Canakinumab for the treatment of gout

Gout is the one of the most common forms of inflammatory arthritis in adults. As the incidence and prevalence of gout are increasing and many patients cannot tolerate or have contraindications to standard treatments, there is a need for new, more effective therapeutic agents. IL-1β is a proinflammatory cytokine that plays a pivotal role in the pathogenesis of gouty arthritis. Several inhibitors of IL-1 have been elaborated to date. Canakinumab is a fully human monoclonal antibody to IL-1β developed by Novartis. According to recently published results of clinical trials, canakinumab may provide a safe and effective alternative treatment option for gout flares for patients in whom standard therapies are not advised.

KEYWORDS: canakinumab ■ gout ■ IL-1β

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Canakinumab is a fully human monoclonal antibody targeting IL-1β that has an expanding list of clinical indications. IL-1β is a proinflammatory cytokine that plays a key role during inflammation and is implicated in acute and chronic autoimmune diseases [1]. It is synthesized as a precursor peptide (pro-IL-1β) that undergoes proteolytic cleavage and excretion into the extracellular space. The principal pathway of IL-1β processing occurs via the inflammasome complex that activates caspase-1. Once secreted, IL-1β acts on target cells through the IL-1RI receptor. Dysregulated IL-1β secretion is observed in several autoimmune diseases, specifically in autoinflammatory diseases, and the clinical manifestations can be significantly relieved by IL-1β blockade [2].

Clinical pharmacology
■ Mode of action
Canakinumab is a high affinity, fully human monoclonal antihuman IL-1β antibody of the IgG1/κ isotype. It was generated using a transgenic mouse strain capable of producing human IgGκ monoclonal antibodies. Transgenic mice were immunized with human IL-1β and hybridomas were evaluated by ELISA, resulting in the selection of canakinumab [3].

Canakinumab binds to human IL-1β with high affinity, with a dissociation constant of approximately 35–40 pM [4]. Upon binding to canakinumab, the antibody-IL-1β complex is unable to attach to the cell surface receptor therefore interrupting IL-1β-dependent signaling.

■ Pharmacokinetics
The *in vitro* biological activity of canakinumab was determined in primary human cell cultures. Canakinumab neutralized the bioactivity of recombinant human IL-1β *in vitro* in human dermal fibroblasts. It also inhibited the bioactivity of natural IL-1β released from human peripheral blood mononuclear cells [5].

Canakinumab was identified as a typical IgG-type antibody with low serum clearance and long terminal half-life (6.5–8 days in marmosets and 15 days in rhesus monkeys) in preclinical safety studies. In marmosets, canakinumab was well tolerated at all dose levels investigated (up to 100 mg/kg intravenously (iv.) and up to 150 mg/kg subcutaneously [sc.]). No treatment-related death or clinical signs were observed. Embryo-fetal development toxicity studies in marmoset monkeys and mice revealed no evidence of embryotoxicity or fetal malformations. A delay in fetal skeletal development was observed in marmosets when using doses 23-fold the maximum recommended human dose. A specific antimouse IL-1β was tested in mice in reproductive toxicity and immunotoxicity studies. No toxicologically significant findings were identified even at doses 15-fold higher than the maximum efficacious dose in that species. These studies supported the use of canakinumab in human subjects [6].

Human studies
More than 30 clinical studies with canakinumab in humans have been conducted to date. A total of more than 1000 subjects (including more than 40 children aged ≥4 years) have been enrolled. Canakinumab was studied in healthy subjects, in

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patients with cryopyrin-associated periodic syndromes (CAPS), rheumatoid arthritis (RA), systemic onset juvenile idiopathic arthritis (SoJIA), mild asthma, wet macular degeneration, atherosclerosis and gout among others. Safety, tolerability and efficacy data are available from more than 1000 subjects.

■ Human pharmacokinetics

In human studies, canakinumab has a half-life of between 21 and 30 days. The pharmacokinetic (PK) parameters of canakinumab were determined in asthma, RA, psoriatic and CAPS patients. The PK of canakinumab is linear with no evidence of a time-dependent change. In adult CAPS patients, canakinumab was absorbed slowly after sc. administration of a single 150-mg dose, reaching peak serum concentration (C_{max} of 16 ± 3.5 µg/ml) in approximately 7 days. Half-life is long (mean: 26 days) after single sc. administration. The absolute bioavailability is estimated to be 70%. Serum clearance was slow after sc. administration depending on body weight but not on gender or age and was estimated to be 0.174 l/day in a typical CAPS patient of 70 kg. In pediatric CAPS patients, the pharmacokinetics of canakinumab was comparable with those seen in adults. Peak concentration occurred between 2 and 7 days following a single sc. administration 150 mg or 2 mg/kg. Terminal half-life ranged from 22.9 to 25.7 days in pediatric CAPS patients [6].

Human safety & efficacy data
■ Study in healthy volunteers

Canakinumab was safe and well tolerated in healthy subjects in doses administered up to 900 mg by 600 mg iv. plus 300 mg sc. No immunogenicity was observed during this period. Total IL-1β (free IL-1β and [canakinumab: IL-1β] complex) was increased in serum after canakinumab treatment but no free IL-1β was detected indicating the sufficient capture of IL-1β [7]. Canakinumab treatment did not significantly affect serum levels of IL-1 receptor antagonist (IL-1Ra), IL-6 or TNF-α in healthy volunteers.

■ Studies in patients

Canakinumab was first studied in CAPS. In the Phase II study, patients received canakinumab for more than 300 days. Four CAPS patients were exposed to canakinumab for more than 2.5 years (NCT00487708) [8,101]. Canakinumab was administered in sc. doses following a disease relapse: adults received 150 mg sc., children were treated with a dose of 2 mg/kg sc. Canakinumab induced fast and long-lasting response in CAPS

patients regarding physician's global assessment of disease activity (fever, joint pain, myalgias, headache, conjunctivitis, fatigue) and skin disease. Following a single sc. administration of 150 mg canakinumab, 96.6% of the patients achieved complete clinical response in 2–9 days [8]. There was no statistically significant difference in the median time to relapse after 150 mg sc. dose between any subpopulations. In the Phase II and pivotal Phase III CAPS study, no death was reported and five severe advere events (SAEs) were documented. The most frequent adverse events (AEs) were infections (upper respiratory tract and nasopharyngitis) in both the adult and the pediatric population. No immunogenicity was observed [8–10].

