

Janssen (J&J)	RWJ-445380
Mechanism of Action	<p>RWJ-445380 is an orally active, high affinity inhibitor of cathepsin S.</p> <p>Link to the NCBI Gene/protein data for the gene: http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=2545</p>
Overview	<p><u>Target Biology:</u> Cathepsin S is a lysosomal cysteine protease that plays an important role in the biosynthesis and maturation of major histocompatibility complex (MHC) class II molecules. Cathepsin S participates in the proteolysis of the MHC class II chaperone protein invariant chain (Ii) and its activity is required for efficient loading of peptides onto MHC class II molecules and subsequent antigen-specific activation of T cells. Cathepsin S is found in the lysosome of dendritic cells, B cells and macrophages, all of which are key antigen presenting cells (APCs) of the immune system. The inhibition of cathepsin S is hypothesized to attenuate autoimmunity by altering antigen presentation in the context of MHC class II molecules (Saegusa et al. 2002). Relevant to the proposed clinical use, a cathepsin S knockout strain of mice (CS-/- I-Aq mice) showed reduced incidence and severity of disease in the collagen-induced model of the autoimmune disease rheumatoid arthritis, compared to I-Aq wild-type mice (Nakagawa et al. 1999). Treatment of human B cell lines and primary human dendritic cells with RWJ-445380 results in the accumulation of a 10kDa polypeptide fragment (Iip10) derived from the invariant chain, which serves as a marker of biologic activity. Furthermore, this inhibitor blocked the proliferation of T cells in response to tetanus toxoid.</p> <p><u>Pharmacology:</u> RWJ-445380 is a potent, orally active, selective and noncovalent inhibitor of human cathepsin S (inhibition constant, $K_i = 6 \pm 2$ nM). RWJ-445380 (also referred to as JNJ-16240159 and R306224) represents a novel class of immunomodulatory compound. It is inactive against other proteases, including closely related cathepsins.</p>
Safety/Tolerability	<p><u>Toxicology:</u> RWJ-445380 was not genotoxic and did not show substantial adverse effects on prenatal development in rats and rabbits. It was not acutely toxic up to single oral doses of 2000 mg/kg. In the 4-week and 13-week toxicity studies, the most common treatment-related effect was hyperbilirubinemia, which was most likely related to species-specific metabolic effects on the clearance of bilirubin (e.g., glucuronide conjugation of bilirubin and its extracellular transport). In dogs with high drug exposure in the 4-week study, vacuolation consistent with phospholipidosis was seen in lymphocytes and macrophages of multiple tissues/organs. The vacuolation/phospholipidosis was not associated with necrosis or degeneration and was essentially devoid of any functional impairment. In general, phospholipidosis and hyperbilirubinemia were reversed or partially reversed by the end of post-dosing recovery periods of up to 1 month.</p> <p><u>Clinical Studies—Safety Observations:</u> Data thus far suggest RWJ-445380 to be safe and tolerable. Overall, the most common adverse event reported with RWJ-445380 has been itching (pruritus). In healthy volunteers, pruritus occurred after multiple dosing with doses of 250 mg and above, and appears to be dose-related with respect to onset, severity and duration; in all cases, pruritus resolved after drug discontinuation. In psoriasis patients, the incidence of pruritus also appears to be dose-related. No clinically significant trends have been observed in clinical laboratory parameters.</p>
Additional Information	<p><u>Clinical Experience:</u> Original indications for RWJ-445380 related to chronic inflammatory diseases such as plaque psoriasis and rheumatoid arthritis (RA). Nine clinical studies with RWJ-445380 have been completed: 7 Phase 1 studies in healthy normal volunteers, and 2 Phase 2a studies in psoriasis and RA. RWJ-445380 has been studied in more than 200 subjects in Phase 1 clinical pharmacology trials and more than 240 patients with psoriasis or rheumatoid arthritis in clinical studies. Two Phase 2a</p>

	<p>studies of 12 weeks treatment with RWJ-445380 include a completed study in patients with plaque psoriasis and a study in patients with active rheumatoid arthritis despite methotrexate therapy. No efficacy was observed in the Phase 2a studies.</p> <p><u>Pharmacokinetics:</u> The mean half-life was 14 to 18 hours across all doses. C_{max} and AUC were linear over the 100 to 750 mg and 100 to 1000 mg dose ranges, respectively. RWJ-445380 has a high volume of distribution (V/F) and low to moderate clearance (CL/F). Plasma levels of N-desmethyl-RWJ-445380 (a major metabolite) were low. The amount of drug excreted in the urine was low (0.01–0.1%) and there was little excretion of the N-desmethyl metabolite in the urine.</p> <p>Steady state was achieved after 4–5 days of dosing. Steady-state parameters were found to be dose proportional between the 50–750 mg doses. Steady-state pharmacokinetics was also observed to be invariant with time, as there was no unexpected accumulation with multiple dosing and no evidence of autoinduction or autoinhibition. The half-life after multiple dosing was approximately 15 to 21 hours in both males and females.</p>
Suitable for and Exclusions	<p>Studies in psoriasis and RA are not of interest.</p> <p>Toxicology package supports studies up to 12 weeks duration.</p>
Clinical Trials	<p>http://www.clinicaltrials.gov/ct2/results?term=RWJ-445380</p>
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>CNS penetration is unknown.</p> <p>RWJ-445380 is not suitable for use in pediatric studies.</p>
Publications	<p>none</p>