

ILARIS[®] (canakinumab)

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List of abbreviations

AUC	area under the curve of blood/plasma concentration versus time
ADR	adverse drug reaction
AE	adverse event
BMI	body mass index
BP	blood pressure
CAPS	Cryopyrin-associated periodic syndromes
C _{min}	minimum blood/plasma concentration
C _{max}	maximum blood/plasma concentration
CI	confidence interval
CrCl	creatinine clearance
CRP	C-reactive protein
CV	coefficient of variation
DBP	diastolic blood pressure
EOS	end of study
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HV	healthy volunteer
IgG	immunoglobulin G
IL-1 β	interleukin 1 β
i.m.	intramuscular(ly)
ITT	intent to treat
K _d	apparent dissociation constant
N	number of patients in study/treatment group
NSAID	non-steroidal anti-inflammatory drug
MDRD	modification of diet in renal disease study
PD	pharmacodynamics
PK	pharmacokinetics
p.o.	per os/oral(ly)
RA	rheumatoid arthritis
SAA	serum amyloid A
SAE	serious adverse event
s.c.	subcutaneous(ly)
SE/SEM	standard error (of the mean)
SD	standard deviation
SF-36	medical outcome short form health survey
SBP	systolic blood pressure
t $\frac{1}{2}$	elimination half-life

Tmax time of maximum blood/plasma concentration
VAS visual analogue scale

Executive Summary

Gouty arthritis is a chronic, progressive inflammatory arthritis. It is the most common inflammatory arthritis in the US, affecting 3.9% (8.3 million) of US adults, primarily men and is increasing in prevalence (Zhu et al. 2010). Gouty arthritis is an extremely painful and highly debilitating condition which can ultimately lead to irreversible joint damage.

Attacks of gouty arthritis result from monosodium urate (MSU) crystal deposition in and around the joint area. Activation of the NLRP3 inflammasome (also known as NALP 3 inflammasome) upon phagocytosis of MSU crystals by macrophages results in the activation of IL-1 β (from pre-IL1-1 β through caspase1 activation) and its subsequent secretion (Dinarello 2009). IL-1 β promotes an inflammatory cascade that induces neutrophil infiltration of the synovium and further cytokine release, leading to joint pain and swelling.

Genetic ablation of IL-1 or neutralizing IL-1 in animal models of MSU crystal-induced inflammation inhibited neutrophil migration and joint inflammation (Martinon et al 2006, Torres et al 2009). These observations suggest that by selectively targeting IL-1 β and neutralizing this important cytokine, canakinumab may be effective in blocking the inflammation, and therefore pain of gouty arthritis attacks.

The ultimate goal of therapy for the gout patient is to prevent attacks. This can be achieved in a number of patients by bringing elevated uric acid under control to prevent crystal formation. However, this is not achievable for all patients and even those with urate levels in the normal range may continue to have acute gout attacks.

The mainstays for treatment of acute attacks are the use of NSAIDs, colchicine, steroids, and/or narcotics. For a variety of reasons, there exists a subset of patients who require alternative treatment options due to frequent and/or severe attacks that may not be adequately managed with conventional therapy of NSAIDs or colchicine. For such patients additional treatment options for acute pain, beyond steroids and narcotics, are needed. Additionally, gouty arthritis attacks are unpredictable and may be frequent. A therapeutic option that could both treat the acute attack and delay the occurrence of new attacks would provide a novel approach for this patient population.

Canakinumab is a high-affinity, targeted human monoclonal antibody that selectively binds and neutralizes IL-1 β and thereby interrupts the signaling pathway of crystal-induced inflammation in gouty arthritis. It does not bind IL-1 α or IL-1 receptor antagonist (IL-1ra), thus avoiding potential toxicities and unwanted effects associated with broader inhibition of this signaling pathway potentially related to the anti-tumor surveillance (Elkabets 2009). Furthermore, C-reactive protein (CRP), an indicator of inflammatory disease, was rapidly reduced to normal levels in early clinical studies with canakinumab.

ILARIS (canakinumab, ACZ885) was initially approved in June 2009 for cryopyrin-associated periodic syndrome (CAPS) for adults and children age four years of age and older.