A Phase II study was conducted in 53 RA patients. Altogether, 38 patients received canakinumab iv. Canakinumab showed efficacy as demonstrated by the number of ACR20 and ACR50 responders and significant improvement was observed in other assessments as DAS28, Health Assessment Questionnaire scores, high-sensitivity C-reactive protein, patient's global assessment of disease activity and physicians' global assessment of disease activity. No significant difference was demonstrated in ACR70 responders compared with placebo. Regarding safety issues, no deaths were observed, approximately five SAEs occurred, most commonly infections. Overall, the rate of AEs was similar in the treatment and placebo groups. Canakinumab was well tolerated and the safety profile of canakinumab was comparable to that of placebo (NCT00619905) [4,102].

In a Phase II SoJIA study, altogether 23 children received a single sc. injection of 0.5–9 mg/kg canakinumab followed by re-dosing upon relapse. Approximately 60% of the patients classified responders achieving an adapted pediatric ACR50 at 2 weeks. No death or discontinuation due to AEs was observed. Three SAEs related to study drug were reported. Altogether 80% of children presented AEs but there was no obvious relationship between the frequency and type of AEs and dose. sc. injections were well tolerated and no severe tolerability reactions were reported. No anticanakinumab antibody formation was detected (NCT00426218) [11,103].

There are two further Phase III studies in SoJIA. One has been completed recently and the second is still ongoing. The study NCT00889863 that is still ongoing is a two-part study to assess the sustained efficacy of canakinumab and the ability to taper steroids [104]. NCT00886769 is also a Phase III study already completed to assess the initial efficacy and safety

of canakinumab over a 4-week period in patients with SoJIA having a flare [105,106].

A study of 22 patients with mild asthma and 18 healthy subjects was conducted where canakinumab showed a modest effect on attenuating the late-phase allergen response. One SAE has been reported that was not attributed to the study medication. No anticanakinumab antibodies were detected. No other clinical or laboratory data showed significant changes from pretreatment [12].

iv. canakinumab was studied in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (NCT00503022) [107]. A significant change in central retinal thickness was observed in canakinumab-treated patients after 1 month. Two SAEs were observed but none of them was suspected to be related to the study drug.

There is an ongoing study of sc. canakinumab in atherosclerosis for the prevention of recurrent cardiovascular events after myocardial infarction (CANTOS study). The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with myocardial infarction will prevent recurrent cardiovascular events [101].

Canakinumab is also being studied in several other conditions such as osteoarthritis, TNF-receptor-associated periodic syndrome, diabetes, Schnitzler syndrome (a condition of urticaria, fever, bone pain, arthritis and an IgM gammopathy), urticarial vasculitis, pyoderma gangrenosum, hyper IgD syndrome and chronic obstructive pulmonary disease [106].

Canakinumab in gouty arthritis
■ Rationale for IL-1 inhibition in gout
Inflammation in acute gout is induced by tissue deposits of monosodium urate (MSU) crystals that elicit cellular responses when they come into contact with different cell types (monocytes/macrophages, neutrophils or mast cells). The result is the release of inflammatory mediators such as proinflammatory cytokines, chemokines, prostaglandins and nitric oxide [13,14]. A typical acute flare of gout peaks in 1–2 days is followed by spontaneous resolution over the following 10 days. This process is thought to be driven by the production of anti-inflammatory cytokines by macrophages [15].

Among the many cytokines implicated, IL-1 has a special role. MSU crystals induce IL-1 release from different cell types [16] through innate immune pathways such as TLR2 and TLR4 on the surface of monocytes and macrophages [17] and activation of the intracellular inflammasome complex [18]. IL-1 has two forms:

IL-1α that is constitutively secreted in many cell types and IL-1β that is processed through the activation of the inflammasome from its proform (pro-IL-1β), mainly in monocytes and macrophages. Pro-IL-1β is cleaved by the enzyme caspase-1 (previously known as IL-1-converting enzyme) to its mature form IL-1β. A number of different inflammasomes have been described, but the NLRP3 inflammasome plays a key role in mediating MSU-induced inflammation. The NLRP3 inflammasome is activated by endogenous or exogenous danger signals such as various kinds of microorganisms, metabolic alterations and microcrystals like MSU and calcium pyrophosphate and results in IL-1β release [18]. It is still not clear how the activation of the inflammasome is regulated within the cell. A number of intracellular mediators are involved in controlling inflammasome activation. One hypothesis postulates that the generation of reactive oxygen species following cell contact with danger signals may be an intermediate step in activating caspase-1 and IL-1β release. Extracellular ATP can also activate the inflammasome by increasing potassium efflux via the P2X7 receptor and thereby changing intracellular calcium concentration. These complex regulatory mechanisms could explain why, despite the continual presence of MSU crystals in the joint in patients with gout, inflammation is episodic [19].

Besides the induction of IL-1β secretion, recent studies showed that MSU crystals are able to induce the release of IL-1α *in vivo* [20]. There are also inflammasome-independent mechanisms that are responsible for partial activation of IL-1β. Both *in vitro* and *in vivo* studies showed that other enzymes than caspase-1-like elastase and proteinase-3 are also able to process pro-IL-1β into active fragments [21,22].

Another important factor in MSU crystals-induced inflammatory reaction is preactivation of cells. Using pure MSU crystals alone, even at very high doses, no IL-1β production was observed [23]. This observation corresponds to the situation in patients with gout who have deposition of tophi without experiencing continuous inflammatory reactions. In these patients, inflammatory attacks are often triggered by copious meal consumption. A recent study showed synergistic activity of C18 fatty acids and MSU crystals in the induction of IL-1β production *in vitro* and *in vivo* as well [23]. FIGURE 1 shows mechanisms of MSU crystal-induced IL-1β production.

