A SINGLE SUBCUTANEOUS DOSE OF KU-AS-272 ELICITS COMPLETE LOSS OF SPERMATOGENIC SUPPORT IN ADULT MALE RATS

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We are developing KU-AS-272 as a single dose injectable small molecule pet sterilant that has potent anti-spermatogenic activity. Previous studies showed that a single 6mg/kg dose maintained sterility 6 months later in 40% of adult male rats. We have now completed a single subcutaneous (SQ) dose escalation study at 6, 12, 25 and 50 mg/kg KU-AS-272 in 70 day old male rats, and examined testis and epididymis histopathology 5, 30 and 58 days post-dose. Testis and epididymal weights were significantly lower ($P \leq 0.05$) at all doses beginning after 5 days and remained so for the entire post-dose period, which is a complete spermatogenic cycle. All doses above 6 mg/kg produced complete loss of all spermatogenic cells from day 5 post dose, which remained so for the entire post-dose monitoring period. At the 6 mg/kg dose, only 2% of the tubules contained any spermatogenic cells. Progressive testicular calcification and loss of Sertoli cells reaching 40% and 60% of calcified tubules by day 58 were seen with 25 and 50 mg/kg, respectively; and pyknotic nuclei were beginning to show in the interstitial space with the high doses. Circulating inhibin B, which is a marker for testis health, was reduced to undetectable levels in all doses above 6 mg/kg for the entire monitoring period, and significantly lower at 6 mg/kg. Testosterone (T) levels were not significantly reduced at day 58 at any of the doses relative to controls. Preliminary safety analysis showed that 6 and 12 mg/kg KU-AS-272 had no noticeable side effects, and the 25 and 50 mg/kg doses produced dose-related transient lethargy, and mild and transient diarrhea. All animals at 25 and 50 mg/kg doses recovered to normal within 1 and 2 days post dose, respectively. The two higher doses were associated with a transient 0.6% and 4.2% decline in body weight 2 days after dosing that was restored to normal weight gain compared to controls by day 5 post-dose. No other side-effects were observed in any animal or any dose for the remainder of the study. Pharmacokinetic (PK) analysis showed the KU-AS-272 has a desirable drug profile following either single oral, subcutaneous or intramuscular route with high bioavailability, rapid absorption, and a long elimination half-life. Analysis of testis levels of KU-AS-272 indicate significant levels of the compound 4 days after dosing, long after KU-AS-272 was eliminated from the circulation. The findings in rat suggest that KU-AS-272 has high promise as a single dose sterilizing agent. A proof of concept study in adult male dogs is currently under way. (Supported by NIH and KU Institute for Advancing Medical Innovation).