

Canakinumab

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Canakinumab (ACZ885, Ilaris) is a human anti-IL-1 β monoclonal antibody developed by Novartis. Its mode of action is based on the neutralization of IL-1 β signaling, resulting in suppression of inflammation in patients with disorders of autoimmune origin. In June 2009 the drug was approved by the US Food and Drug Administration for the treatment of familial cold auto-inflammatory syndrome and Muckle-Wells syndrome, which are inflammatory diseases related to cryopyrin-associated periodic syndromes. The drug is currently being evaluated for its potential in the treatment of rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, chronic obstructive pulmonary disease, type 1 and 2 diabetes and ocular diseases. Reports from clinical trials suggest that canakinumab is well-tolerated in most patients, and no serious adverse effects have been reported. The drug provides significant advantages over existing competitive therapies, including bimonthly administration and approved use in children.

Introduction

Interleukin-1 (IL-1) consists of a group of cytokines that activate the expression of several pro-inflammatory genes. The 11 members of the IL-1 family of genes include IL-1 β , as well as the anti-inflammatory interleukin-1-receptor antagonist (IL-1Ra) that acts as a regulator of IL-1 β signaling. Numerous studies suggest that the severity of inflammation is influenced by the relative amounts of IL-1 and IL-1Ra.¹ This model is supported by two recent studies of ten infants with homozygous germ-line mutations in IL-1 family genes.^{2,3}

IL-1 β is a pro-inflammatory cytokine that acts as mediator of the peripheral immune response during infection and inflammation, but is also implicated in acute and chronic autoimmune diseases, diabetes, pain and neurological disorders.⁴ Data from animal model and in vitro studies suggest that IL-1 β is a more potent mediator of inflammation than IL-1 α .⁵ IL-1 β is initially synthesized in the form of a precursor peptide (pro-IL-1 β) that is cleaved in the inflammasome complex by caspase-1, and secreted into the extracellular space. There are two IL-1 receptors, IL-1RI and IL-1RII; IL-1 β exerts its action on target cells through the receptor IL-1RI.

IL-1 β can be released by various cell types, including macrophages, keratinocytes, fibroblasts, microglia and astrocytes, as well as mast, endothelial, neuronal and Schwann cells.^{6,7} Dysregulated IL-1 β activity is characteristic of autoimmune diseases and may occur due to either abnormally increased levels of the cytokine, or qualitative or quantitative deficiency of IL-1RI endogenous antagonist. IL-1 β is specifically implicated in several autoinflammatory diseases.

Canakinumab is a human IgG κ monoclonal antibody targeting IL-1 β that was developed by Novartis for the treatment of immune disorders. The drug was granted orphan drug status by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In June 2009, FDA approved canakinumab for treatment of two forms of cryopyrin-associated periodic syndrome (CAPS), Muckle-Wells syndrome (MWS) and familial cold auto-inflammatory syndrome (FCAS). The product was approved in Switzerland for these forms of CAPS, as well as neonatal-onset multisystem inflammatory disease (NOMID) in July 2009. EMA's Committee for Medicinal Products for Human Use has adopted a positive opinion of canakinumab as a treatment for CAPS. To date, the majority of clinical studies of canakinumab have been in CAPS and three forms of arthritis [rheumatoid arthritis (RA), systemic-onset juvenile idiopathic arthritis (SoJIA) and gout arthritis]. The drug is also being evaluated in chronic obstructive pulmonary disease (COPD), diabetes and age-related macular degeneration.

Etiology and Current Treatment of CAPS and Arthritis

Cryopyrin-associated periodic syndrome. CAPS comprises a group of rare, but severe, inherited autoimmune disorders associated with over-secretion of IL-1. These distinct conditions include MWS, FCAS and NOMID, which is also referred to as chronic infantile neurologic, cutaneous and articular syndrome (CINCA). Patients may experience inflammation of the skin, eyes, bones, joints and meninges, accompanied by severe fatigue, fever, myalgia, chronic anemia and learning difficulties. The disease is often associated with mutations in the NLRP3 gene that encodes for the protein cryopyrin, a component of the inflammasome complex that regulates the production and secretion of IL-1 β .⁸ Immune cells from patients with NOMID secrete higher levels of active IL-1 β compared to monocytes from healthy subjects, but there is no difference in the IL-1Ra production between the two groups.⁹ It has been proposed that secretion of IL-1 β is high enough in patients with NOMID to account for the disease,

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and that there is also increased production of IL-1Ra, but not enough to keep IL-1 β activity under control.¹

Riloncept (Regeneron Pharmaceuticals) was approved for the treatment of CAPS disorders by FDA in 2008.¹⁰ The product is a dimeric, glycosylated fusion protein comprising the extracellular domain of IL-1 receptor and the Fc domain of human IgG1. Like canakinumab, riloncept is designed to bind and neutralize IL-1. Riloncept binds both IL-1 α and IL-1 β with high affinity, and so it has been suggested that riloncept might have better inhibitory effect *in vivo* compared to other IL-1 blockers.¹¹

Rheumatoid arthritis. RA is a chronic, auto-inflammatory disease of the joints that can cause damage to cartilage and bone, resulting in severe pain, stiffness and deformity. In addition to the local degenerative effect, it can also induce systemic inflammatory processes that may cause fever, headache and fatigue. The disease is potentially debilitating and significantly reduces the quality of life. The etiology of RA is not yet understood; treatment focuses on controlling the inflammatory response with non-steroidal and steroidal anti-inflammatory drugs such as ibuprofen, methotrexate (MTX), azathioprine and cyclophosphamide.¹²

Biological therapeutics for RA that have been approved recently interfere with the biological activity of the proinflammatory cytokine TNF α (etanercept, infliximab, adalimumab golimumab), B and T immune cells (rituximab and abatacept, respectively) or IL-1 β (anakinra, canakinumab). Anakinra (Amgen Inc.) is a functionally debilitated analog of IL-1Ra that competes with IL-1 β for binding to the cell surface receptor, but does not elicit a downstream response, and therefore suppresses inflammatory activity.