Clinical features induced by dysregulated IL-1β production are fever, arthritis, rash and
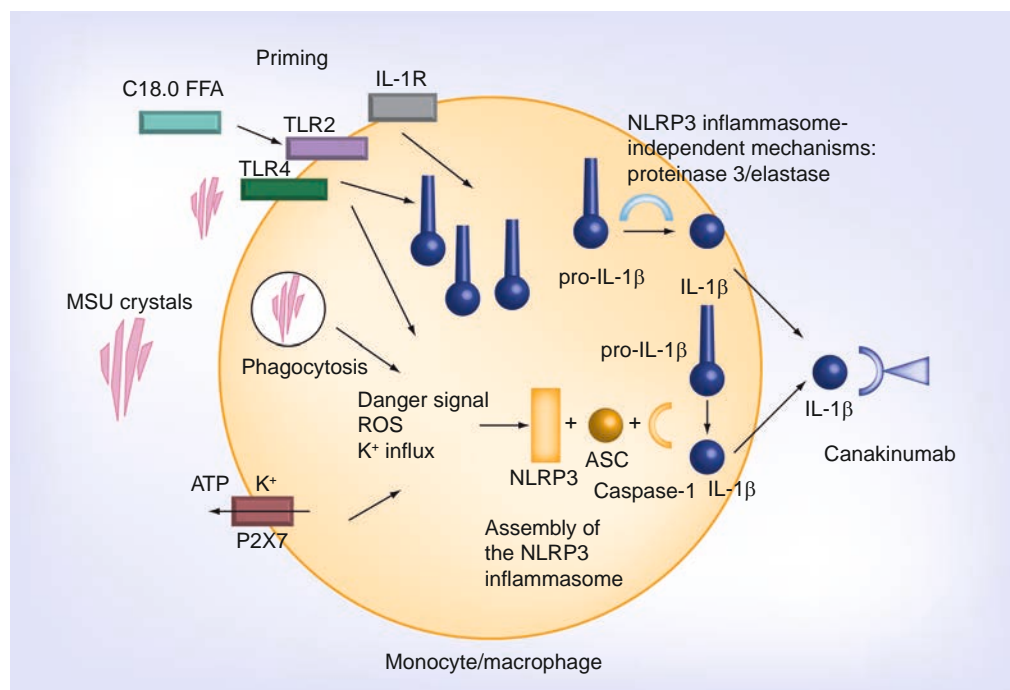
Figure 1. Mechanisms of monosodium urate crystal-induced IL-1β production. A first signal (priming) is needed for the production of intracellular pro-IL-1β. This preactivation can be triggered for example by C.18.0 FFA via TLR2 or by other TLRs or IL-1R. Then a second signal initiates the assembly of the inflammasome. The second signal can be the stimulation of the P2X7 receptor by extracellular ATP or the phagocytosed MSU crystals. These events induce potassium efflux and ROS production that leads to the inflammasome assembly. The activated NLRP3 inflammasome then process IL-1β from pro-IL-1β via caspase-1. There are other enzymes, protease-3 and elastase, that can process IL-1β from its proform in an inflammasome-independent way. Mature IL-1β is then secreted to the extracellular space. Canakinumab blocks IL-1β with high affinity and high specificity. MSU: Monosodium urate; ROS: Reactive oxygen species.

CNS involvement. These symptoms are characteristics of the hereditary autoinflammatory syndromes where mutations in the NLRP3 gene results in constitutive IL-1β production [24]. In acute gout, MSU crystal-induced IL-1β production leads to local and systemic symptoms such as arthritis and fever.

Clinical aspects of IL-1 inhibition in gout

As IL-1β is a pivotal proinflammatory cytokine strongly associated with the inflammation in gout, recently developed IL-1-blocking agents are being investigated as potential treatment options. There are four inhibitors that have been studied to date: anakinra (IL-1Ra), rilonacept (IL-1 Trap), canakinumab and XOMA 052 (gevokizumab) (monoclonal antibodies to IL-1β).

Anakinra is a recombinant, nonglycosylated form of the human IL-1Ra. It consists of 153 amino acids and has a molecular weight of 17.3 kDa. Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type I receptor (IL-1RI) that is expressed in a wide variety of tissues and organs. The absolute bioavailability of anakinra after a 70 mg sc. bolus injection in healthy subjects is 95%. In subjects with RA, maximum plasma concentrations of anakinra occurred 3–7 h after sc. administration of anakinra at clinically relevant doses (1–2 mg/kg); the terminal half-life ranged from 4 to 6 h. In RA patients, no unexpected accumulation of anakinra was observed after daily sc. doses for up to 24 weeks [25].

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human IL-1RI component and IL-1 receptor accessory protein linked in line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1Ra with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1Ra were 0.5, 1.4 and 6.1 pM, respectively. The average trough levels of rilonacept were approximately 24 mcg/ml at

steady-state following weekly sc. doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks. Bioavailability of rilonacept after a sc. injection is estimated to be approximately 50%. Its terminal half-life is 7.72 days [26,27].

XOMA 052 is a Human Engineered™ IgG2 antibody with 97% human sequence and a half-life of 22 days. It has an ultra-high binding affinity for IL-1β of 300 fM. Besides its high specificity for IL-1β it simultaneously reduces the affinity of IL-1β for IL-1RI while leaving affinity for IL-1RII and the soluble inhibitory receptors largely unaffected by antibody binding. XOMA 052 is a potent inhibitor of IL-1β activity both *in vitro* and *in vivo* [28].