This document summarizes the efficacy and safety data from the clinical development program supporting the use of canakinumab for treatment of acute gout attacks and reduction in frequency of subsequent attacks in gouty arthritis patients.

The proposed indication reflects the population studied and the data from the pivotal trials:

ILARIS (canakinumab) is an interleukin-1 β blocker indicated for the treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDs or colchicine. ILARIS has also been shown to extend the time to next attack and reduce the frequency of subsequent attacks.

This intended gouty arthritis population for this treatment option includes patients who are intolerant of or contraindicated to NSAIDs and/or colchicine or for those who have inadequate response to these conventional anti-inflammatory agents. It is estimated that this novel, potent, targeted anti-inflammatory monoclonal therapy would be considered a treatment option for only a small proportion (<10%) of the overall treated gouty arthritis patients in the US (~300,000 patients).

The program for the treatment of acute gouty arthritis attacks consisted of a phase 2 dose-finding study (H2255) and two identical 12 week pivotal phase 3 core studies (H2356 and H2357). Each of these studies included an additional 12 week, double-blinded extension (H2356E1 and H2357E1) for a combined total of 24 weeks of observation. A second extension study (12 months duration for a total of 18 months) is currently ongoing for each of these studies. Study H2356 core and its E1 extension was conducted primarily in Europe while Study H2357 core and its E1 extension was conducted primarily in the US.

The phase 2 study evaluated a wide dose range (10 mg–150 mg) of canakinumab. Based on superior efficacy with 150 mg administered subcutaneously and an acceptable safety profile, this dose was selected to carry forward in the two phase 3 studies. These data and the proposed phase 3 study designs, including dose selection, patient criteria and study endpoints were discussed and agreed with FDA prior to initiation of the phase 3 program.

The two pivotal gouty arthritis phase 3 trials were identical in design. The primary objectives for both pivotal phase 3 trials were to confirm that 150 mg of canakinumab, given subcutaneously, provided superior pain relief on the patient's assessment of pain on a 0-100 mm visual analogue scale (VAS) at 72 hours, and was superior in delaying the time to the first new gout attack compared with an active comparator (triamcinolone acetonide (TA) 40 mg, intramuscularly administered) over 12 weeks.

The VAS pain intensity co-primary variable was analyzed using an analysis of covariance model with adjustments for treatment as a factor and baseline VAS and BMI as covariates. This analysis is equivalent to one that uses change from baseline VAS pain as the response variable. The co-primary time to first new attack variable was analyzed using a Cox regression model containing treatment and BMI. From this model hazard ratios were estimated for the risk of a new attack.

To enter the study, patients were required to have had at least three gout attacks in the prior 12 months and have evidence of contraindication (absolute or relative), or intolerance or lack of efficacy with NSAIDs or colchicine, based on medical history. At entry, patients had to be experiencing an acute attack of ≤ 5 days since onset, with pain intensity > 50 mm on the 0-100 mm VAS.

Both co-primary endpoints (VAS pain and time to next attack) were statistically and clinically significant in each core study individually and in the pooled analysis. The results also demonstrated that the delay in subsequent attacks continued through the entire 24 week period post-randomization in the E1 extension portions of the trials.

For the VAS pain co-primary endpoint at the 72 hours, the estimated difference between canakinumab and the active comparator was statistically significant and clinically meaningful with canakinumab superior to the active comparator [-11.4 mm, $p=0.0005$ for in H2356; and -9.8 mm in H2357, $p=0.0018$].

Within the canakinumab groups for the acute attack, canakinumab treated patients had early clinically meaningful mean VAS pain score reduction of -16.1 mm (H2356) and -16.6 (H2357) from baseline at 6 hours, the earliest measurement, after treatment was initiated. By 48 hours the mean reduction was > -40 mm in both studies and by 72 hours, the time of the primary endpoint, the mean VAS pain score reduction was -45.9 mm in H2356 and -53.4 mm in H2357, the study conducted primarily in the US.

