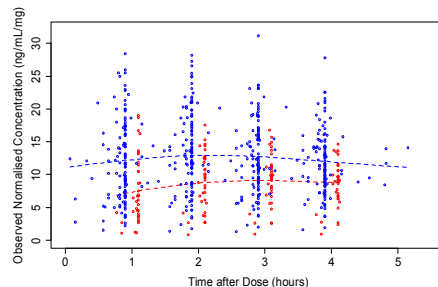
At the extremes (especially when combined with the age, not shown) large differences in exposure are predicted (See Figure 3 for males and females by weight alone).

Figure 3. Population predictions for parent AUC for males and females (40 years old) by weight for a 10 mg dose



- Can these covariate effects be seen in the raw data? Yes (See Figure 4 below).
- Do these PK covariates translate to efficacy/biomarkers? Preliminary graphical analysis for CRP and DAS28 by sex suggests not when data is baseline corrected (not shown). Concentration response has not been performed on the study data.

Figure 4. Normalised concentration versus time after dose for males (red) and females (blue) with data smooth (dashed lines) Male points shifted right and females points shifted left for clarity



Conclusions

- Variability appeared to be overestimated (by VPC) with inclusion of BLQ and taper data.
- Covariates age, weight and sex, in combination, predict AUC differences > 2- fold at their extremes.
- Post hoc graphical analysis suggests the strong sex covariate on PK did not translate to clinically meaningful efficacy differences.