Janssen (J&J)	CNTO-888/Carlumab
Mechanism of Action	Fully human IgG1 kappa antibody, selective for CC-chemokine ligand 2 (CCL 2) http://www.ncbi.nlm.nih.gov/gene/6347 http://iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=771
Overview	Carlumab is a fully human IgG1 kappa antibody, selective for CCL2, with binding affinity to human CCL2 of 10 pM (BIAcore). Carlumab neutralizes CCL2-induced chemotaxis by THP-1 leukemia cell line, inhibits CCL2-induced calcium mobilization (IC_{50} of 10nM), and, in a tumor-cell–induced angiogenesis model, inhibits angiogenesis at lowest dose of 0.01 mg/kg. CCL2 is a chemoattractant for mononuclear cells, T cells, natural killer (NK) cells and fibrocytes. CCL2 mediates many biological activities, including inflammation, cell activation and migration, angiogenesis, and fibrosis. CCL2 plays an important role in fibrosis by modulating: fibroblast collagen synthesis, myofibroblast differentiation, fibroblast survival and fibrocyte recruitment. *In vitro* data: CCL2 stimulation of the idiopathic pulmonary fibrosis (IPF)–derived lung fibroblast cells induced marked increases in the mRNA for α-smooth muscle actin (a marker of myofibroblasts) and procollagen I when compared to control lung fibroblasts *In vivo* data: In mouse model of lung and skin fibrosis (FITC-induced lung fibrosis and bleomycin-induced lung and skin fibrosis) neutralization of the murine orthologs of human CCL2, (JE/MCP5) protected against fibrosis as measured by collagen content in affected organs. Non-human primate data: In the presence of increasing free serum CCL2 concentrations, Carlumab was able to inhibit delayed-type hypersensitivity (DTH) response (macrophages infiltration in the skin at the site of challenge) in a dose- and time-dependent manner.
Safety/Tolerability	Toxicology: No nonclinical safety issues were identified to preclude clinical development of Carlumab. Clinical Studies—Safety Observations: In clinical trials, there were no safety signals observed for Carlumab, with no evidence of markedly increased infection rates in any of the active treatment groups compared to placebo.
Additional Information	Clinical Experience: A Phase 2a double-blind, placebo-controlled, parallel-group, dose-ranging study evaluating the efficacy and safety of Carlumab administered intravenously in subjects with IPF has been completed. In the IPF trial, 3 dose levels were used: 1, 5 and 15 mg/kg. Dosing was done intravenously every 4 weeks, over a period of 48 weeks with primary end point at 52 weeks and follow-up to 72 weeks. No dose group of Carlumab met the primary endpoint defined as percent change from baseline in forced vital capacity (FVC) through week 52 or any of the major secondary endpoints. The sensitivity and subgroup analyses on the primary endpoint showed consistent results. Pharmacokinetics and Immune Response Profile: C_{max} and AUC tau after 1st dose appear to increase in a dose-proportional manner. Mean clearance and mean steady-state volume are dose-independent after the 1st dose and mean terminal half-life ranged from 6.29 to 7.61 days. No apparent development of anti-drug antibody to Carlumab.

	Pharmacodynamic (PD) Findings: Dose-dependent increases in total and free CCL2 were observed in all dose groups post Carlumab administration. Overall, the biomarker data showed that total CCL2 was not saturated by Carlumab and that free CCL2 was only transiently suppressed after treatment. Both PK profile and PD findings were observed in oncology and IPF subjects.
Suitable for and Exclusions	Suitable for systemic sclerosis, atherosclerosis, diabetic nephropathies, liver fibrosis, type 2 diabetes Studies of IPF should be excluded.
Clinical Trials	http://clinicaltrials.gov/ct2/show/NCT00786201?term=CNTO-888&rank=1 http://clinicaltrials.gov/ct2/show/NCT01204996?term=CNTO-888&rank=2 http://clinicaltrials.gov/ct2/show/NCT00537368?term=CNTO-888&rank=3 http://clinicaltrials.gov/ct2/show/NCT00992186?term=CNTO-888&rank=4
Additional Characteristics: CNS Penetrance/Pediatric Diseases	CNS penetrance has not been explored. Carlumab is not suitable for use in pediatric studies.
Publications	Obmolova G et al., Mol Immunol. 2012 Jun;51(2):227–33. Structural basis for high selectivity of anti-CCL2 neutralizing antibody CNTO 888. Fetterly GJ et al., J Clin Pharmacol. 2013 Oct;53(10):1020–7. Utilizing pharmacokinetics/pharmacodynamics modeling to simultaneously examine free CCL2, total CCL2 and carlumab (CNTO 888) concentration time data. Sandhu SK et al., Cancer Chemother Pharmacol. 2013 Apr;71(4):1041–50. A first-in-human, first-in-class, phase I study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 in patients with solid tumors. Pienta KJ et al., Invest New Drugs. 2013 Jun;31(3):760–8. Phase 2 study of Carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Raghu G et al., Am J Respir Crit Care Med. 2013;187:A3376. A phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of the safety and efficacy of CNTO 888 (carlumab) in patients with idiopathic pulmonary fibrosis; Philadelphia, ATS 2013. Raghu G et al., Am J Respir Crit Care Med. 2013;187:A3377. Predictors of mortality in idiopathic pulmonary fibrosis: Results from 72 week Phase II study of CNTO888 (Carlumab). Abstract 40935, Immunology/Inflammation: Human Studies (AII); Philadelphia, ATS 2013.