For the co-primary endpoint of time to first new attack highly statistically significant hazard ratios of 0.45 ($p=0.001$) and 0.32 ($p<0.0001$), for H2356 and H2357, respectively, were observed in favor of canakinumab. This pattern was retained through the additional 12 week extension studies with estimated hazard ratios of 0.48 ($p=0.0003$) and 0.44 ($p<0.0001$) through the 24 week total observation period from randomization in H2356E1 and H2357E1.

Most patients (68 % in H2356E1; 75% in study H2357E1; and 72% of patients overall) were without a new attack through 24 weeks post-randomization. Among patients who did receive retreatment during the 24 weeks of the core and extension studies, the response to the initial treatment was predictive of the response to subsequent treatments. Thus, for the few patients who do not have a good reduction in pain initially and have another attack, re-treatment is not recommended.

The overall safety experience includes over 2,500 patients from the use of canakinumab in CAPS, RA, gout and clinical trials in other indications. Thus, the overall safety is examined across a variety of patient populations, doses, durations and routes of administration.

The initial focus in the safety section will be on the safety observed in the treatment of gouty arthritis program. The integrated safety experience observed in the overall gout population and the RA population will follow. Finally, the entirety of the safety database is examined, by indication, for events of special interest, including, infections and malignancies, hematologic and serum chemistry changes, cardiac, renal or hepatic events, as well as immunogenicity and potential hypersensitivity events.

In the pivotal gouty arthritis trials, including the double blind E1 extensions through 24 weeks of observation, there was a higher incidence of adverse events in H2356E1 and H2357E1, respectively with canakinumab (62.8% and 69.6 %) compared with TA (48.7% and 57.0 %), driven primarily by an imbalance in infections (22.1% and 18.8% with canakinumab vs. 15.7% and 8.8% with TA). This imbalance is consistent with increased risk of infections previously identified in the approved CAPS indication.

Although most infections were mild or moderate upper respiratory infections, there were four serious infections in the phase 3 pivotal gouty arthritis studies (1.6%) that required hospitalization (two abscesses, one pneumonia and one gastroenteritis). Among these, one clinically complicated case of pneumonia in a patient with multiple co-morbidities, died during the second extension (E2) approximately three months after the second dose and last dose of canakinumab, the remainder were treated, recovered and continued in the study. An imbalance in the incidence of infections was not seen at the 150 mg dose in the rheumatoid arthritis (RA) dataset. None of the infections observed in the entire safety database were identified as opportunistic. An increased risk of infections, including serious infections, is included as a Warning in the currently approved label for CAPS.

There was also a higher incidence of serious adverse events (SAEs) reported for patients on canakinumab than on triamcinolone acetonide in each of the pivotal gouty arthritis studies. In general, these SAEs were single occurrences, without a consistent pattern, and were not suspected by the investigator to be related to study drug. These are all discussed in further detail in the integrated safety section.

Mild hematologic effects with decreases in white blood cells, neutrophils and platelets associated with canakinumab were also observed. All resolved without intervention and there were no events of bleeding that were associated with the transient thrombocytopenia. In the pooled gouty arthritis dataset, one patient treated with canakinumab had a serious infection (jaw abscess) from Day 29 to 86 and, a low neutrophil count ($1.5 \times 10^9/L$) on Day 58. This patient had low neutrophil count at baseline, Day 4 ($1.9 \times 10^9/L$) and normal neutrophil counts on Day 28 ($3.13 \times 10^9/L$), one day before the infection, and again on Day 86 ($2.57 \times 10^9/L$). All of the data on infections and decreased neutrophils are discussed in depth in the section on Safety topics special interest.

Additionally in the gouty arthritis population, mild transient increases in uric acid levels were observed with canakinumab. This is likely due to the mechanism of action by which IL-1 β inhibition results also in inhibition of IL-6, a known uricosiuric. The elevations of serum urate were modest and transient.

There were no new safety signals and no negative impacts on hepatic, renal or cardiac systems that emerged.

The safety data supports a positive benefit/risk profile for the use of canakinumab for the selected population in the proposed indication for patients with severe gouty arthritis who may not be candidates for NSAIDs or colchicine and for whom a prolonged interval between attacks is important.

