Eli Lilly and Company	LY2828360
Mechanism of Action	Cannabinoid receptor 2 (CB2) agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=57 http://www.ncbi.nlm.nih.gov/gene/1269
Overview	LY2828360 is a small molecule CB2 receptor agonist. LY2828360 is a potent and efficacious CB2 agonist with similar affinity for the human and rat CB2 receptors (human CB2 Ki 40 nM, rat CB2 Ki 37 nM). LY2828360 is selective for CB2 over CB1, in a human CB1 functional assay; there was an average of only 15 percent maximal stimulation of CB1 at 100,000 nM. In contrast, LY2828360 has an EC_{50} value of 20 nM for the human CB2 receptor and stimulation up to 87 percent of the maximal response. LY2828360 is > 100 fold selectivity against non-related receptors.
Safety/Tolerability	There was no change in rate-corrected QT interval (QTc) in dogs and the IC_{50} for hERG channel inhibition was 9.5 µM. In 4-week rat and dog studies, the dose-limiting effects were CNS-related clinical signs, and dogs were more sensitive to these effects than were rats. In dogs, doses ≥ 5 mg/kg produced sustained ataxia, tremors, and stereotypical behaviors which were considered adverse. The NOAEL in dogs was 2 mg/kg. In dogs, there is a clear dose-related progression from less severe signs such as ataxia and tremors at lower doses to more severe effects such as convulsions at higher doses. LY2828360 has been given to 28 healthy subjects including 16 women and 12 men as single doses up to a maximum dose of 100 mg. In addition, 24 people including 4 women and 20 men, have taken LY2828360 up to a maximum dose of 85 mg for as long as two weeks. No specific risks or discomforts associated with LY2828360 were observed in these men and women compared to placebo. Oral administration of LY2828360 appears to be well absorbed and is associated with a long terminal $t_{1/2}$. 80 mg of LY2828360 dosed QD orally for 4 weeks was well tolerated, however no biomarker or target engagement readout was assessed for the CB2 mechanism in this study.
Additional Information	Dose response studies in a standard monoiodoacetate (MIA) induced knee injury model (Bove et al., 2003) at either 1 or 2 hours post-dose showed significant pain reduction with 0.3 and 1 mg/kg p.o. of LY2828360. Administration of a CB2 specific antagonist (SR144528) resulted in blockade of LY2828360-induced efficacy, confirming that the pain reduction in the MIA model was CB2-dependent. LY2828360 has also demonstrated efficacy at 1 mg/kg in a meniscal tear (MT) model of osteoarthritis (OA) where joint destruction and pain occurs due to surgical destabilization of the knee joint (Janusz et al., 2002). As in the MIA model, 1 mg/kg p.o. of LY2828360 significantly inhibited pain in the MT model.
Suitable for and Exclusions	LY2828360 is suitable for studying both peripheral and central role(s) for CB2 receptors in disease pathophysiology. Biomarker and target engagement studies are also worth considering for this mechanism. There is evidence for the role of this target in controlling cancer pain and an emerging role in controlling addiction.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=LY2828360
Publications	None