To date, no head-to-head studies have compared anakinra to the TNF α inhibitors, but indirect data suggests that anakinra's efficacy may be inferior to infliximab and etanercept.¹³ Because of the lower efficacy, anakinra is mainly administered to RA patients that have shown no clinical improvement in therapy with one or more TNF α blockers. It is not clear whether the poorer clinical benefits of anakinra when compared to TNF α blockers are due to the greater biological relevance of the TNF α signal over IL-1 β in RA pathogenesis, or the short half-life of anakinra in systemic circulation, which might prohibit sufficient exposure for maximal inhibition at the target tissue to be achieved.¹⁴

Systemic-onset juvenile idiopathic arthritis (SoJIA). SoJIA is defined as a subtype of juvenile idiopathic arthritis (JIA). The clinical features are characterized by remitting fever, typical erythematous skin rash and arthritis. During the initial phase of SoJIA, as well as during relapse flares, there is an early activation of the vascular endothelium with expression of leucocyte adhesion molecules such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), followed by perivascular infiltration of neutrophils and pro-inflammatory activated monocytes.¹⁵ The systemic and local features of SoJIA are thought to be induced by activation of a network of cytokines released from activated phagocytes and endothelial cells. Important pro-inflammatory cytokines secreted by these phagocytes are TNF α , IL-1 and IL-6. The therapeutic approach in SoJIA patients focuses on the effective suppression of uncontrolled systemic and local inflammation to

attain disease remission and avoid chronic disease complications. Despite these established therapeutic approaches, about 50% of patients exhibit drug resistance associated with remitting flares, or depend on high-dose steroids.^{16,17} Treatment with anakinra reduces the clinical and laboratory features of disease activity in SoJIA patients who are resistant to conventional therapy, including TNF α blockers.⁵ Tocilizumab (Chugai), an anti-IL-6 receptor mAb, has also shown efficacy with regard to control of disease activity in SoJIA.^{18,19}

Gout arthritis. Gout disease is caused by deposition of monosodium urate crystals due to chronic hyperuricemia above 6.5 mg/dL,²⁰ and attacks of gout are characterized by pain and inflammation. Urate crystals activate the inflammasome complex, inducing the release of pro-inflammatory cytokines such as IL-1 β , IL-8 and TNF.²¹ Gout incidence and prevalence has nearly doubled in the US during the past decades.²² The cause of the disease may be linked to hereditary disorders of uric acid metabolism or lifestyle factors such as dietary habits, alcoholism and obesity. Administration of drugs that reduce renal urate excretion may also contribute to the development of symptoms. Treatment focuses on the elimination of existing crystals, inhibition of inflammation and long-term reduction of serum urate levels. Allopurinol is widely used to inhibit the conversion of purine into uric acid. Probenecid is a second-line treatment option for patients who do not benefit from allopurinol. Anti-inflammatory drugs such as corticosteroids and the IL-1 inhibitors anakinra, riloncept and canakinumab are also being studied in treatment-refractory gout patients.²³

Preclinical Development

Canakinumab was generated using UltiMab technology (Medarex).^{24,25} The UltiMab platform consists of a transgenic mouse strain capable of producing multiple high-affinity human sequence IgG κ mAbs. The light transgene is partly derived from a yeast artificial chromosome encompassing nearly half of the human V κ region, while the heavy-chain transgene encodes for human μ and γ 1 constant regions. The transgenic mice were immunized with a recombinant form of human IL-1 β . The supernatants from the generated hybridomas were evaluated using an ELISA screening method to determine the specificity and affinity of the secreted antibodies, resulting ultimately in the selection of canakinumab. The marketed product is expressed in a murine Sp2/0-Ag14 cell line; both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at Asn 298.²⁶

Canakinumab binds to human IL-1 β with high affinity; the antibody-antigen dissociation equilibrium constant is approximately 35–40 pM.^{25,27} The antigenic epitope includes Glu 64, which is essential for the recognition of human IL-1 β by the antibody. Although the epitope appears to be outside the IL-1 β /IL-1R interface, the canakinumab/IL-1 β complex is unable to attach to the cell surface receptor, and so IL-1 β -dependent signaling is interrupted. The stoichiometry of IL-1 β neutralization by canakinumab was assessed by competitive binding studies using soluble IL-1 receptors.²⁵

Due to its high affinity and specificity, canakinumab was considered particularly suitable for therapeutic applications. The *in vitro* biological activity of canakinumab was determined in primary human cell cultures. Exposure of human dermal fibroblasts to canakinumab inhibited IL-1 β -stimulated IL-6 secretion.²⁵ The mouse IL-1 receptor can be activated by human IL-1 β , and so mouse arthritis models were used to validate the efficacy of canakinumab *in vivo*. Study results demonstrated that canakinumab is able to fully suppress IL-1 β -mediated joint inflammation and cartilage destruction in these models.^{27,28}

As canakinumab does not bind rodent IL-1 β , fertility in mice was assessed using a murine analog of canakinumab. Male mice were treated weekly starting four weeks prior to mating and continuing through three weeks after mating. Female mice were treated weekly for two weeks prior to mating through gestation day 3 or 4. The murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous (sc) doses up to 150 mg/kg.²⁶ No long-term animal studies have been performed to assess the carcinogenic potential of canakinumab, and the mutagenic potential of canakinumab has not been evaluated.

Pharmacokinetic, Pharmacodynamic and Safety Data

The safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of 1, 3 and 10 mg/kg canakinumab were assessed in healthy subjects.²⁹ The drug was administered as intravenous (iv) infusions on days 1 and 15. A total of 24 subjects participated; canakinumab was administered to six subjects, and two received placebo in each cohort. Total canakinumab, free IL-1 β and total IL-1 β (free IL-1 β + mAb-IL-1 β complex) in serum were measured by ELISA assay. The investigators reported no evidence of drug related changes in vital signs, electrocardiography, spirometry or lab values at any dose. There were mild, non-specific adverse events (nausea, vomiting, headache) in the 3 mg/kg and 10 mg/kg dose cohorts. The PK were linear and typical for an IgG-type antibody, with a low distribution volume (5.4 L) and low clearance rate (terminal half-life 33 days). Free IL-1 β in serum was close to or below the limit of detection (0.02 pM) in all samples, suggesting that almost all IL-1 β molecules were blocked by the mAb. In contrast, total IL-1 β increased after treatment; mean C_{max} was 1.2, 1.2 and 1.5 pM for 1, 3 and 10 mg/kg antibody respectively, at days 42–56 after the first infusion. Canakinumab was found to be safe and well-tolerated. Importantly, at all time points total canakinumab was in molar excess by more than 20,000-fold compared to the total IL-1 β . The observed IL-1 β production/release rate predicted that free IL-1 β may be reduced by >90% for more than 60 days following a single dose of 10 mg/kg of canakinumab.²⁹

