AstraZeneca	AZD1656
Mechanism of Action	Glucokinase (GK; hexokinase 4) activator http://www.ncbi.nlm.nih.gov/gene/2645
Overview	AZD1656 is a potent, selective (>100-fold versus hexokinase 1 and 2 and a pharmacology screening panel), activator of human and rat glucokinase *in vitro*; EC_{50} = 0.057 and 0.072 µM, respectively, for the recombinant enzymes, which translates into cellular systems (EC_{50} = 1.39 and 0.47 µM in human and rat hepatocytes, respectively). AZD1656 reduces plasma glucose levels in a dose-dependent fashion, with a rapid onset of action, in normo-glycaemic insulin resistant rats and diabetic mice, when dosed acutely and when dosed once daily for up to 28 days.
Safety/Tolerability	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 as well as alone and in combination with other blood glucose control agents in diabetic patients at 200 mg daily for up to 6 months duration. In both healthy volunteers and diabetic patients no significant clinical effects other than glucose lowering were noted. Preclinical studies of up to 12 month duration have been performed. These revealed a potent glucose lowering effect, and thereby, the results of chronic toxicology studies in healthy animals were confounded by severe hypoglycaemia at higher doses and sequalae such as Wallerian type nerve degeneration and skeletal muscle fibre degeneration. Additional changes, also considered secondary to hypoglycaemia, were seen in the liver (loss of hepatocellular glycogen).
Additional Information	In a Phase 2 study in Japanese type 2 diabetic subjects, AZD1656, given BID at high (40 – 200 mg/day), medium (20 – 140 mg/day) and low (10 – 80 mg/day) doses over a 4 month period, has been found to lower HbA1c and fasting plasma blood (FPG) glucose levels with a 50 mg dose producing compound levels of ~2 x EC_{50} in plasma. However, this effect was transient trending towards pre-dose levels between weeks 8 and 16 and there was no statistically significant change in either HbA1c or FPG from baseline at 4 months.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Proposed indications should be evaluated against the risk of hypoglycaemia in non-diabetic subjects. Proposals related to renal transplant will not be considered.
Clinical Trials	https://clinicaltrials.gov/ct2/results?term=AZD1656&Search=Search ; https://www.clinicaltrialsregister.eu/ctr-search/search?query=azd1656 ; http://www.astrazenecaclinicaltrials.com/Submission/View?id=1344
Additional Characteristics: CNS penetrance	AZD1656 has low CNS penetration and, thus, is probably not suitable for a CNS indication. With evidence of effect tolerance, may be best suited to acute (< 1 week) applications.
Publications	https://www.ncbi.nlm.nih.gov/pubmed/?term=AZD1656