

Bristol-Myers Squibb	BMS-820132
Mechanism of Action	Glucokinase (GK) activator http://www.ncbi.nlm.nih.gov/gene/2646
Overview	Partial glucokinase (GK) activator with balanced hepatic and extra-hepatic distribution for the treatment of type 2 diabetes mellitus (T2DM). Partial GK activation and peripheral plus hepatic distribution may reduce the risk of hypoglycemia observed with several non-tissue-selective full GK activators no longer being developed. BMS-820132 activates GK with an EC ₅₀ of 73 nM at 5 mM glucose and 39 nM at 12 mM. It increases the rate of glucose turnover from 36 to 65 glucose molecules/sec (an increase of 180%) at high glucose concentrations (50 mM) in contrast to that measured for full GK activators (250% increase). BMS-820132 has balanced hepatic and extra-hepatic distribution (liver-to-plasma ratios of 1 and 2 in mice and rats in vivo, respectively). In animal models, BMS-820132 increases fasting insulin, decreases fasting plasma glucose, decreases glucose excursion, increases insulin secretion, decreases in endogenous glucose production and increased glucose utilization have been demonstrated. Based on in vitro data, BMS-820132 has minimal drug-drug interaction potential.
Safety/Tolerability	Based on the results from nonclinical toxicity studies, the most likely clinical safety concern associated with BMS 820132 is hypoglycemia.
Additional Information	<p>The safety, tolerability, PK, and PD of BMS-820132 have been investigated in two single ascending dose studies in healthy subjects and in subjects with T2DM on metformin, and in a 2 week multiple ascending dose study in subjects with T2DM on metformin. In these studies, evidence of GK activation was observed and, as expected, subjects with T2DM tolerated substantially higher doses than healthy subjects from the perspective of excessive glucose lowering. In general, the PD of BMS-820132 is consistent with the PK profile. BMS-820132 is considered to be safe and generally well-tolerated in patients with T2DM over the dose range studied (up to 450 mg) with PK/PD properties amenable to once- or twice daily dosing.</p> <p>A liver-selective GK activator (BMS-922212) has also been developed but not studied in humans to date. This compound may be available to investigators as a non-clinical tool compound.</p>
Suitable for and Exclusions	Suitable for administration to patients with T2DM for 4 weeks in duration (current limit supported by toxicology studies). Currently not for use in women of child-bearing potential nor in pediatric populations.
Clinical Trials	http://www.clinicaltrials.gov/ct2/results?term=BMS-820132
Publications	None