With the exception of XOMA 052, which is currently in Phase II studies, the other three agents are available in the market, though none of them are officially approved for the treatment of gouty arthritis. In case of anakinra, besides some case reports, one clinical study has been published of ten patients with acute gout who presented either intolerance or contraindications to NSAID or colchicine. In all patients 100 mg of sc. anakinra daily for 3 days was used. The study showed rapid clinical response in all patients and no AEs were observed [29]. Rilonacept was investigated in a small placebo-controlled study of ten patients with chronic gout. Patients received sc. rilonacept once a week beginning with a loading dose of 320 mg, followed by 160 mg once a week. It showed a significant reduction in pain and signs of inflammation [30]. Rilonacept was also effective in the prevention of acute gout during initiation of urate-lowering therapy [31]. A large Phase III study with rilonacept in patients with acute gout attack has recently been completed (NCT00856206) [108]. sc. rilonacept was compared with *per os* indomethacine treatment in subjects with gout flare who are on urate-lowering therapy. Inhibition of IL-1 with rilonacept did not provide additional pain relief within 72 h of flare onset. These results suggest that inhibition of IL-1 by rilonacept in acute gout flare is clinically less effective than for gout flare prophylaxis [32].

Canakinumab studies in gout

Up to ten clinical studies with canakinumab have been conducted or are ongoing in gouty arthritis to date (TABLE 1). The target dose of canakinumab was determined in a Phase II trial (NCT00798369) in 200 gout patients who were refractory or contraindicated to NSAIDs or colchicine [109]. The results of this study indicated that canakinumab is effective in treating acute gout flares in these patients inducing rapid and sustained pain reduction and reducing risk of recurrent flares. Superior efficacy was shown by 150 mg canakinumab sc. compared with 40 mg triamcinolone acetonide intramuscular in all assessments, including time to 50% reduction in pain, patient's and physician's global assessment, reduction in markers of inflammation, rescue medication use and risk of recurrent flares [33,34]. By contrast, lower doses of canakinumab did not reach statistically significant differences compared with triamcinolone acetonide for most efficacy parameters (FIGURE 2). Canakinumab was generally well tolerated. No specific organ toxicity or dose-related effect was observed. Four SAEs were reported but they were not considered to be related to study medication.

An exploratory proof-of-concept study was conducted to evaluate the safety and efficacy of canakinumab for inflammation and pain associated with acute gouty arthritis in hospitalized patients (NCT00663169) [110]. The study is completed to date but the results are not published.

Another study evaluated canakinumab compared with colchicine for prophylaxis of signs and symptoms of acute flares in chronic gout patients initiating allopurinol therapy (NCT00819585) [111]. Single canakinumab doses ≥50 mg or 4-weekly doses provided superior prophylaxis against flares compared with daily colchicine 0.5 mg. There was a 64–72% reduction in the risk of experiencing ≥1 flare for canakinumab doses ≥50 mg versus colchicine at 16 weeks and the percentage of patients experiencing ≥1 flare was significantly lower for all canakinumab doses versus colchicine [35].

Additional long-term safety of canakinumab up to 1 year has been investigated in an open-label extension study (NCT00927810) to collect further efficacy and tolerability data [112]. Patients from the study (NCT00819585) were treated on demand with canakinumab in this extension study [101,111].

The results of two Phase III studies are also available. Trial NCT01029652 and NCT01080131 were designed to demonstrate that canakinumab given upon acute gout flares relieves the signs and symptoms and prevents recurrence of gout flares in patients with frequent flares of gout for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective [113,114]. The efficacy of canakinumab was compared with the corticosteroid triamcinolone acetonide. Patients received either canakinumab 150 mg sc. or triamcinolone acetonide 40 mg intramuscular Canakinumab provided a statistically significant reduction in pain intensity in the target joint at time points

Study identification number (status)	Study purpose	Clinical phase	Treatment arms	Ref.
Table 1. Canakinumab trials in gout.				
NCT00663169 CACZ885A2212 (Completed)	An exploratory proof-of-concept study to evaluate the safety and efficacy of canakinumab for inflammation and pain associated with acute gouty arthritis	Phase II	Experimental: Canakinumab Active comparator: Canakinumab	[110]
NCT00819585 CACZ885H2251 (Completed)	A 24-week, dose-ranging, multicenter, double-blind, double-dummy, active-controlled study to evaluate canakinumab for prophylaxis of signs and symptoms of acute flares in chronic gout patients initiating allopurinol therapy	Phase II	Experimental: Canakinumab 25 mg sc. Canakinumab 50 mg sc. Canakinumab 50 mg sc. followed by canakinumab 25 mg sc. Canakinumab 100 mg sc. Canakinumab 200 mg sc. Canakinumab 300 mg sc. Active comparator: Colchicine 0.5 mg capsule orally	[30,111]
NCT00927810 CACZ885H2251E1 (Completed)	This 24-week open-label extension study is designed to provide additional long-term safety data up to a total of 1-year for patients rolling over from the core study: NCT00819585	Phase II	Experimental: Canakinumab	[111,112]
NCT00798369 CACZ885H2255 (Completed)	This 8-week study is designed to determine the target dose of canakinumab for the management of acute flare in gout patients who are contraindicated to NSAIDs and/or colchicine compared with the corticosteroid triamcinolone acetonide	Phase II	Experimental: Canakinumab 10 mg sc. Canakinumab 25 mg sc. Canakinumab 50 mg sc. Canakinumab 90 mg sc. Canakinumab 150 mg sc. Active comparator: Triamcinolone acetonide 40 mg im.	[28,29, 109]
NCT01029652 CACZ885H2356 (Completed)	To demonstrate that canakinumab given upon acute gout flares relieves the signs and symptoms and prevents recurrence of gout flares in patients with frequent flares of gout for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective. The efficacy of canakinumab was compared with the corticosteroid triamcinolone acetonide	Phase III	Experimental: Canakinumab 150 mg sc. Active comparator: Triamcinolone acetonide 40 mg im.	[113]
NCT01071213 CACZ885H2356E1 (Completed)	An extension study to collect additional safety, tolerability and efficacy data in patients who have completed the core study NCT01029652	Phase III	Experimental: Canakinumab 150 mg sc. Active comparator: Triamcinolone acetonide 40 mg im.	[116]
NCT01160016 CACZ885H2356E2 (Ongoing, but not recruiting participants)	A second extension study is to collect long-term safety and tolerability data and additional efficacy data in patients who are treated on demand upon flare with canakinumab	Phase III	Experimental: Canakinumab 150 mg sc.	[117]
NCT01080131 CACZ885H2357 (Completed)	To demonstrate that canakinumab given upon acute gout flares relieves the signs and symptoms and prevents recurrence of gout flares in patients with frequent flares of gout for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective. The efficacy of canakinumab was compared with the corticosteroid triamcinolone acetonide	Phase III	Experimental: Canakinumab 150 mg sc. Active comparator: Triamcinolone acetonide 40 mg im.	[114]
NCT01137344 CACZ885H2357E1 (Completed)	An extension study is to collect additional safety, tolerability and efficacy data in patients who have completed the core study NCT01080131 to support the registration of canakinumab for the indication of gout	Phase III	Experimental: Canakinumab 150 mg sc. Active comparator: Triamcinolone acetonide 40 mg im.	[114,118]
NCT01194921 CACZ885H2357E2 (Recruiting)	A second extension study to collect long-term safety and tolerability data and additional efficacy data in patients who are treated on demand upon flare with canakinumab	Phase III	Experimental: Canakinumab 150 mg sc.	[119]