The peak serum concentration of canakinumab (C_{max} = 16 \pm 3.5 μ g/mL) was recorded approximately seven days after sc administration of a single, 150-mg sc dose to adult CAPS patients.²⁶ The mean terminal half-life was 26 days. The absolute bioavailability of sc-injected canakinumab was estimated to be 70%.²⁶ Canakinumab's volume of distribution varied according to body weight, and was estimated to be 6.01 liters in a typical

CAPS patient weighing 70 kg. The calculated accumulation ratio was 1.3-fold following six months of sc administration of 150 mg canakinumab every eight weeks.²⁶ The drug's clearance rate varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg. There was no acceleration of the clearance rate or time-dependent change in the PK properties of canakinumab following repeated administration. No sex- or age-related PK differences were observed after correction for body weight.²⁶

A Phase 1 study (NCT004212260) to evaluate the safety, tolerability, PK and PD of a single ascending dose of canakinumab administered either sc or iv in healthy Japanese male volunteers is currently ongoing. The study includes 48 subjects 20 to 45 years of age, and has not yet been completed.

Over 800 patients and healthy volunteers have been treated with canakinumab in clinical studies;²⁶ a total of 15 patients experienced serious adverse reactions during these studies. Adverse events included infections, gastrointestinal disorders and vertigo. None of the patients that received the drug in clinical trials for CAPS, RA and SoJIA tested positive for anti-canakinumab antibodies at any of the time points.^{26,27,30} Interactions between canakinumab and other pharmaceutical agents, including IL-1 blockers, have not been investigated in formal studies.

Phase 2 and 3 Clinical Studies

Canakinumab is currently under intensive clinical investigation in patients with IL-1 β -mediated autoimmune disorders such as CAPS (three completed and two active trials; Table 1), RA (five completed or terminated and three active trials; Table 2), SoJIA (four active trials, Table 3), and gout arthritis (one completed and three active trials; Table 3). In addition, canakinumab has been studied as a treatment for diabetes (three active trials; Table 4), COPD (one active trial; Table 4) and macular degeneration (one active trial).

Studies in CAPS

The efficacy and safety of canakinumab were assessed in a Phase 1/2 study (NCT00487708) study of four patients with MWS who carried NLRP3 gene mutations. Data from the study were used to create a simulation model suitable for designing a confirmatory Phase 3 study. The drug was administered iv at a dose of 10 mg/kg, and a second infusion of 1 mg/kg iv was administered after relapse. A rapid improvement in MWS symptoms was reported within two days, and complete remission after eight days. Remission had a median duration of 185 days (range 168–203 days), while additional dosing after relapse resulted in a median symptom-free period of 90 days. The drug was well-tolerated.³¹

Patients were studied for 16 canakinumab administration cycles in total, and were observed for up to 1.5 years. Individual PK/PD measurements were taken after each cycle. PK profiles were processed to create the simulation model. The model fitted the previous PK and clinical remission data, with canakinumab having a plasma half life of 29 days and a critical drug

Table 1. Canakinumab studies in cryopyrin-associated periodic syndrome

Clinical phase	Study design	Results	NCT number; status
Phase 1/2 (refs. 31–33)	Four CAPS patients were studied for 16 canakinumab administration cycles in total for up to 18 months. Individual PK/PD measurements were taken after each cycle.	The PD/PK data were used to construct a simulation model of canakinumab treatment. The model predicted that a regular dosing of 150 mg canakinumab every eight weeks would be optimal for maintaining the critical drug concentrations and ensuring a low risk of relapse in patients over 40 kg.	NCT00487708; Completed
Phase 2 (ref. 30)	CAPS (n = 12) patients with the NLRP3 mutation and active disease were given a single dose of 150 mg canakinumab; re-dosing occurred in case of relapse within seven days.	All 12 patients treated with canakinumab achieved a complete and rapid clinical and serological response. Two patients were given adjusted canakinumab dose. Median time to re-dosing was 92 days (nine patients) after the first and 66 days (six patients) after the second treatment cycle. Two patients remained relapse-free for 106 days.	Completed
Phase 2	In the first pilot stage, five patients will undergo PK/PD assessments in blood and cerebrospinal fluid (CSF). In stage 2, patients will be treated for 24 weeks (every eight weeks) with the dosing regimen based on the assessment of the efficacy and PK/PD profile in stage 1. Long term efficacy will be evaluated.	The results of the study were not available as of September 2009.	NCT00770601; Recruiting
Phase 3	Three-part, randomized, 48-week duration study in patients with CAPS. A total of 35 patients were treated with 150 mg canakinumab for eight weeks (part 1). Responders were randomized in a 24 week withdrawal study (part 2) and re-entered treatment for 16 weeks (part 3)	97% of patients responded to canakinumab in part 1 and remained in remission during treatment in part 2. 81% of the patients in the placebo group in part 2 relapsed. 90% of patients completed part 3 in full remission. CRP and SAA values were normalized upon treatment with canakinumab	NCT00465985; Completed
Phase 3	A six month to two year study including 169 patients with FCAS, MWS or NOMID rolled over from trials NCT00487708 and NCT00465985; patients are treated with sc canakinumab. The aim of the study is to provide long term safety and efficacy data.	The results of the study were not available as of September 2009.	NCT00685373; Recruiting

CAPS, cryopyrin-associated periodic syndrome; NLRP3, nod-like receptor pyrin domain-containing 3; PD/PK, pharmacokinetics/pharmacodynamics; FCAS, familial cold auto-inflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; CRP, C-reactive protein; SAA, serum amyloid A.

concentration of 1.1 µgram/mL where there was a 50% probability of clinical relapse. Analysis of canakinumab PK data suggested that the probability of inflammatory relapse due to overexpression of IL-1β was inversely related to the drug concentration. The simulation model created from the study data predicted that a regular dosing of 150 mg canakinumab every eight weeks should maintain drug concentrations, with low probability of relapse in patients over 40 kg.^{32,33}

