Intra-oral flumazenil (FL) administration a comparative pharmaokenetic and physiologic study. C Eslinger*, Unkel J, Sweatman TW, Arheart K, Mandrell T and Kahn M. University of Tennessee, Memphis, TN.

Purpose: To determine bioavailability, local tissue toxicity and physiologic effects of FL in dogs following intralingual (IL) and oral submucosal (SM) administration.

Methods: Five lightly anesthetized male dogs (approx. 20 kgs) were challenged with midazolam (0.5mg/kg; IV) and their blood oxygen saturation (O_2 sat) levels recorded for 30 minutes. Weekly thereafter, animals received midazolam followed 2 minutes later by FL (0.2mg; 2ml) administered IV, SM or IL. Blood samples (0-30 minutes) were obtained for HPLC analysis of flumazenil and midazolam and 0_2 sat values were recorded, as above. Intralingual injection site photographs (taken at 24 & 48 hrs after dosing) were inspected for inflammation by unbiased raters and histologic examination of biopsy samples was conducted one week later.

Results: Administration of IV flumazenil resulted in a statistically significant ($p<0.0035$) reduction in recovery time (1 +/- 1 vs. 7 +/- 1 min, respectively) and co-incident serum flumazenil drug levels of > 10 ng/ml. Commensurate with drug pharmacology (lower and later peak FL levels), O_2 sat recovery times following SM or IL dosing were longer than with IV administration (4.2 +/- 1.1 and 4.6 +/-1.1 min for SM and IL, respectively). Both were significantly shorter than control values. No evidence of inflammation was observed following IL or SM drug administration in this and earlier dog studies.

Conclusions: Both IL and SM drug administration appear safe and produce serum drug levels that can meliorate respiratory depression. Further studies are warranted.