Pfizer Inc.	PF-04136309
Mechanism of Action	Chemokine (C-C motif) receptor 2 (CCR2) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59&familyId=14 http://www.ncbi.nlm.nih.gov/gene/729230
Overview	PF-04136309 is a potent (IC_{50} of 3 – 5 nM), selective (> 200-fold to other human chemokines and a pharmacology screening panel), competitive, and reversible full antagonist of the human CCR2 receptor. CCR2 is the primary receptor for monocyte chemoattractant protein-1 (MCP-1) and is expressed on multiple leukocyte subtypes, especially monocyte/macrophages, as well as many mesenchymal cells participating in tissue repair and pathological processes.
Safety/Tolerability	PF-04136309 at 500 mg BID for 14 days was safe and generally well tolerated in subjects with knee osteoarthritis (OA) pain. The most commonly reported all causality adverse events, which were higher incidence than in the placebo group, were headache (7.7% versus 3.8%), and constipation, dizziness, muscle spasms and acne (each 2.6% versus 0%); the majority of these were mild in severity. Nonclinical toxicology data support clinical studies up to 4 weeks in duration.
Additional Information	Systemic target coverage in healthy subjects was demonstrated by: a) maximal inhibition of *ex vivo* whole blood MCP-1 stimulated pERK expression for ≥ 12 hours at doses ≥ 150 mg, and b) a decrease in peripheral blood monocyte count with plateau at ~30% decrease between 150 – 450 mg BID. While not superior to naproxen, there was evidence of efficacy in the 2-week knee OA pain study. PF-04136309 is up to 5-fold less potent on rat CCR2 and does not bind to canine CCR2.
Suitable for and Exclusions	Clinical trials in subjects with normal ECGs, no clinically significant hematologic disorder or abnormal hematologic index, no evidence of orthostatic hypotension, for up to 4 weeks in duration.
Clinical Trials	http://www.clinicaltrials.gov/search?term=%22PF-04136309%22
Publications	http://pubs.acs.org/doi/pdfplus/10.1021/ml200199c