As a targeted therapy against IL-1 β , canakinumab directly neutralizes one of the key inflammatory pathways involved in the pathogenesis of gouty arthritis. Canakinumab at 150 mg s.c. administered early during the gouty arthritis attack, showed substantial efficacy benefits in the treatment of gouty arthritis in two identical randomized, controlled clinical trials against an active comparator. Canakinumab also delayed the time to subsequent attacks, as shown by reducing the probability of a new attack, thereby increasing the number of patients free of new attacks and reducing the average number of attacks per patient. This effect

was observed during both the 12 week and 24 week periods studied. Efficacy during re-treatment is predictable

No new safety risks were identified in the gouty arthritis program beyond those identified for the CAPS indication. The identified risks linked to the use of canakinumab relate primarily to infections. Important potential risks based on the mechanism of action and molecular properties are outlined in the safety section. These include, but are not limited to, opportunistic infections, neutropenia, immunogenicity/ allergenicity, injection site reactions and increased risk of malignancy.

In summary, canakinumab has a positive overall benefit/risk ratio for the intended population of gouty arthritis patients who cannot obtain adequate response with NSAIDs and/or colchicine. It is generally well tolerated with an acceptable safety profile. In patients who have failed or cannot take first-line therapies, there is a need for effective management of an attack of gouty arthritis. By lowering the frequency of attacks and thereby reducing the need for use of additional medications, canakinumab can provide meaningful benefit for the relatively small (estimated approximately 300,000 patients in the US) who need new options. By neutralizing a key cytokine that causes the inflammatory pain, canakinumab can alleviate the suffering associated with an attack of gouty arthritis for this group.

1 Introduction

1.1 Unmet medical need in gouty arthritis

Gouty arthritis is a chronic, progressive inflammatory arthritis. It is the most common inflammatory arthritis in the US, affecting 3.9% (8.3 million) of US adults, primarily men, and its prevalence is increasing (Zhu et al 2010).

Attacks of gouty arthritis result from monosodium urate (MSU) crystal deposition in and around the joint area. Activation of the inflammasome upon phagocytosis of MSU crystals (e.g., by macrophages) results in secretion of IL-1 β . IL-1 β promotes an inflammatory cascade that induces neutrophil infiltration of the synovium, leading to joint pain and swelling.

Gouty arthritis attacks are characterized by acute, exquisitely painful and debilitating episodes of inflammation. In a study of 298 gouty arthritis patients, 62% described the pain of an attack as “severe,” “very severe,” or the “worst imaginable.” The average pain of an attack was rated as 6.72 (out of 10) on a visual analog scale (Lee et al 2009). Indeed, the pain of a gouty arthritis attack can have substantial negative impact on the patient, limiting physical activity, reducing work productivity, and can lead to excessive healthcare utilization (Lee et al 2009, Singh et al 2010, Edwards et al 2011).

The mainstay of treatment for gouty arthritis attacks are anti-inflammatory therapies, including NSAIDs, colchicine, and corticosteroids. Many patients are well-managed with these treatments. However, there is a subset of patients who cannot obtain an adequate response with conventional agents due to absolute or relative contraindications, being intolerant, or experiencing suboptimal efficacy with these medications (Keenan et al 2011). Today, this patient population lacks a treatment option.

A brief review of traditional therapies for gouty arthritis attacks highlights this treatment challenge for physicians and the medical need for patients.

NSAIDs are used widely to relieve pain and inflammation in gouty arthritis, but may not be advisable in patients with certain comorbidities (e.g. chronic kidney disease, chronic liver disease, cardiovascular disease, heart failure, peptic ulcer disease) or who are receiving comorbidity-related medications, such as antiplatelet agents or blockers of the renin-angiotensin-aldosterone system.

Colchicine is used less frequently, compared with NSAIDs, as the narrow therapeutic index of colchicine also carries with it risk of neuromuscular toxicity and rhabdomyolysis. Risk of toxicity is increased in patients with chronic kidney disease or chronic liver disease, and the drug is contraindicated in patients with those comorbidities who are also receiving P-glycoprotein inhibitors or strong CYP450 3A4 inhibitors.