A single-center, interim, open label Phase 2 study evaluated the safety and efficacy of canakinumab.³⁰ The 12 patients (seven females and five males) carried the NLRP3 mutation and had confirmed active disease requiring medical intervention. Patients received a single sc injection of canakinumab (150 mg for adults; 2 mg/kg for children), and were re-dosed on relapse. In case of incomplete response within seven days, 5 mg/kg iv canakinumab was administered. Complete response was defined by (i) physician's global assessment of disease activity and assessment of skin disease as ≤2 on a 5-point scale (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe), and (ii) normal serum values (<10 mg/L) of C-reactive protein (CRP) or serum amyloid A (SAA). Patient age range was 4.3 to 47.4 years (median 27.6 years); four

children below 14 years were included. Prior to the trial, nine patients had been treated with anakinra doses up to 8 mg/kg. All 12 patients treated with canakinumab achieved a complete and rapid clinical and serological response. Two children and one adult did not respond completely within seven days, and each received an additional 5 mg/kg iv canakinumab dose. Median time to relapse and re-dosing was 92 days (nine patients) after the first, and 66 days (six patients) after the second, treatment cycle. Two patients remained relapse-free for 106 days. Canakinumab was generally well-tolerated, and the adverse effects were upper respiratory tract infections (seven events) and elevated pancreas amylase and lipase (two events). A serious adverse event (vertigo) was experienced by one patient.³⁰

The safety and efficacy of canakinumab, and the utility of S100A12 as a biomarker for inflammation, were evaluated in a study of eight CAPS patients. The protein S100A12 is a pro-inflammatory member of the damage-associated molecular pattern molecules. It is expressed in activated granulocytes and binds to RAGE, a receptor found on endothelium and various cells of the immune system. S100A12 has been proposed as a marker of inflammation activity in patients with CAPS.³⁴ The

Table 2. Canakinumab studies in rheumatoid arthritis

Clinical phase	Study design	Results	NCT number; status
Phase 1/2 (ref. 27)	Patients (n = 53) with active RA under treatment with stable doses of methotrexate were randomized into four cohorts receiving 0.3, 1, 3 and 10 mg/kg canakinumab on days 5 and 15.	Clinical improvement was observed at week 6 in the 10 mg/kg treatment group, according to ACR20 criteria, with reduction of mean CRP values and normalization of its levels within a few days after treatment with 10 mg/kg canakinumab. Canakinumab administration to methotrexate-refractory patients resulted in clinical improvement.	NCT00619905; Completed
Phase 1/2	A four-arm study of canakinumab at doses of 10 mg/kg sc, 5 mg/kg iv, 2 mg/kg sc or 1 mg/kg iv, in 11 patients (18–75 years of age) with established RA.	The results of the study were not available as of September 2009.	NCT00505089; Terminated
Phase 1/2	A 12-week trial including 80 adult patients with RA. Patients were randomized into two groups receiving either placebo or canakinumab. The aim of the study is to investigate the biomarker profile of patients that respond to canakinumab treatment compared to those that do not.	The results of the study were not available as of September 2009.	NCT00504595; On-going, but not recruiting patients
Phase 2	A 12-week study designed to evaluate canakinumab risk-benefit profile in 273 patients with active RA receiving methotrexate (three groups with escalating sc dose regimens and one placebo group).	The results of the study were not available as of September 2009.	NCT00424346; Completed
Phase 2	A 76-week extension study of 208 patients with active RA who participated in the core NCT00424346 trial. Long-term safety and efficacy data according to the ACR20 criteria will be assessed during treatment with 300 mg canakinumab.	The results of the study were not available as of September 2009.	NCT00471198; Terminated
Phase 2	A 2-year study designed to evaluate the long-term safety, tolerability and efficacy of canakinumab in 160 patients with active RA.	The results of the study were not available as of September 2009.	NCT00784628; Terminated
Phase 2	A 54-week trial to assess the long-term safety and tolerability of canakinumab in 179 patients (18 to 75 years of age) with RA	The results of the study were not available as of September 2009.	NCT00554606; Recruiting
Phase 2/3	A 26-week, two arm study in 87 early RA patients receiving methotrexate. Patients (18 to 75 years of age) were randomized into two groups: iv canakinumab + methotrexate or placebo + methotrexate.	The results of the study were not available as of September 2009.	NCT00487825; On-going, but not recruiting patients

RA, rheumatoid arthritis; ACR20, American College of Rheumatology 20%; CRP, C-reactive protein.

goal of this trial was to assess the predictive value of S100A12 in CAPS therapy with anakinra and canakinumab. Eight patients (one male, seven females) with confirmed NLRP3 mutations and active disease participated in this trial. All patients were treated with anakinra; after a withdrawal period of up to two weeks, the patients were treated with canakinumab. MWS disease activity score (MWS-DAS), SAA, CRP and S100A12 values were recorded one day before and during treatment with anakinra (day 30–120) and canakinumab (day 8). MWS-DAS, and all inflammation markers fell rapidly at or below baseline, while S100A12 levels were significantly lower with canakinumab compared to anakinra therapy. Canakinumab treatment resulted in S100A12 values within the normal limits (<120 ng/ml) for most patients (88%); S100A12 values were within the normal limits for 50% of those treated with anakinra. S100A12 expression strongly correlated with MWS-DAS disease activity ($p < 0.05$) and classical inflammatory parameters. Study data indicated that treatment with canakinumab was superior to anakinra at normalizing S100A12 levels in MWS patients. The investigators concluded

that S100A12 was a sensitive marker of inflammation in patients with MWS, and could be a valuable parameter to monitor response to anti-inflammatory drugs.³⁵

An ongoing Phase 2 open-label study (NCT00770601), sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Disorders, will examine whether canakinumab is safe and effective for treating patients with NOMID. The minimum eligibility age for this study is two years; a total of 25 to 30 patients are expected to enroll and receive six months of treatment. The trial consists of two stages. In the first pilot stage, five patients will undergo PK/PD assessments in blood and cerebrospinal fluid. Canakinumab efficacy will be monitored by recording the inflammatory and relapse events to confirm the dose and dosing regimen before enlarging the number of patients enrolled in the study. Following stage 1, 20 additional patients will be enrolled for a second confirmatory stage. In stage 2, patients will be treated with a dose and dosing regimen based on the assessment of the efficacy and PK/PD profile in stage 1. Each stage will include a 3-week screening period in which pre-treatment

Table 3. Canakinumab studies in systemic-onset juvenile idiopathic arthritis and gout arthritis