im.: Intramuscular; sc.: Subcutaneous.
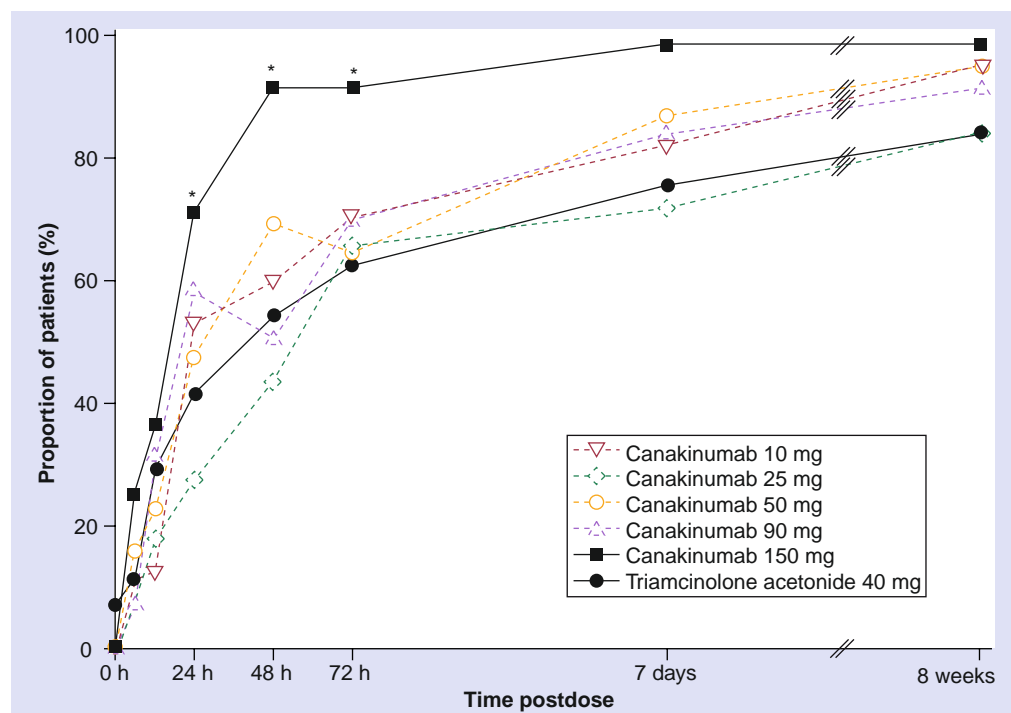
Figure 2. Percentage of patients experiencing no or mild pain, following administration of study drug. Pain reduction in patients with acute gout flare after single dose of canakinumab 150 mg subcutaneous compared with triamcinolone acetonide. The percentage of patients with no or mild pain was numerically greater in most canakinumab groups compared with triamcinolone acetonide from 24 to 72 h postdose and the difference was statistically significant for the 150-mg group at these time points (*p < 0.05 for canakinumab 150 mg vs triamcinolone acetonide 40 mg). Reproduced from study NCT00798369 [34,109].

from 12 h to 7 days postdose compared with triamcinolone acetonide. The median time to 50% reduction in baseline pain (VAS) was significantly less with canakinumab (48 h) than with triamcinolone acetonide (72 h). Canakinumab also delayed the time to first new flare compared with triamcinolone acetonide and percentage of patients with at least one new flare was lower with canakinumab than with triamcinolone acetonide in both studies [36–38].

Commercial information

Canakinumab (Ilaris®, Novartis Pharma S.A.S., France) was approved by the US FDA in 2009 for the treatment of CAPS in adults and children aged 4 years and older including familial cold autoinflammatory syndrome and Muckle–Wells syndrome. The recommended dose is 150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight ≥15 kg and ≤40 kg. For children 15–40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Canakinumab is administered every 8 weeks as a single dose via sc. injection [6].

Canakinumab was also approved by the EMA. The market authorization is valid throughout the EU since October 2009. Canakinumab is approved by the EMA to treat adults and children aged 4 years and older with a body weight of above 15 kg, who have the following types of CAPS: Muckle–Wells syndrome, neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurological, cutaneous, articular syndrome), severe forms of familial cold autoinflammatory syndrome and familial cold urticaria. As the number of patients with CAPS is low, the diseases are considered 'rare', and canakinumab was designated an 'orphan medicine' on 20 March 2007. This product is no longer an orphan medicine. Upon request of the marketing authorization holder, canakinumab has now been removed from the Community Register of orphan medicinal products. Dosage recommendation is similar to that of the FDA. For patients weighing from 15 to 40 kg the recommended dose is 2 mg/kg body weight as a single injection every 8 weeks. For patients weighing more than 40 kg, the recommended dose is 150 mg every 8 weeks. If the patient's symptoms do not improve after 7 days, a second dose can be considered and if the symptoms subsequently improve the patients should then be maintained on a double dose (300 mg or 4 mg/kg) every 8 weeks [39].