Local and systemic corticosteroids are often used when a patient is unable to obtain an adequate response to NSAIDs and/or colchicine, however, this option may put the patient at risk for fluid retention, elevated blood pressure, and dysglycemia. These effects may be of particular concern when corticosteroids are repeatedly administered in patients with frequent attacks and comorbidities such as diabetes, hypertension, or heart failure.

In addition to anti-inflammatory therapies, it is important to consider urate-lowering therapy, which is used to prevent gouty arthritis attacks by reducing serum uric acid levels. The effectiveness of urate-lowering therapy in preventing attacks is proven. This benefit is dependent upon achieving target uric acid levels at which attacks occur less frequently (<6 mg/dL). However, many patients fail to achieve adequate uric acid control; only about 50% of treatment-compliant patients reach the desired target levels (Halpern et al 2009a).

Moreover, urate-lowering therapy, like many chronic, maintenance therapies, is associated with high non-adherence rates – approximately 50% for allopurinol, the most widely prescribed urate-lowering therapy (Solomon et al 2008, Halpern et al 2009a, Harrold et al 2009). One factor that may contribute to non-adherence with this class is the increase in acute attacks of gout that can be observed shortly after initiating urate-lowering medication. Anti-inflammatory agents may be provided in this setting to reduce the likelihood of such “paradoxical flares.” In addition, it is clear that some patients will experience attacks of gouty arthritis in the setting of normal (<6 mg/dL) serum urate levels (Halpern et al 2009b, Wu et al 2009).

Gouty arthritis is an ancient disease, with a well-described pathophysiology. The current standard of care for gouty arthritis attacks is composed of traditional anti-inflammatory agents whose utility may be limited, particularly in patients with prohibitive comorbidities and medications. Therefore, there is a need for a new option to treat gouty arthritis attacks, particularly for those patients who are frequently flaring and unable to obtain an adequate response to NSAIDs or colchicine.

1.2 Mechanism of action of canakinumab

Canakinumab (ACZ885) is a high-affinity human monoclonal antibody targeted against interleukin-1 β (IL-1 β), developed to bind and neutralize the excess IL-1 β produced in medically appropriate inflammatory diseases. IL-1 β is released by mononuclear phagocytes upon injury or infection and plays a dominant role in the pathobiology of inflammatory conditions, including Cryopyrin-Associated Periodic Syndrome (CAPS) and gouty arthritis attacks. Canakinumab, by interrupting the signaling pathway of crystal-induced inflammation, both treats and reduces subsequent gouty arthritis attacks.

Gout is a condition characterized by the deposition of uric acid crystals primarily in joints. Uric acid crystals may then trigger an acute inflammatory response in the affected joint which results in extreme pain and edema. On a cellular level, gouty attacks are characterized by massive infiltration and activation of neutrophils into the joint cavity (Schumacher 2008, Popa-Nita and Naccache 2010). A causal relationship between monosodium urate crystals (MSU) and neutrophil influx and activation was demonstrated in animals (Phelps and McCarty 1966, Martin et al 2009).

The cellular pathophysiological mechanism of joint inflammation in gout has been recently connected to the hyperproduction of IL-1 β by selective activation of the NLRP3 inflammasome by monosodium urate (MSU) crystals (Di Giovine et al 1987, Martinon et al 2006). IL-1 β is produced as an inactive precursor protein (pro-IL-1 β) which remains intracellular. The production of pro-IL-1 β is tightly regulated at the transcriptional level.

Typically, IL-1 β mRNA is induced by cytokines, interleukins or ligands of Toll-like receptors. The cleavage of the pro-IL-1 β precursor by caspase I and release of bioactive IL-1 β from cells is regulated at the post-translational level by the inflammasome, a multi-protein complex which is able to respond to extracellular and intracellular stimuli (Martinon and Tschopp 2004).

Proteins constituting the inflammasome belong to a large family termed Nod-like receptors (NLRs) (Petrilli et al 2007). NLRP3 is an extensively studied member of the NLR family consisting of different domains which facilitate the interaction with other inflammasome components and likely regulate its activity. The inflammasome can be assembled by different components in different cell types and conditions; however, the NLRP3 seems to play a pivotal role in the regulation of the inflammasome by ATP, aluminium hydroxide and importantly in gout – uric acid (Martinon et al 2007, Eisenbarth and Flavell 2009).