Clinical phase, indication	Study design	Results	NCT number; status
Phase 1/2, SoJIA (refs. 37, 38)	Patients (n = 23; 4–19 years) with active SoJIA received single canakinumab s.c. injection (0.5–9 mg/kg) and re-dosing upon relapse. Relapse was defined as reappearance of fever and/or systemic manifestations of disease with elevated CRP or according to ACRped criteria for flare.	Interim results indicate 59% of patients responded to canakinumab and achieved ACRped50 or better at Day 15, while a full response was reached in 4 cases (18%). For canakinumab doses <3, 3, >3 mg/kg, the probability of relapse within one month was 19, 17 and 7%, respectively. Steroid was tapered in 70% of responders.	NCT00426218; Active, but not recruiting
Phase 3, SoJIA	A 4-week study to assess the initial efficacy and safety of canakinumab in an estimated total of 122 patients (2–19 years of age) with relapsing SoJIA with at least two joints with active disease.	The results of the study were not available as of September 2009.	NCT00886769; Recruiting participants
Phase 3, SoJIA	A two-part study of 214 SoJIA patients (2–19 years) who will be administered canakinumab or placebo. The aim of the trial is to evaluate the sustained efficacy of canakinumab in the double-blind part 2 and the ability to taper steroids in the open label part 1.	The results of the study were not available as of September 2009.	NCT00889863; Recruiting participants
Phase 3, SoJIA	A 4-week study of 100 SoJIA patients (minimum age of two years) who participated in NCT00889863 or NCT00886769, and responded to treatment with canakinumab but clinically deteriorated afterwards. Patients will be retreated with 4 mg/kg canakinumab sc for a maximum of two years.	The results of the study were not available as of September 2009.	NCT00891046; Recruiting participants
Phase 2, gout	An 8-week study of 200 adult gout patients that were randomized into six study arms (10, 25, 50, 90 or 150 mg canakinumab, or 40 mg triamcinolone acetonide). The aim of the study was to determine the target dose for management of acute flares in gout patients that were refractory or contraindicated to NSAIDs or colchicine.	The results of the study were not available as of September 2009.	NCT00798369; Completed
Phase 2, gout	An active-controlled study of a single canakinumab dose in 44 hospitalized adult patients with acute gout to evaluate safety and efficacy profile.	The results of the study were not available as of September 2009.	NCT00663169; Recruiting participants
Phase 2, gout	A 24-week study including 440 adult gout patients randomized into seven arms of various canakinumab doses on day 1 (25 mg sc, 50 mg sc, 50 mg sc followed by 25 mg sc, 300 mg sc, 100 mg sc, 200 mg sc) or 0.5 mg colchicine capsules daily during a treatment period of 16 weeks.	The results of the study were not available as of September 2009, were available.	NCT00819585; On-going, but not recruiting
Phase 2, gout	An open label, extension study of 300 adult gout patients rolled over from study NCT00819585; the goal is to collect additional long-term (one year) safety, efficacy and tolerability data.	The results of the study were not available as of September 2009.	NCT00927810; Recruiting participants

SoJIA, systemic-onset juvenile idiopathic arthritis; CRP, C-reactive protein; ACR, American College of Rheumatology; NSAID, non-steroidal anti-inflammatory drug.

parameters will be collected, a run-in period (only for patients who discontinued anakinra), a baseline evaluation prior to each drug administration, a 24-week treatment period with fixed dosing of canakinumab, and a study completion visit. Patients with body weight greater than 40 kg will receive canakinumab 150 mg sc, while the dose for patients with a body weight less than or equal to 40 kg will be 2 mg/kg. Canakinumab will be administered every eight weeks, followed by an observation period after each injection in order to evaluate the response to treatment. Patients who do not achieve complete remission following canakinumab injection in any treatment period will be re-dosed

within day 15. As of September 2009, the study was ongoing and no interim data was available.

The simulation model developed from NCT00487708 study data was used to design a confirmatory Phase 3 study (NCT00465985). The trial consisted of a three-part, double-blind, placebo-controlled, randomized withdrawal study of 48-week total duration in patients with CAPS.³⁶ Thirty-five patients (9 to 74 years of age) participated in part 1, and received 150 mg of canakinumab sc for eight weeks. Patients with a complete response to treatment entered part 2, and received either 150 mg of canakinumab or placebo every eight weeks for up to 24

Table 4. Canakinumab studies in additional indications

Clinical phase, indication	Study design	Results	NCT number; status
Phase 1/2, asthma (ref. 39)	Double-blind study of two administrations of 10 mg/kg canakinumab or placebo on days 0 and 15 to 16 patients with mild asthma. PD20 FEV1 Allergen challenge was performed on days 0 and 28.	Canakinumab was safe and well-tolerated. Modeled data suggested 10 mg/kg would decrease IL-1 β by >90% for a 14-week period.	Completed
Phase 2, diabetes	The study includes 231 adult patients (18–70 years) with type 2 diabetes mellitus randomized into canakinumab and placebo groups to evaluate whether canakinumab can lower HbA1c or peak glucose levels in response to an oral glucose tolerance test.	The results of the study were not available as of September 2009.	NCT00605475; Recruiting participants
Phase 2/3, diabetes	A 4 month-duration study of 600 adult (18–74 years) patients with type 2 diabetes already under treatment with maximum dose of metformin. Four groups of patients will receive monthly canakinumab doses for four months plus metformin; a fifth group will receive placebo plus metformin. Patients will then enter a 24 to 48 month extension at a selected dose to further characterize safety and efficacy.	The results of the study were not available as of September 2009.	NCT00900146; Recruiting participants
Phase 1/2, COPD	The study includes 130 adult patients (40–80 years) with COPD randomized into a canakinumab-treated (dose escalation) and a placebo group	The results of the study were not available as of September 2009.	NCT00581945; On-going, but not recruiting

PD20, provocation concentration 20%; FEV1, forced expiratory volume in 1 sec; HbA1c, hemoglobin A1c; COPD, chronic obstructive pulmonary disease.

weeks. Patients that either completed part 2 or relapsed proceeded to part 3, and received at least two more doses of canakinumab during a 16-week, open-label, active treatment period. The therapeutic responses were assessed using disease-activity scores and analysis of CRP and SAA levels. A complete response was defined as (1) ratings of no or minimal disease activity according to physician's assessment of disease activity (PHY) and assessment of rash, and (2) serum levels of CRP and SAA less than 10 mg/L. A disease flare (relapse) was defined as a CRP and/or SAA values greater than 30 mg/L, and either a score of greater than minimal for PHY or a score of minimal for PHY accompanied by a rash assessed as more than minimal.