Ilaris is approved in more than 40 countries to treat adults and children suffering from CAPS that affect approximately one in one million people. According to sales information of 2010 this market reached US$26 million compared with $3 million in 2009 [115]. Novartis is pursuing expansion into additional indications. Positive results were shown with RA [4] and gout [33–35] and larger clinical trials are ongoing in CAPS, gout and atherosclerosis as a promising indication. In SoJIA a proof-of-concept study has also shown positive results [11] and the results of the other larger SoJIA studies are not yet published.

Conclusion

Canakinumab is a fully human monoclonal antibody to IL-1β. It is developed by Novartis and is approved for the treatment of CAPS in adults, adolescents and children aged 4 years and older by the FDA and the EMA. Other IL-1-blocking agents in the market are rilonacept (Arcalyst™) and anakinra (Kineret®). The advantages of canakinumab compared with these agents are its high specificity to IL-1β and longer half-life. IL-1β is proved to be one of the most important inflammatory cytokines involved in acute gouty inflammation, therefore acute gout is a promising indication for canakinumab treatment. Up to ten clinical studies with canakinumab have been conducted in acute gout to date. The target dose of canakinumab was determined as a single dose of 150 mg sc. in gout flare. This treatment showed superior efficacy compared with 40 mg triamcinolone intramuscular in all assessments during the Phase II study. Canakinumab showed promising results in gout flare prophylaxis as well. Single doses ≥50 mg provided superior prophylaxis compared with daily colchicine. Phase III studies recently showed that canakinumab 150 mg sc. relieves the signs and symptoms and prevents recurrence of gout flares in patients with frequent flares of gout for whom NSAIDs and/or colchicine are contraindicated. Canakinumab is safe and effective alternative for the treatment of acute gout flares for patients that are refractory to standard treatment or have contraindication.

Future perspective

The role of IL-1β has become more important in inflammatory and autoimmune diseases. IL-1-blocking agents have recently been developed for a range of therapeutic indications. Most of these molecules act by blocking the IL-1 receptor or the IL-1β cytokine.

Canakinumab is the third IL-1 inhibitor that has been approved for the treatment of inflammatory disorders after anakinra and rilonacept. It has several advantages compared with these other agents. Canakinumab is highly specific for IL-1β and does not interfere with other IL-1 pathways. It has a longer half-life therefore it does not need to be administered in high doses or in frequent injections.

Standard treatment of acute gout includes NSAIDs or colchicine. However, gout patients frequently have multiple comorbidities therefore NSAIDs or colchicine are often contraindicated. As the incidence and prevalence of gout are increasing [40,41] there is a need for more effective treatments especially for patients that are refractory to standard treatment or have contraindications. Canakinumab is a safe and effective choice for the treatment of acute gout flares and significantly reduces the risk of recurrent flares. It is inappropriate to treat all cases of acute gout in this way, but it is a promising alternative therapy. Other conditions have been successfully treated with the IL-Ra including Still's disease (both juvenile onset and adult types), Schnitzler's syndrome and acute arthritis due to calcium pyrophosphate dihydrate. Suggesting that inflammasome-mediated IL-1 production has a role in the pathophysiology, canakinumab is currently being tested in some of these conditions. In the future, the field of inflammasome research will continue to expand and new therapeutics will target inflammasome activity directly. A selective inhibitor of inflammatory caspases, VX-765 (Vertex Pharmaceuticals, Cambridge, MA, USA) blocks IL-1 secretion in mice and *in vitro* in human cells from patients carrying NLRP3 mutations [42]. Another compound, 17-DMAG, a water-soluble HSP90 inhibitor, which blocks the NLRP3 inflammasome assembly has shown promising results in mice [43]. The increasing knowledge on the mechanism of the inflammatory response to MSU crystals will provide as well new targets for drug development.

Executive summary

- Canakinumab is a high-affinity fully human monoclonal antihuman IL-1β antibody.
- Canakinumab has the pharmacokinetics of an IgG1-type antibody: low volume distribution, low clearance and long half-life (26 days).
- Canakinumab is approved by the US FDA and the EMA in more than 40 countries for the treatment of cryopyrin-associated periodic syndromes.
- Ongoing canakinumab studies target other promising indications such as systemic-onset juvenile idiopathic arthritis, gout and athrosclerosis.
- IL-1β has a pivotal role in inflammatory reactions in acute gout.
- IL-1 inhibition is a safe and effective alternative treatment option in gout flares.
- IL-1 inhibitors on the market to date: anakinra, rilonacept and canakinumab.
- Canakinumab 150 mg subcutaneous provides rapid and sustained pain relief in acute gouty arthritis and significantly reduces the risk of recurrent flares.
- Advantages of canakinumab compared with other IL-1-blocking agents: high specificity to IL-1β, longer half-life therefore no need for high doses or frequent injections.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest

1   Dinarello CA. A clinical perspective of IL-1β as the gatekeeper of inflammation. *Eur. J. Immunol.* 41(5), 1203–1217 (2011).

2   Church LD, Cook GP, McDermott MF. Primer: inflammasomes and interleukin 1beta in inflammatory disorders. *Nat. Clin. Pract. Rheumatol.* 4(1), 34–42 (2008).

3   Dhimolea E. Canakinumab. *MAbs* 2(1), 3–13 (2010).

4   Alten R, Gram H, Joosten LA *et al.* The human anti-IL-1beta monoclonal antibody ACZ885 is effective in joint inflammation models in mice and in a proof-of-concept study in patients with rheumatoid arthritis. *Arthritis Res. Ther.* 10(3), R67 (2008).

