Concentration Analysis:

- 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 prednisolone 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 objects with RA.
- To perform a limited evaluation of covariates for parent and metabolite in the study population.

**Methods**

**Population sampling:**

- Weeks 2, 4, 6, 10, 12 (±3 days) at time 0 (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 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-Tech (Shanghai China).
- A validated LC-MS/MS method was used; calibration range from 1.0-500 ng/mL for PF-00251802 and 0.5-500 ng/mL for PF-04015475.

**Population PK Modeling:**

- NONMEM 7.2 was used to fit parent and metabolite data in ordinary space (1607 concentrations from 279 subjects).
- A two-compartment disposition model with first order absorption was used for parent and a 1-compartment model for metabolite.
- Inter-individual variability (IVIV) (CL, V2 and ka for parent; CLm and metabolite central volume V3 for metabolite) were modeled exponentially.
- Females and males for parent was fixed but re-estimated periodically.
- Covariates were assessed on parent first prior to simultaneous assessment as described in Fig. 1.
- Visual predictive checks were performed for model assessment.

**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).

- A although the simulated and observed 5% and 95th 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=600) improves the VPC.

The major effects with data reduction are:

- Reduction in parent IVIV 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 CLm 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.

**Discussion**

The most important covariate, sex, showed that compared to a reference male age of 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).

**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)

**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males (n=43)</th>
<th>Females (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Median (range)</td>
<td>Mean Median (range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.47 (55-25)</td>
<td>53.16 (55-18-4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.42 (80.5-50-128)</td>
<td>72.9 (69.15-76.4-144)</td>
</tr>
</tbody>
</table>

**Figure 2. Prediction corrected VPC of Simultaneous parent and metabolite Model**

(A=Full data set, B=Dataset without BLQ and without taper data, CMT=parent and CMT=metabolite)

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.

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