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Toxicokinetics of Pirfenidone in Dogs Following Inhalation in a Nebulized Aerosol Formulation

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PURPOSE

To assess the toxicokinetics (TK) exposure of pirfenidone (AP01) during a 28-day oronasal dog inhalation toxicity study.

OBJECTIVE(S)

AP01 is a proprietary inhaled pirfenidone formulation for nebulization and treatment of idiopathic pulmonary fibrosis.

METHOD(S)

The study consisted of 5 groups of male and female dogs. Group 1 through 5 received oronasal inhalation once daily for up to 4 hours for 28 days. Groups 1 received air control and Group 2 received the vehicle control. The study design and the achieved doses of pirfenidone in Groups 3, 4, and 5 are summarized in Table 1. The achieved pulmonary dose was calculated as follows:

Achieved Pulmonary dose (mg/kg/day) = (RMV x Active Concentration x T x D)/(BW)

where:

RMV (L/min) = Respiratory Minute Volume (0.608 x [BW (kg)]$^{0.852}$ L/min.

Active concentration (mg/L) = aerosol concentration of active ingredient.

T (min) = exposure duration (T equals 1 hour for the low dose, 2 hours for middle dose and 4 hours for control and high dose)

D = 25 % was assumed for total aerosol deposition fraction.

BW (kg) = mean body weight per sex per group.

Blood samples were collected on Days 1 and 28 over a 12 hour post-inhalation period. The plasma was analyzed for pirfenidone by a HPLC-MS/MS method with a linear range of 5.00 to 5,000 ng/mL. The TK parameters were calculated by non-compartmental analysis using validated Phoenix WinNonlin Professional 7.0.

RESULT(S)

Following single or once daily oronasal inhalation doses of pirfenidone for 28 days to male and female dogs, pirfenidone was absorbed into the systemic circulation with the highest concentrations observed at the immediate post-inhalation sampling time points (T_{max} was 1.00, 2.00 and 4.00 h for low, middle and high dose, respectively; Table 2 and Figure 1). Day 1 pirfenidone exposure, C_{max} and $AUC_{(0-T)}$ in females and $AUC_{(0-T)}$ in males, appeared to increase with increasing pirfenidone dose (Table 2 and Figures 1 and 2). Day 28 $AUC_{(0-T)}$ of pirfenidone increased with dose in both sexes. Day 1 C_{max} in males and Day 28 C_{max} in both sexes did not increase with dose.

Day 28 exposure in males appeared slightly higher than that in females for the middle dose and was similar to that in females for the lowest and the highest doses (Table 2, Figures 1 and 2). Pirfenidone displayed multi-exponential decay with fast elimination after the cessation of inhalation followed by a slower elimination phase on both days with $T_{1/2}$ mean values ranged from 2.15 to 8.12 h (Figure 1 and Table 2).

In general, pirfenidone exhibited slight accumulation after 28 days of repeated once-daily dosing in both sexes where Day 28 exposure appeared to higher than that on Day 1 for all doses except for the highest dose in females which was similar to that on Day 1 (Table 2, Figures 1 and 2). In males, Day 28/Day 1 ratios for dose normalized pirfenidone mean C_{max} values were 1.97, 1.73 and 1.91 for the lowest, middle and highest pirfenidone doses, respectively (Table 2). Corresponding ratios for dose normalized mean $AUC_{(0-T)}$ were 1.76, 1.52 and 1.75 (Table 2). In females, Day 28/Day 1 ratios for dose normalized pirfenidone mean C_{max} values were 2.11, 1.71 and 1.15 for the lowest, middle and highest pirfenidone doses, respectively. Corresponding ratios for dose normalized pirfenidone mean $AUC_{(0-T)}$ were 1.60, 1.60 and 1.11 (Table 2).

Figure 1: Mean Plasma Concentration-Time Profiles of Pirfenidone in Dogs on Days 1 and 28 Following Exposure to Pirfenidone by Inhalation

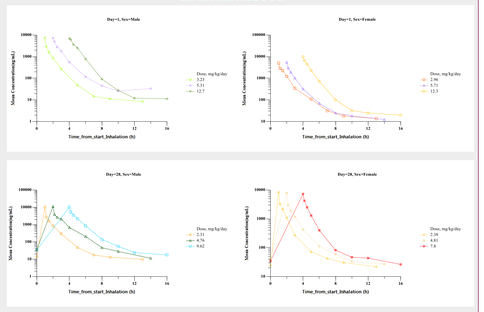

Figure 2: $AUC_{(0-T)}$ of Pirfenidone vs. Pirfenidone Dose in Dogs on Days 1 and 28 Following Exposure to Pirfenidone by Inhalation