5   Church LD, McDermott MF. Canakinumab, a fully-human mAb against IL-1beta for the potential treatment of inflammatory disorders. *Curr. Opin. Mol. Ther.* 11(1), 81–89 (2009).

6   Ilaris®, prescribing information. Novartis Pharma Stein AG, Stein, Switzerland (2009).

7   Bonner J, Lloyd P, Lowe P *et al.* PK/PD, safety and tolerability of a human anti-IL-1B monoclonal antibody (ACZ885) in healthy subjects. Presented at: *Annual Congress of the European Respiratory Society.* Munich, Germany, 2–6 September 2006.

8   Kuemmerle-Deschner JB, Ramos E, Blank N *et al.* Canakinumab (ACZ885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). *Arthritis Res. Ther.* 13(1), R34 (2011).

- **Efficacy of canakinumab in cryopyrin-associated periodic syndrome patients.**

9   Lachmann HJ, Lowe P, Felix SD *et al. In vivo* regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. *J. Exp. Med.* 206(5), 1029–1036 (2009).

10   Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB *et al.* Canakinumab in CAPS Study Group. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N. Engl. J. Med.* 360(23), 2416–2425 (2009).

- **Efficacy of canakinumab in cryopyrin-associated periodic syndrome patients.**

11   Ruperto N, Quartier P, Wulffraat N *et al.* Evaluation of safety and preliminary efficacy of canakinumab (ACZ885), a new IL-1-beta blocking monoclonal antibody, in children with systemic juvenile idiopathic arthritis (sJIA). *Arthritis Rheum.* 60(10), 2055 (2009).

12   Pascoe S, Kanniess F, Bonner J *et al.* A monoclonal antibody to IL-1B attenuates the late asthmatic response to antigen challenge in patients with mild asthma. Presented at: *Annual Congress of the European Respiratory Society.* Munich, Germany, 2–6 September 2006.

13   Martin WJ, Walton M, Harper J. Resident macrophages initiating and driving inflammation in a monosodium urate monohydrate crystal-induced murine peritoneal model of acute gout. *Arthritis Rheum.* 60(1), 281–289 (2009).

14   Schiltz C, Lioté F, Prudhommeaux F *et al.* Monosodium urate monohydrate crystal-induced inflammation *in vivo*: quantitative histomorphometric analysis of cellular events. *Arthritis Rheum.* 46(6), 1643–1650 (2002).

15   Yagnik DR, Evans BJ, Florey O *et al.* Macrophage release of transforming growth factor beta1 during resolution of monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum.* 50(7), 2273–2280 (2004).

16   Di Giovine FS, Malawista SE, Nuki G *et al.* Interleukin 1 (IL 1) as a mediator of crystal arthritis. Stimulation of T cell and synovial fibroblast mitogenesis by urate crystal-induced IL 1. *J. Immunol.* 138(10), 3213–3218 (1987).

17   Liu-Bryan R, Scott P, Sydlaske A *et al.* Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum.* 52(9), 2936–2946 (2005).

18   Martinon F, Pétrilli V, Mayor A *et al.* Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature.* 440(7081), 237–241 (2006).

- **Importance of the NLRP3 inflammasome in monosodium urate crystal-induced inflammation.**

19   Martinon F. Mechanisms of uric acid crystal-mediated autoinflammation. *Immunol. Rev.* 233(1), 218–232 (2010).

20   Narayan S, Pazar B, Ea HK *et al.* Octacalcium phosphate (OCP) crystals induce inflammation *in vivo* through IL-1 but independent of the NLRP3 inflammasome. *Arthritis Rheum.* 63(2), 422–433 (2011).

21   Joosten LA, Netea MG, Fantuzzi G *et al.* Inflammatory arthritis in caspase 1 gene-deficient mice: contribution of proteinase 3 to caspase 1-independent production of bioactive interleukin-1beta. *Arthritis Rheum.* 60(12), 3651–3662 (2009).

22   Coeshott C, Ohnemus C, Pilyavskaya A *et al.* Converting enzyme-independent release of tumor necrosis factor alpha and IL-1beta from a stimulated human monocytic cell line in the presence of activated neutrophils or purified proteinase 3. *Proc. Natl Acad. Sci. USA* 96(11), 6261–6266 (1999).

23 Joosten LA, Netea MG, Mylona E *et al.* Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1β production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. *Arthritis Rheum*. 62(11), 3237–3248 (2010).

▪▪ **Role of free fatty acids in IL-1β secretion induced by monosodium urate crystals.**

24 Agostini L, Martinon F, Burns K *et al.* NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity* 20(3), 319–325 (2004).

25 Kineret®, prescribing information. US FDA (2001–2003).

26 Acralyst™, prescribing information. US FDA (2008).

27 Acralyst™, product information. EMA (2009).

28 Owyang AM, Issafras H, Corbin J *et al.* XOMA 052, a potent, high-affinity monoclonal antibody for the treatment of IL-1β-mediated diseases. *MAbs* 3(1), 49–60 (2011)

29 So A, De Smedt T, Revaz S *et al.* A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res. Ther.* 9(2), R28 (2007).

▪ **Efficacy of anakinra in acute gout.**

30 Terkeltaub R, Sundy JS, Schumacher HR *et al.* The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann. Rheum. Dis.* 68(10), 1613–1617 (2009).

▪ **Efficacy of rilonacept in gouty arthritis.**

31 Schumacher HR, Sundy JS, Terkeltaub R *et al.* Placebo controlled study of rilonacept for gout flare prophylaxis during initiation of urate-lowering therapy. *Arthritis Rheum*. 59, S1096 (2009).

32 Terkeltaub R, Schumacher R, Curtis C *et al.* Evaluation of rilonacept in patients with gouty arthritis experiencing an acute gout attack. *Arthritis Rheum*. 62, S64 (2010) (Abstract 153).

33 So A, De Meulemeester M, Pikhlak A *et al.* Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, Phase II, dose-ranging study. *Arthritis Rheum*. 62(10), 3064–3076 (2010).

