Eli Lilly and Company	LY2590443
Mechanism of Action	5-Hydroxytryptamine 7A (5-HT7A) receptor antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=12 http://www.ncbi.nlm.nih.gov/gene/3363
Overview	LY2590443 is a small molecule receptor antagonist. It is potent (human Ki 19 nM, rat Ki 8.5 nM) and selective , > 100- fold over related 5-HT and unrelated receptors.
Safety/Tolerability	LY2590443 has a weak interaction with hERG (IC50 42 mM). Non-clinical toxicology data supports dosing in man for up to 4 weeks in duration.
Additional Information	LY2590443 is potent and efficacious in the rat dural plasma protein extravazation (PPE) model of migraine. Complete inhibition of PPE in the dura was observed with a 1 mg/kg dose and a peak plasma concentration of 115 ng/mL. The inhibitory effects of LY2590443 in the PPE model were present for at least 18 hours and efficacy was retained with sub-chronic dosing (5days). Brain penetration in rats at an oral dose of 10 mg/kg was determined to be low with brain/plasma ratio of 0.044. A safety, tolerability, and efficacy study of LY2590443 in the treatment of acute migraine headache demonstrated that a 200 mg was well tolerated and clinical exposure (Tmax 0.5-4 hour, Cmax 495ng/ml) exceeded efficacy target from rodent PPE model. Subjects at 400 or 800 mg had more adverse events than at lower doses (higher rates of somnolence, fatigue, and paresthesia). No clinical effect was observed at 200mg.
Suitable for and Exclusions	Clinical studies up to 4 weeks in duration. Role of peripheral 5-HT7A in human physiology and disease pathophysiology.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=LY2590443
Publications	None