In part 1 of the study, 34 of the 35 patients (97%) had a complete response to a single dose of canakinumab. Markers of inflammation normalized within eight days of treatment in most patients. Normalization in the mean CRP and SAA values was sustained throughout part 1 in patients continuously treated with canakinumab. Complete responders without disease flare from part 1 were randomized (1:1) to canakinumab or placebo in part 2. Of the 31 that entered part 2, all 15 patients receiving canakinumab remained in remission, while relapse occurred in 13 of the 16 patients (81%) receiving placebo ($p < 0.001$). At the end of part 2, median CRP and SAA values were normal (<10 mg per liter for both measures) in patients receiving canakinumab, but were elevated in those receiving placebo ($p < 0.001$ and $p = 0.002$, respectively). All patients treated with canakinumab in part 2 had no or minimal symptoms. Of the 31 patients that entered part 3, 29 completed the protocol and 28 of these remained in remission. Administration of canakinumab to patients who had

received placebo in part 2, and were experiencing a relapse at the start of part 3, resulted in decreased levels of CRP and SAA. Two patients who received canakinumab had serious adverse events in part 3; use of canakinumab was associated with an increase in the rate of suspected infections ($p = 0.03$).

A Phase 3 study (NCT00685373) initiated in May 2008 is expected to enroll 169 patients with FCAS, MWS or NOMID who had previously participated in studies of canakinumab, or are newly identified. The patients (three years and older) will be given sc canakinumab for a minimum of six months and a maximum of two years. The goal of the study is to provide long term safety and efficacy data for the use of canakinumab in patients with CAPS. Adverse events will be measured, as well as number of disease relapses, immunogenicity and PK data. No interim results were available as of September 2009.

Studies in Rheumatoid Arthritis

The safety, tolerability and pharmacodynamic activity of canakinumab in MTX-refractory RA patients were assessed in a proof-of-concept Phase 1/2 study (NCT00619905).²⁷ Patients with active RA who were enrolled in this dose escalation study were under treatment with stable doses of MTX (10 mg/week for approximately three months), had disease duration of at least six months before randomization, and had not responded to at least one anti-rheumatic drug in the past, but were not deemed refractory to all therapies. The first 32 patients were randomized into four groups. Canakinumab iv doses of 0.3, 1, 3 and 10 mg/kg, were administered on days 1 and 15 for each cohort. In

each group, six patients received canakinumab and two patients were administered placebo. To increase the statistical power, 21 patients were added to the 10 mg/kg cohort (14 patients received canakinumab and seven received placebo), resulting in a total of 20 patients in the 10 mg/kg cohort, and a total of 15 patients who received placebo. The clinical benefit (according to the American College of Rheumatology 20% improvement criteria) achieved at week 6 in the 10 mg/kg treatment group was not statistically significant ($p = 0.085$). However, the disease activity score was significantly reduced after four weeks for patients in the 10 mg/kg cohort.²⁷

The majority of responders had improved symptoms within the first three weeks after canakinumab treatment, indicating a rapid effect of the drug. There was a significant reduction in the mean values of CRP marker and normalization of its levels within a few days after the beginning of treatment with 10 mg/kg canakinumab. Similar improvements were observed in the other active treatment cohorts. Two infections thought to be related to treatment were identified in the 1 mg/kg dose group (one case of erysipelas and one case of pulmonary infection). No serum anti-drug antibodies were detected during the study. Overall, the investigators concluded that canakinumab administration to MTX-refractory patients resulted in clinical improvement, but they also pointed out the need for additional studies to assess the efficacy in RA and determine the optimal dose regimen.²⁷

Seven additional clinical studies in patients with RA were terminated, completed or ongoing as of September 2009. These studies were designed to assess the route of administration, biomarker profiles and immunogenicity of canakinumab, as well as the long-term effects of the drug in RA patients.

A Phase 1/2 (NCT00505089) randomized, open-label study was designed to evaluate the PK and total IL1 β PD relationship in joint fluids of patients with RA who were treated with different doses of canakinumab (1, 2, 5 and 10 mg/kg), and compare sc to iv administration of the drug. The study was initiated in August 2007 and has been terminated; results were not available as of September 2009.

An ongoing Phase 1/2 study (NCT00504595) will assess the safety, efficacy and response to canakinumab treatment using the American College of Rheumatology (ACR) criteria of 20% improvement in symptoms (ACR20). The study will also establish a biomarker profiles for adult patients with established RA who respond to treatment and those who do not.

A Phase 2, 12-week study (NCT00424346) is designed to evaluate the risk-to-benefit ratio of three sc canakinumab dose regimens compared to placebo in patients with active RA who were also under treatment with stable MTX therapy (greater than or equal to 7.5 mg/week). The study was completed in December 2008, but the data has not been published as of September 2009.

A Phase 2, 76-week extension study (NCT00471198) was designed to collect long-term safety and tolerability data on administration of 300 mg canakinumab to patients with active RA who participated in the NCT00424346 study. The study was intended to investigate efficacy by assessing the response to treatment according to ACR20 criteria. Immunogenicity of

canakinumab was assessed after the 76 weeks of repeat exposure. The study was initiated in April 2007 and has been terminated; results were not available as of September 2009.

A Phase 2 study (NCT00784628) was designed to assess the safety, tolerability, efficacy and immunogenicity of canakinumab administration over a period of two years. A total of 160 adult patients with active RA were to be enrolled. The study was initiated in October 2008, but has been terminated.

An ongoing, 54-week, Phase 2 trial (NCT00554606) is primarily designed to assess adverse events and infections associated with long-term use of canakinumab in 179 adult RA patients. The long-term efficacy, as well as preservation or improvement of joint structure, and long term maintenance of health-related quality of life will also be assessed. The study was still recruiting participants as of September 2009.

An ongoing, placebo-controlled, 26-week, Phase 2/3 study (NCT00487825) is designed to evaluate the safety and efficacy of combined iv canakinumab and oral MTX therapy in 87 adult patients with early RA. This study was initiated in March 2007, and is ongoing but not recruiting patients. The primary outcome measure is a 50% improvement in symptoms (ACR50) at 6, 14 and 26 weeks. Secondary outcome measures are ACR20, 70 and 90 for the combination of canakinumab and MTX compared to treatment with MTX alone, as well as the biomarker profile in patients who responded to treatment (assessed by the ACR20 at weeks 6, 14 and 26) compared to non-responders.

