Preclinical and clinical data implicate dynorphin and the kappa opioid receptor (KOR), through which it acts, in a variety of disorders such as anxiety and depression. While the potential therapeutic utility of KOR antagonists has been long-recognized, several challenges limited the development of this class of molecules including lack of selectivity for KOR over the closely homologous mu opioid receptor (MOR), a long pharmacodynamic duration of action which exceeded pharmacokinetic exposure as well as non-mechanism-based toxicological findings. Here, we report on the identification of novel KOR antagonists that exhibit potency, selectivity and medication-like duration of action suitable for clinical development.

One particular compound, 1-(6-ethyl-8-fluoro-4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)quinolin-2-yl)-N-(tetrahydro-2H-pyran-4-yl)piperidin-4 amine (BTRX-335140), has been discovered as a potent and selective KOR antagonist, endowed with favorable in vitro ADMET and in vivo pharmacokinetic profiles and medication-like duration of action in mouse, rat and non-human primate pharmacodynamic models.

BTRX-335140 has been evaluated in Phase 1 single and multiple dose studies aimed at understanding the safety, tolerability, and pharmacokinetic profile of the molecule in healthy human volunteers. The occupancy-exposure-dose relationships of BTRX-335140 have also been studied in a positron-emission tomography (PET) study. The results generated to date support continued assessment of BTRX-335140 in translational and clinical studies and has provided information regarding relevant doses to test in efficacy studies. The continued development of BTRX-335140 may provide an additional treatment option in a novel target class for those suffering from neurobehavioral disorders.