

Liver Selective Glucokinase Activation for Treating Type 2 Diabetes: Translation from Mouse to Man

Kasim A. Mookhtiar, , Debnath Bhuniya, Siddhartha De, Anita Chugh, Jayasagar Gundu, Venkata Palle, Dhananjay Umrani, Nimish Vachharajani, Vikram Ramanathan and Rashmi H. Barbhaiya

Advinus Therapeutics Ltd, Hinjewadi, Pune - 411057, and Peenya Industrial Area, Bangalore – 560058, India

Glucokinase (GK), the physiological glucose sensor in glucose responsive tissues, plays a pivotal role in plasma glucose homeostasis through control of insulin secretion in pancreatic beta cells and hepatic glucose production in the liver. Small molecule GK activators have been shown to be effective antihyperglycemic agents. However, these molecules have revealed hypoglycemia as an unwanted mechanism-based effect. Previous studies in transgenic mice have shown that liver selective increase in GK has an antihyperglycemic effect without hypoglycemia. In this study, we describe a liver selective small molecule GK activator, GKM-001, that recapitulates the benefits seen in the transgenic mouse model published earlier. GKM-001 allosterically activates GK in vitro. When dosed in mildly diabetic diet-induced obese mice, the compound dose dependently improves glucose tolerance in an oral glucose tolerance test. However, in fasted normal mice the compound has little effect on plasma glucose levels even at doses ten fold higher than those that show efficacy in the DIO mice. Pharmacokinetic studies showed that the compound had 10-fold higher levels in liver compared to plasma. These studies suggest that greater safety may be obtained with liver selective GK activation.