AstraZeneca	AZD1656
Mechanism of Action	Glucokinase (GK) activator http://www.ncbi.nlm.nih.gov/gene/2646
Overview	AZD1656 is a potent, orally bioavailable activator of GK. AZD1656 has been developed for use in treatment of hyperglycemia in patients with Type 2 diabetes mellitus. GK catalyses the conversion of glucose to glucose 6-phosphate. GK activity is rate-limiting for glucose uptake and utilization in pancreatic β-cells, where it plays a major role in regulating insulin secretion, and also in liver parenchymal cells (hepatocytes), where it regulates hepatic glucose utilization. AZD1656 is a potent activator of recombinant human and rat glucokinase *in vitro;* EC_{50}'s = 0.057µM and 0.072 µM, respectively. It is slightly less potent for dog GK. AZD1656 causes a dose-dependent reduction in plasma glucose levels with a rapid onset of action in normo-glycemic insulin resistant rats and in diabetic mice in a dose-dependent fashion when dosed acutely and when dosed once daily for up to 28 days.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD1656 including pivotal reproductive toxicity studies and general toxicity studies of 3 month duration in mouse, 6 month duration in rat and 12 month duration in dog. Identified target organs relate to prolonged periods of induced hypoglycemia. AZD1656 has been studied in single doses of up to 180 mg and multiple doses to 150 mg BID for 8 days in healthy volunteers. In both healthy volunteers and diabetic patients no significant clinical effects other than glucose lowering were noted.
Additional Information	AZD1656 has been studied alone and in combination with other blood glucose control agents in diabetic patients. Three Phase 2a studies have been conducted up to 90 mg BID for 28 days (monotherapy, add-on to metformin, add-on to insulin) and two Phase 2b trials of 4 months duration. AZD1656 has been demonstrated to effectively lower blood glucose levels in human trials.
Suitable for and Exclusions	Reproductive toxicity studies support the inclusion of women of child -bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. As with all diabetic treatments, those intending pregnancy or pregnant should stop experimental medicine and switch to insulin. Data are not available to support inclusion of pediatric patients at this point. AstraZeneca has taken the decision not to progress AZD1656 as the profile achieved in Phase 2B evaluations did not meet predefined internal criteria for the product. Proposed indications should be evaluated against the risk of hypoglycemia in non-diabetic subjects at the current dose range. Proposals for use in diabetes, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD1656
Publications	None