AstraZeneca	AZD3355/Lesogaberan
Mechanism of Action	Gamma-aminobutyric acid receptor B ($GABA_B$) agonist http://www.ncbi.nlm.nih.gov/gene/2550; http://www.ncbi.nlm.nih.gov/gene/9568
Overview	AZD3355 increased intracellular Ca^{2+} with an EC_{50} of 8 nM in CHO cells transfected with human $GABA_{B1a/2}$ and displaced radioactive GABA binding from rat brain membranes with an IC_{50} of 2 nM. In a broad enzyme and receptor screen, AZD3355 (10 µM) was only found to also interact significantly with $GABA_A$ (600 more selective for $GABA_B$) receptors. In the dog, when administered directly into the stomach, AZD3355 reduced transient lower esophageal sphincter relaxations (TLESRs), producing approximately 50% inhibition at 3 mg/kg (compound levels of about 600 times the EC_{50} in plasma).
Safety/Tolerability	AZD3355 has been administered to healthy volunteers in single doses of up to 500 mg and in multiple ascending doses of up to 130 mg per day for 7 days. Clinically relevant increases in liver enzymes have been reported in two 28-day Phase 2 studies, which returned to normal values after dosing was stopped. Preclinical studies of up to 12-month duration and lifetime bioassays in rat and mouse have been performed. Collectively they present a benign toxicity profile with no indication of hepatic effect. AZD3355 has been shown to induce decreased body weight and decreased food consumption. A dose-dependent diuretic effect was also noted in rats.
Additional Information	In healthy volunteers, AZD3355 dosed at 0.8 mg/kg produced a 36% reduction in TLESRs at plasma compound concentrations of approximately 120 times the EC_{50}. In patients with gastroesophageal reflux disease (GERD), AZD3355 at 65 mg twice daily (BID), compared to placebo as add-on treatment to a proton pump inhibitor (PPI), reduced the number of TLESRs by 25%, increased lower esophageal sphincter (LES) pressure by 28%, and reduced the number of reflux episodes by 47% during 0 to 3 hours post-prandially. In a dose-finding study on GERD symptoms, 4 doses of AZD3355 (60, 120, 180 and 240 mg BID) for 4 weeks as add-on to PPI, statistically significant efficacy was demonstrated at the highest dose (response rates of 26% for the treatment group compared to 18% for placebo).
Suitable for and Exclusions	Preclinical reproductive toxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Due to the previously observed increases in liver enzymes, proposals should be for diseases that require short-term dosing regimens with appropriate liver monitoring and exclusion of patients or volunteers with liver abnormalities, or alternatively for diseases of severe unmet medical need where a case for tolerating potential adverse events can be made.
Clinical Trials	http://www.clinicaltrials.gov/ct2/results?term=AZD3355&Search=Search; https://www.clinicaltrialsregister.eu/ctr-search/search?query=azd3355
Additional Characteristics: CNS Penetrance/Pediatric Diseases	AZD3355 has low CNS penetration and, thus, is probably not suitable for a CNS indication. Pediatric disease proposals will be considered (≤ 28 days dosing duration based on prior clinical exposures). However, due to the lack of juvenile toxicology data or prior experience in pediatric subjects, use will depend on risk/benefit, dosing duration and regimen, and age of the pediatric population.
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD3355%20or%20lesogaberan