Absorption, Distribution, Metabolism, and Excretion of \([^{14}\text{C}]\text{ON} \ 01910.\text{Na (Rigosertib) in Dogs after a Single Intravenous Infusion}}\)

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**Purpose**

To characterize the absorption, distribution, metabolism and excretion of \([^{14}\text{C}]\text{ON} \ 01910\) in bile duct-intact and bile duct-cannulated male and female dogs after a single 50 mg/kg 24-hour intravenous (IV) infusion.

**Methods**

A single 50-mg/kg 24-hour IV infusion of \([^{14}\text{C}]\text{ON} \ 01910.\text{Na was administered to bile duct-intact and bile duct-cannulated male and female dogs. Blood, plasma, bile, excreta and tissue samples were collected and analyzed by liquid scintillation counting for total radioactivity content. Plasma, urine, bile and feces samples were extracted, as appropriate, for radioactivity, and the extracts were analyzed by high performance liquid chromatography with radiochemical detection and by LC-MS/MS for identification of parent compound and metabolites. Pharmacokinetic parameters were calculated by using WinNonlin Professional Edition, Version 5.2 (Pharsight Corporation).**

**Results**

Concentrations of radioactivity in blood and plasma and concentrations of ON 01910 in plasma reached steady-state by 6 hours after the start of IV infusion. ON 01910 was the main circulating radioactive component that accounted for 72% to 98% of total radioactivity exposure. Minor metabolites included isomers of ON 01910 [ON 46070 (M14) and Z-ON 01910 (M15)], ON 01500 (M20; N-dealkylation), glucuronide conjugates (M13 and M16), and ON 012160 (M35; oxidative decarboxylation). ON 01910 was eliminated primarily as unchanged drug in feces (66% to 68% of dose; bile duct-intact) and in bile (82% to 86% of dose; bile duct-cannulated), with minimal excretion in urine (3% to 5% of dose). Metabolites in excreta cumulatively accounted for up to approximately 12% of the dose.

**Conclusion**

The extensive excretion of ON 01910 in feces or bile, low renal excretion and minimal metabolism indicate that biliary clearance was the major route of elimination of ON 01910 in both male and female dogs. No sex-dependent differences in the disposition of ON 01910 were observed. ON 01910 was eliminated primarily as unchanged drug in feces via biliary excretion, similar to what has been observed in rats (Abstract AM-13-2619). Minor differences in circulating and excreted metabolites were observed between rats and dogs.