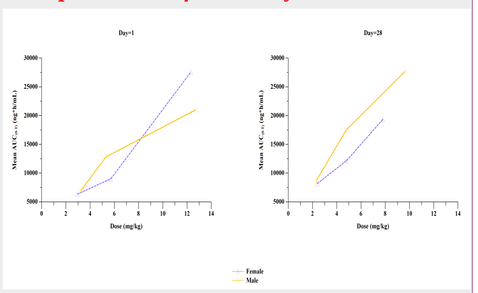

Table 1 Study Design

Group	Study Day	Sex	Proposed Pirfenidone Dose (mg/kg/day)	Achieved Pirfenidone Dose (mg/kg/day)
3	1	M	2	3.23
3	28	M	2	2.31
4	1	M	4	5.31
4	28	M	4	4.76
5	1	M	8	12.7
5	28	M	8	9.62
3	1	F	2	2.96
3	28	F	2	2.38
4	1	F	4	5.71
4	28	F	4	4.81
5	1	F	8	12.3
5	28	F	8	7.8

Table 2 Mean TK Parameters

Sex		Male			Female		
Day 1	Group	3	4	5	3	4	5
	Achieved Dose (mg/kg)	3.23	5.31	12.7	2.96	5.71	12.3
	T_{max}, h	1.00	2.00	4.07	1.00	2.00	4.00
	C_{max}, ng/mL	7,400	7,200	7,110	4,990	5,500	10,000
	C_{max}/Dose, (ng/mL)/mg/kg	2,290	1,360	560	1,690	963	814
	$AUC_{(0-T)}$, ng·h/mL	6,920	12,800	21,000	6,360	9,010	27,500
	$AUC_{(0-T)}$/Dose, (ng·h/mL)/mg/kg	2,140	2,420	1,650	2,150	1,580	2,240
	$AUC_{(0-inf)}$, ng·h/mL	7,020	13,000	21,000	6,470	9,140	27,700
	$T_{1/2}$, h	8.12	5.50	2.15	3.70	6.28	3.98
	Ratio for Mean C_{max}/Dose (Male/Female)	1.36	1.41	0.688	-	-	-
	Ratio for Mean $AUC_{(0-T)}$/Dose (Male/Female)	0.995	1.53	0.737	-	-	-
Day 28	Achieved Dose (mg/kg)	2.31	4.76	9.62	2.38	4.81	7.8
	T_{max}, h	1.00	2.00	4.00	1.06	2.00	4.03
	C_{max}, ng/mL	10,400	11,200	10,300	8,480	7,920	7,300
	C_{max}/Dose, (ng/mL)/mg/kg	4,500	2,350	1,070	3,560	1,650	936
	$AUC_{(0-T)}$, ng·h/mL	8,690	17,500	27,700	8,170	12,200	19,300
	$AUC_{(0-T)}$/Dose, (ng·h/mL)/mg/kg	3,760	3,670	2,880	3,430	2,530	2,480
	$T_{1/2}$, h	5.23	3.45	3.02	6.33	5.49	5.37
	Ratio for Mean C_{max}/Dose (Male/Female)	1.26	1.42	1.14	-	-	-
	Ratio for Mean $AUC_{(0-T)}$/Dose (Male/Female)	1.10	1.45	1.16	-	-	-
	Ratio for Mean C_{max}/Dose (Day 28/Day 1)	1.97	1.73	1.91	2.11	1.71	1.15
	Ratio for Mean $AUC_{(0-T)}$/Dose (Day 28/Day 1)	1.76	1.52	1.75	1.60	1.60	1.11

CONCLUSION(S)

The systemic TK exposure of pirfenidone was demonstrated during a 28-day oronasal inhalation dog toxicity study. Pirfenidone was absorbed into the systemic circulation with the highest pirfenidone concentrations observed at the immediate post-inhalation sampling time points (i.e., within 3 min post-inhalation). Day 1 pirfenidone exposure, C_{max} and $AUC_{(0-T)}$ in females and $AUC_{(0-T)}$ in males, appeared to increase with increasing pirfenidone dose. Day 28 $AUC_{(0-T)}$ of pirfenidone increased with dose in both sexes. Day 1 C_{max} in males and Day 28 C_{max} in both sexes did not increase with dose.

The exposure of pirfenidone on Day 1 in males appeared to be equal to that in females for the lowest dose, higher than that in females for the middle dose and slightly lower than that in females for the highest dose. Day 28 exposure in males appeared slightly higher than that in females for the middle dose and was similar to that in females for the lowest and the highest doses. Pirfenidone exhibited slight accumulation after 28 days of repeated daily dosing in both sexes.

FUNDING/GRANT/ENCORE/REFERENCE OR OTHER USE

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