Studies in SoJIA and Gout Arthritis

Systemic-onset juvenile idiopathic arthritis (SoJIA). Canakinumab has been designated as an orphan drug for treating SoJIA in the US, European Union and Switzerland, and has fast-track status for this indication in the US. A total of four studies of canakinumab as a treatment for this indication are ongoing.

In an open-label, staggered dose-escalation Phase 1/2 study (NCT00426218), patients 4–19 years old received a single canakinumab sc injection (0.5–9 mg/kg) and re-dosing upon relapse.^{37,38} Response was measured according to modified ACR criteria (ACRped30, defined as minimum of 30% improvement in 3 of 6 variables with worsening of no more than one variable by greater than 30%). Relapse was defined as reappearance of fever or systemic manifestations of the disease with elevated CRP or flare. A total of 23 patients with active disease were included in the study, although one patient was excluded from final analysis due to protocol violation. In a preliminary report of results for 19 children, 58% (11/19) of the patients achieved at least an ACRped50 response at day 15.³⁷ The time to relapse after the first dose ranged from 23 to greater than 200 days.

Of the total 22 patients, 13 (59%) responded to canakinumab and achieved ACRped50 or better at day 15.³⁸ Full response was reached in four cases (18%). The baseline parameter that best predicted response was the number of active joints (median: 33.5 for non-responders, 9 for responders). Median estimated time to relapse was 56 days (95% CI: 32–100) for doses less than 3 mg; 60 days (38–95) for the 3 mg dose; and 90 days (45–181) days for doses greater than 3 mg/kg, with a 19, 17 and 7% probability

of relapse within one month, respectively. Injections were well-tolerated, and no serum antibodies against canakinumab were detected. The recorded adverse events were mainly infections and gastrointestinal disorders. Serious adverse events were experienced only by two patients and were resolved during treatment.³⁸

A Phase 3 randomized, double-blind, placebo-controlled, single-dose study (NCT00886769) began in July 2009 to assess the initial efficacy and safety of canakinumab administration over a four week period in patients with relapsing SoJIA. An estimated 122 patients (2 to 19 years of age) with at least two joints with active arthritis are expected to enroll in this study. The primary outcome measure is the proportion of patients who meet the adapted ACR pediatric 30 criteria by day 15.

A randomized two-part study Phase 3 study (NCT00889863) initiated in June 2009 will evaluate the sustained efficacy of canakinumab in 214 patients who are 2–19 years of age and have active SoJIA. The ability to taper steroids will be assessed in the open label part 1, which will have a maximum duration of 32 weeks, and the time to relapse during canakinumab treatment will be assessed in the double-blind part 2 of the study.

An open-label extension Phase 3 clinical trial was initiated in August 2009 (NCT00891046) in order to assess the long-term efficacy, safety and immunogenicity of canakinumab in patients with SoJIA. Approximately 100 patients (minimum age of two years) who participated in studies NCT00889863 or NCT00886769, and who responded to treatment with canakinumab but clinically deteriorated afterwards, will be retreated with 4 mg/kg sc every four weeks for a maximum of two years.

Gout arthritis. Four clinical studies of administration of canakinumab to gout arthritis patients are ongoing or have been completed as of September 2009. The goals of the studies include comparisons of the efficacy of canakinumab to that of triamcinolone acetonide or colchicine, and assessment of the long-term safety and efficacy of the drug in adult gout patients.

An 8-week, adaptive, dose-ranging, multi-center, single-blind, double-dummy, active-controlled Phase 2 trial (NCT00798369) was designed to determine the target dose of canakinumab (10, 25, 50, 90 or 150 mg) in the management of acute flares in 200 gout patients who were refractory or contraindicated to non-steroidal anti-inflammatory drugs or colchicine. The efficacy of canakinumab was compared to that of triamcinolone acetonide administered in 40 mg doses. The primary completion date was August 2009; results were not available as of September 2009.

An ongoing Phase 2 proof-of-concept, randomized, double-blind, double-dummy, active-controlled study (NCT00663169) will evaluate the safety and efficacy of a single canakinumab dose in 44 hospitalized adult patients (18–80 years) with acute gout. The primary outcome measure of the study is self-assessed response to treatment at 72 hours post-dose. Secondary outcome measures include time to walk independently and time to recurrence of the symptoms of acute gout during treatment period of 72 hours, change in CRP, SAA and measurement of pain from baseline to last visit (maximum of four months), and PK of the drug.

A 24-week, dose-ranging, multi-center, double-blind, double-dummy, active-controlled Phase 2 study (NCT00819585) will

evaluate canakinumab for prophylaxis against the signs and symptoms of acute flares in 440 adult chronic gout patients initiating allopurinol therapy. The patients were randomized into 7 study arms, and received 25 mg sc, 50 mg sc, 50 mg sc followed by 25 mg sc, 300 mg sc, 100 mg sc or 200 mg sc canakinumab or 0.5 mg colchicine capsules daily during a treatment period of 16 weeks. The primary outcome measure is the determination of the target dose of canakinumab that leads to efficacy at least comparable to that of colchicine with respect to the mean number of gout flares occurring during 16 weeks. The study is ongoing, with an expected completion date of February 2010.

An open-label, non-randomized extension Phase 2 trial (NCT00927810) was initiated in July 2009 to provide additional long-term (up to 1 year) safety data for 300 patients rolled over from study NCT00819585, and collect further efficacy and tolerability data for all patients.

Clinical Studies in Additional Indications

Asthma. The response to inhaled allergen in asthma has been shown to be driven by T-cell inflammatory responses, with IL-1 β involved in the transduction of the inflammatory signal both in vivo and in vitro. One study evaluated the safety and tolerability of canakinumab in 16 mild asthmatic patients and evaluated its anti-inflammatory effects by assessing the attenuation of the late asthmatic response (LAR) after inhalative allergen challenge.³⁹ This randomized double-blind trial consisted of two administrations of canakinumab (10 mg/kg iv on days 1 and 15) or placebo in patients with mild asthma who were treated concomitantly with other anti-asthmatic drugs. Allergen challenge was performed on days 0 and 28. Based on the generated PK/PD model it was estimated that 10 mg/kg canakinumab would decrease IL-1 β levels by >90% for a 14-week period. In addition, canakinumab treatment appeared to attenuate LAR as compared to pre-treatment values.³⁹ Despite positive results in this small study, canakinumab is no longer under investigation as a treatment for asthma.²⁸

Diabetes. As of September 2009, two clinical studies of canakinumab as a treatment for diabetes had been initiated, and were recruiting patients.

