Supporting Information

Use of Osmotic Pumps to Establish the Pharmacokinetic-Pharmacodynamic Relationship and Define Desirable Human Performance Characteristics for Aggrecanase Inhibitors

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Human PK Projections

Results

The preclinical ACAT-PBPK models produced simulations which were compared to the observed plasma concentrations following single-doses of compound-3 or compound-8. Unadjusted PBPK models (using retrograde Cl) produced reasonably accurate simulations of C0, but failed to capture the terminal elimination phases (t1/2). Modifications in Kp,adipose produced Vss to match the observed Vss, however these simulations failed to capture the time-course or curve shape observed in vivo. For compound-3, a 90% decrease in Q,adipose (for all species) from the default value in each species model, provided an improved fit to the multi-compartment nature of the observed plasma-concentration time curves when compared to the more rapid distributing non-adjusted models. For compound-8, a 10-fold increase in Q,adipose gave a suitable fit for the rat concentration-time curve however the dog and monkey models were insensitive to either Kp or Q,adipose (Figure 10). Despite the insensitive nature of the dog and monkey models, the increased Q,adipose was retained in design of the human model. The i.v. bolus models were then used to simulate a single-oral dose when coupled with species specific ACAT model, as described in Methods. Species specific oral models, provided suitable fits to the observed oral plasma-concentration-time data, both in terms of absorption phase and terminal elimination half-life (Figure 11).

A human ACAT-PBPK models was constructed based on assumptions used in the preclinical models (with no additional model modifications) including Kp,adipose to match the projected Vss (Oie-Tozer) and a 90% decrease or 10-fold increase in Q,adipose for compound 3 and compound-8, respectively. Simulations of seven-days of oral dosing of compounds 3 or 8 were conducted at simulated doses necessary to achieve an unboundC_{min} (e.g., 168 hrs) equal to 10x-IC50. As shown in figure 8, the compound-3 model required a 600 mg QD dose or 40 mg BID, whereas a 45 mg QD simulated dose of compound-8 achieved an unbound C_{min} equal to 10x the IC50.

