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Pirfenidone and its Metabolites 5-Carboxy-Pirfenidone and 5-Hydroxy-Pirfenidone Toxicokinetics in Rats Following Inhalation of a Nebulized Aerosol Formulation

Ahmed A. Kousba[1], Dominic Poulin[2], Mark Surber[3], and L. Steven Beck[3]
[1]BioAgilytix, [2]Charles River Laboratories, [3]Avalyn Pharma, Inc.

BioAgilytix

CONTACT INFORMATION:
Ahmed A. Kousba;
akousba@microconstants.com

PURPOSE

To assess the toxicokinetics (TK) of pirfenidone (AP01) and its main metabolites 5-carboxy-pirfenidone and 5-hydroxy-pirfenidone during a 26-week oronasal rat 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 rats. Group 1 through 5 received oronasal inhalation once -daily for up to 5.67 hours for 26 weeks. Groups 1 received air control and Group 2 received the vehicle control. The achieved doses of pirfenidone in male rats on Day 1 were 0.683, 1.94 and 3.74 mg/kg, on Day 91 were 0.969, 1.76 and 4.24 mg/kg and on Day 182 were 1.13, 1.94 and 3.87 mg/kg for Groups 3, 4 and 5, respectively. The achieved doses of pirfenidone in female rats on Day 1 were 0.721, 2.04 and 3.97 mg/kg, on Day 91 were 1.04, 1.93 and 4.65 mg/kg and on Day 182 were 1.21, 2.13 and 4.26 mg/kg for Groups 3, 4 and 5, respectively.
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
D = 25 10 % was assumed for total aerosol deposition fraction.
BW (kg) = mean body weight per sex per group.

Blood samples were collected on Days 1, 91 and 182 over a 12 hour post-inhalation period. The plasma was analyzed for the analytes by a HPLC-MS/MS method with a linear range from 5.00 to 5,000 ng/mL for pirfenidone, 2.50 to 2,500 ng/mL for 5-carboxy pirfenidone and 0.500 to 500 ng/mL for 5-hydroxy pirfenidone. 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 26 weeks to male and female rats, pirfenidone was absorbed into the systemic circulation and 5-carboxy-pirfenidone and 5-hydroxy-pirfenidone were produced in the systemic circulation with the highest concentrations of the three analytes observed at the immediate post-pirfenidone inhalation sampling time points (Table 1, 2 and 3).

In general, Days 1, 91 and 182 exposure of the three analytes, as represented by the AUC(0-T), appeared to increase with increasing pirfenidone dose, while the Cmax did not increase with increasing pirfenidone dose (Table 1, 2 and 3).

The exposure of the three analytes on Day 91 and 182 appeared to be similar to that on Day 1, indicating no accumulation following once-daily inhalation doses of pirfenidone for 182 days to rats. Overall, the exposure of the three analytes appeared to be similar in both sexes on Days 1 and 91 and slightly lower in males than that in females on Day 182.

The exposure of the metabolite 5-carboxy-pirfenidone was slightly higher (up to 2x) than of the parent compound pirfenidone on Day 1 and similar to that of parent compound pirfenidone on Days 91 and 182. The exposure of the metabolite 5-hydroxy-pirfenidone on Days 1, 91 and 182 was lower (~10-20%) than of the parent compound pirfenidone.

The three analytes displayed multi-exponential decay with fast elimination after the cessation of pirfenidone inhalation followed by a slower elimination phase on all days.

CONCLUSION(S)

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).

The metabolites 5-carboxy-pirfenidone and 5-hydroxy-pirfenidone were produced in the systemic circulation.

Pirfenidone, 5-carboxy-pirfenidone and 5-hydroxy-pirfenidone exposure on Days 1, 91 and 182, as represented by the AUC(0-T), appeared to increase with increasing pirfenidone dose.

The exposure of the three analytes appeared to be similar in both sexes on Days 1 and 91 and appeared to be slightly lower in males than that in females on Day 182. There was no accumulation of the three analytes after 182 days of repeated daily pirfenidone inhalation in both sexes.

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