▪▪ **Efficacy of canakinumab in acute gout.**

34 Schlesinger N, De Meulemeester M, Pikhlak A *et al.* Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat gouty arthritis by suppressing inflammation: results of a randomized, dose-ranging study. *Arthritis Res. Ther.* 13(2), R53 (2011).

▪▪ **Efficacy of canakinumab in acute gout.**

35 Schlesinger N, Mysler E, Lin HY *et al.* Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. *Ann. Rheum. Dis.* 70(7), 1264–1271 (2011).

▪▪ **Efficacy of canakinumab in gout flare prevention.**

36 Schlesinger N, Schumacher R, Bardin T *et al.* Efficacy of canakinumab versus triamcinolone acetonide in acute gouty arthritis patients: results of the β-relieved II study (Response in acute flare and in prevention of episodes of re-flare in gout). *Ann. Rheum. Dis.* 70(Suppl. 3), 186 (2011).

37 So A, Alten R, Bardin T *et al.* A controlled trial of canakinumab vs triamcinolone acetonide in acute gouty arthritis patients: results of the β-relieved study (response in acute flare and in prevention of episodes of re-flare in gout). *Ann. Rheum. Dis.* 70(Suppl. 3), 104 (2011).

38 Schlesinger N, Alten R, Schumacher H *et al.* Efficacy of canakinumab vs triamcinolone acetonide in preventing recurrent flares in acute gouty arthritis patients contraindicated, intolerant or unresponsive to NSAIDS and/or colchicine: results from two pivotal studies. *Ann. Rheum. Dis.* 70(Suppl. 3), 103 (2011).

39 Ilaris®, product information. EMA (2009).

40 So A. Developments in the scientific and clinical understanding of gout. *Arthritis Res. Ther.* 10(5), 221 (2008).

41 Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res. Ther.* 12(6), 223 (2010).

42 Stack JH, Beaumont K, Larsen PD *et al.* IL-converting enzyme/caspase-1 inhibitor VX-765 blocks the hypersensitive response to an inflammatory stimulus in monocytes from familial cold autoinflammatory syndrome patients. *J. Immunol.* 175(4), 2630–2634 (2005).

43 Mayor A, Martinon F, De Smedt T *et al.* A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses. *Nat. Immunol.* 8(5), 497–503 (2007).

■ Websites

101 Safety, efficacy, pharmacokinetics, pharmacodynamics of ACZ885 in patients with NALP3 mutations and clinical symptoms.
www.clinicaltrials.gov/ct2/show/NCT00487708

102 Safety, tolerability, pharmacokinetics and pharmacodynamics of ACZ885 in patients with rheumatoid arthritis with ongoing treatment with methotrexate.
http://clinicaltrials.gov/ct2/show/NCT00619905?term=NCT00619905&rank=1

103 Safety, efficacy and pharmacokinetics of subcutaneous ACZ885 in patients with systemic juvenile idiopathic arthritis (SJIA).
http://clinicaltrials.gov/ct2/show/NCT00426218?term=NCT00426218&rank=1

104 Flare prevention study of canakinumab in patients with active systemic juvenile idiopathic arthritis (SJIA) (β-SPECIFIC 2).
http://clinicaltrials.gov/ct2/show/NCT00889863?term=NCT00889863&rank=1

105 Single-dose study to assess efficacy of canakinumab (ACZ885) in patients with active systemic juvenile idiopathic arthritis (SJIA) (β-SPECIFIC 1).
http://clinicaltrials.gov/ct2/show/NCT00886769?term=NCT00886769&rank=1

106 US NIH Clinical Trials.
www.clinicaltrials.gov

107 Safety and tolerability of an intravenous infusion of ACZ885 in patients with wet age-related macular degeneration.
http://clinicaltrials.gov/ct2/show/NCT00503022?term=NCT00503022&rank=1

108 Review of safety using rilonacept in preventing gout exacerbations (RE-SURGE).
http://clinicaltrials.gov/ct2/show/NCT00856206?term=NCT00856206&rank=1

109 Targeted dose finding of canakinumab (ACZ885) for management of acute flare in refractory or contraindicated gout patients.
http://clinicaltrials.gov/ct2/show/NCT00798369?term=NCT00798369&rank=1

110 Efficacy and safety of a single dose of ACZ885 in hospitalized patients with acute gout.
http://clinicaltrials.gov/ct2/show/NCT00663169?term=NCT00663169&rank=1

111 Evaluating efficacy of canakinumab (ACZ885) in prevention of acute flares in chronic gout patients initiating allopurinol therapy.
http://clinicaltrials.gov/ct2/show/NCT00819585?term=NCT00819585&rank=1

112 Long term study of canakinumab (ACZ885) in patients with gout.
http://clinicaltrials.gov/ct2/show/NCT00927810?term=NCT00927810&rank=1

113 Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine (β-RELIEVED).
http://clinicaltrials.gov/ct2/show/NCT01029652?term=NCT01029652&rank=1

114   Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use NSAIDs and/or colchicines (β-RELIEVED). http://clinicaltrials.gov/ct2/show/NCT01080131?term=NCT01080131&rank=1

115   Novartis Annual Report 2010. www.novartis.com/downloads/newsroom/corporate-publications/novartis-annual-report-2010-en.pdf

116   Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use NSAIDs and/or colchicine (β-RELIEVED).

http://clinicaltrials.gov/ct2/show/NCT01071213?term=NCT01071213&rank=1

117   Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine (β-RELIEVED). http://clinicaltrials.gov/ct2/show/NCT01160016?term=NCT01160016&rank=1

118   Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use non-steroidal anti-inflammatory

drugs (NSAIDs) and/or colchicine (β-RELIEVED II). http://clinicaltrials.gov/ct2/show/NCT01137344?term=NCT01137344&rank=1

119   Canakinumab in the treatment of acute gout flares and prevention of new flares in patients unable to use NSAIDs and/or colchicine (β-RELIEVED II). http://clinicaltrials.gov/ct2/show/NCT01194921?term=NCT01194921&rank=1