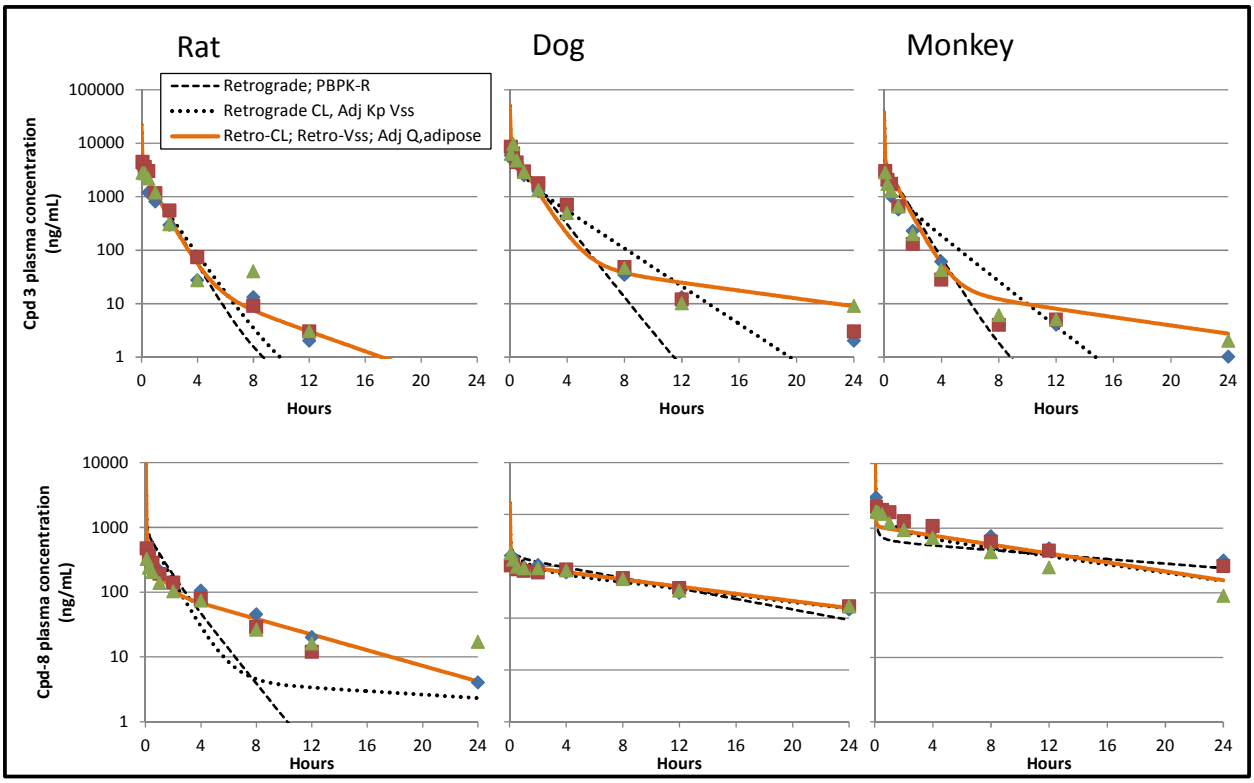

Figure 10. Observed (symbols) and simulated (lines) plasma concentrations of compound-3 or compound-8 following a single i.v. dose in rats, dogs and monkeys.

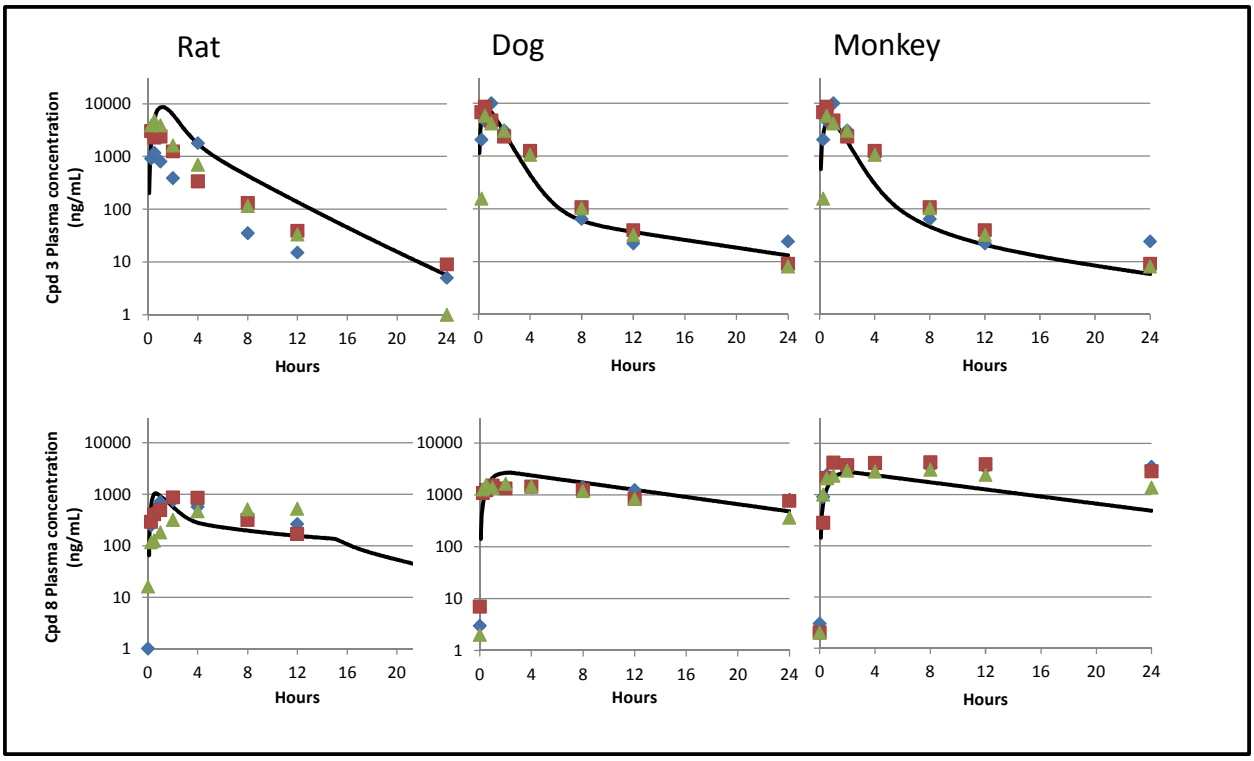

Figure 11. Observed (symbols) and simulated (lines) plasma concentrations of compound-3 or compound-8 following a single oral dose in rats, dogs and monkeys.