An ongoing Phase 2 clinical study (NCT00605475) in 231 adult patients (18–70 years) with type 2 diabetes mellitus is currently evaluating whether canakinumab can lower hemoglobin (Hb) A1c or peak glucose levels in response to an oral glucose tolerance test. Primary outcome measures are safety, tolerability and PD effect of the drug on glycemic indexes. Secondary outcome measures are PK in patients, PD effect of canakinumab on pancreatic beta-cell function and insulin sensitivity, and duration of drug action.

A placebo-controlled Phase 2/3 study of canakinumab (NCT00900146) will evaluate the safety and efficacy of four monthly sc doses of canakinumab for the treatment of hyperglycemia in metformin-treated, adult Type 2 diabetic patients. This dose ranging study will be followed by a 24 to 48 month extension at the selected dose to further characterize the safety and efficacy of canakinumab. An additional primary outcome

Table 5. IL-1 blocking therapies marketed or in development for the treatment of autoimmune disorders

Company	Generic (trade) name	Category	Indication	Status
Amgen	Anakinra (Kineret)	IL-1R antagonist	Rheumatoid arthritis	Marketed
Regeneron	Rilanocept (Arcalyst)	IL-1 β receptor-Fc fusion protein	CAPS (with ongoing studies in rheumatoid arthritis, diabetes and gout)	Marketed
Novartis	Canakinumab (Ilaris)	IL-1 β mAb	CAPS (with ongoing studies in rheumatoid arthritis, gout, SoJIA, COPD, diabetes and macular disease)	Marketed
Xoma	Xoma-052	IL-1 β mAb	Rheumatoid arthritis, diabetes, SoJIA and gout	Phase 2 studies
Kowa	K-832	IL-1 β secretion inhibitor	Rheumatoid arthritis	Phase 2 studies
Cytos Biotechnology	CYT-013-IL1bQb	IL-1 β vaccine	Diabetes, rheumatoid arthritis	Phase 2 studies
Eli Lilly	LY-2189102	IL-1 β mAb	Diabetes, type 2	Phase 1 studies

IL-1, interleukin-1 β ; IL-1R, interleukin-1 receptor; CAPS, cryopyrin-associated periodic syndrome; SoJIA, systemic-onset juvenile idiopathic arthritis; COPD, chronic obstructive pulmonary disease.

measure is the assessment of the effect on HbA1c of four canakinumab doses compared to placebo over four months in diabetic patients who are also receiving metformin.

Chronic obstructive pulmonary disease. An ongoing Phase 1/2 study (NCT00581945) will evaluate the safety, tolerability and efficacy of multiple doses of canakinumab compared to placebo when administered iv to 130 adult patients (40–80 years) with COPD. The primary outcome measure is examination of the impact of canakinumab on pulmonary function in COPD patients for the 45-week duration of the study.

Macular degeneration. One ongoing, randomized, double-blind Phase 1 trial (NCT00503022) is evaluating the tolerability and safety of a single iv canakinumab infusion in patients with wet age-related macular edema. A secondary outcome measure of the study is the assessment of the efficacy of the compound in central macular edema and visual acuity in patients from baseline up to the sixth month.

Future Prospects

Dysregulated IL-1 β activity has become the target of choice for the treatment of inflammatory diseases. The market for IL-1 blocking agents is highly competitive, and multiple candidates are being developed for a range of therapeutic indications (Table 5). Most of these molecules act by blocking the IL-1 β cytokine or its cellular receptor.

Anakinra was the first IL-1 blocker to be approved for the treatment of RA. In addition to RA, anakinra has shown efficacy in several other autoimmune disorders including the inflammation linked to NLRP3 mutations (MWS and NOMID), SoJIA, adult-onset Still disease, Schnitzler syndrome and Sweet syndrome.^{5,40-42}

Canakinumab is the third IL-1 blocker that has been approved for the treatment of autoimmune disorders, and the second drug approved for CAPS, after rilanocept. Canakinumab has several advantages over other IL-1 blockers. Unlike anakinra and rilanocept that block the signals of both the IL-1 α and IL-1 β isoforms, canakinumab is highly specific for IL-1 β , and does not

interfere with other IL-1-activated pathways. Due to its longer half-life, canakinumab can block IL-1 β action for a longer period of time²⁷ without the need for frequent injections or high doses. Notably, in patients with CAPS canakinumab is administered sc every two months,³⁶ as opposed to the weekly or daily injections required for treatment with rilanocept or anakinra, respectively. Xoma-052 (XOMA), another anti-IL-1 β therapeutic mAb, is also being evaluated for the treatment of autoinflammatory diseases, but has not yet been compared to canakinumab.

Medarex and Regeneron are entitled to sales-based royalty payments from the commercial sales of canakinumab, as specified in agreements between these two companies and Novartis. Given its recent approval, sales figures for canakinumab were not available as of September 2009. The sales of the rival drug rilanocept in the CAPS market reached \$11 million in 2008, the year of its approval, and are expected to increase in 2009. Rilanocept will directly compete with canakinumab for the 6,500-patient CAPS market. Novartis is currently pursuing expansion of canakinumab into additional indications, which would increase sales. Canakinumab has already shown positive results in patients with RA,²⁷ and larger clinical trials are ongoing. Encouraged by positive results from a proof-of-concept study in SoJIA patients,³⁸ Novartis commenced three larger studies in mid-2009 to evaluate the efficacy of canakinumab for this indication. Other ongoing clinical trials are examining the safety and efficacy of canakinumab in gout arthritis, COPD, type 2 diabetes and age-related macular degeneration.

Evidence that emerged in the last two decades indicates that the molecular signature in most chronic diseases, including cancer, display similarities to dysregulated inflammatory response. In this context, it has been proposed that IL-1 β targeting agents could potentially be used in inflammation-promoted malignancies such as lung cancer.⁴³ Results from the ongoing clinical trials are expected to advance our knowledge regarding the clinical value of IL-1 blockers, and understanding of the biological relevance of IL-1 β in autoimmune disorders and other diseases.

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