Further studies revealed the role of resident macrophages for urate crystal-induced IL-1 β production and the subsequent chemoattraction of neutrophils (Martin et al 2009). Genetic ablation of IL-1 or neutralizing IL-1 in animal models of MSU crystal-induced inflammation inhibited neutrophil migration and joint inflammation (Martinon et al 2006; Torres et al 2009). All these preclinical experiments in vivo or ex vivo demonstrated a sequence of cellular events which unequivocally establish the pivotal role of IL-1 in inflammation induced by urate crystals.

Thus, canakinumab is the first of a new kind of targeted anti-inflammatory agents that instead of inhibiting late inflammatory events, such as NSAID or steroids, acts very specifically on an early, causal event. The clinical data show that canakinumab not only provides significant pain relief and reduction in inflammation when treating the acute attack, but also delays the onset of new attacks, resulting in a reduced frequency of attacks.

1.3 Regulatory History

The first approval for canakinumab was granted by the FDA (BLA, No: 125,319) in June 2009 for the orphan indication of the treatment of Cryopyrin-Associated Periodic Syndrome (CAPS) in patients ≥ 4 years of age. Since then additional regulatory approvals have been granted by Health Authorities worldwide. Currently canakinumab is approved in more than 45 countries for the treatment of CAPS.

Based on the mode of action, an increased risk of infections was identified as a safety risk associated with canakinumab treatment and is reflected in the currently approved USPI:

“Interleukin-1 blockade may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections. ILARIS has been associated with an increased incidence of serious infections. Physicians should exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Discontinue treatment with ILARIS if a patient develops a serious infection. Do not administer ILARIS to patients during an active infection requiring medical intervention. Infections, predominantly of the upper respiratory tract, in some instances

serious, have been reported with ILARIS. Generally, the observed infections responded to standard therapy.

The most commonly reported adverse reactions associated with ILARIS treatment in the CAPS patients were nasopharyngitis, diarrhea, influenza, headache, and nausea. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.”

The cumulative post-marketing exposure in CAPS since the first launch of the product is estimated to be 314 patient-treatment years (cut-off 31-Dec-2010). Overall, experience from post-marketing confirms that canakinumab is well tolerated and safe with a favorable benefit-risk profile in the approved indication. The post-marketing data are consistent with the safety profile reported from clinical trials in gouty arthritis, with no new risks identified in the gouty arthritis patient population.

For the treatment of gouty arthritis, following the agreement on study design (End of Phase II meeting) in Nov 2009 and pre-submission meeting in June 2010, Novartis Pharmaceuticals submitted a supplemental BLA to the FDA on 28-Feb-2011 to support the use of canakinumab in gouty arthritis. The 120 day Safety Update was submitted on 05-May-2011 and review of this new safety data demonstrates a consistent safety profile when compared to the original submission.

The current application is the first supplemental BLA to be submitted for canakinumab.

1.4 Nonclinical summary

Published preclinical experiments in vivo or ex vivo define the cellular events which establish a pivotal role of IL-1 in the inflammation induced by urate crystals (Phelps and McCarty 1966, Di Giovine et al 1987, Martinon et al 2007, Schumacher 2008, Popa-Nita and Naccache 2010, Martin et al 2009, Torres et al 2009). This hypothesis was proven by the clinical use of recombinant IL-1ra, (anakinra) in acute gout, which led to a rapid relief of symptoms (So et al 2007).

The nonclinical program was completed for the initial BLA supporting approval of the CAPS indication. Following scientific advice by the FDA, the nonclinical program was determined adequate to support the gouty arthritis indication. Thus no new/additional toxicological investigations were performed.

The toxicological testing of canakinumab followed the recommendations provided by FDA to support the clinical development program of this biotechnology product. The design of the non-clinical testing program for canakinumab was based also on the ICH S6 guidance for the non-clinical development of biotechnology pharmaceuticals.

The nonclinical experiments in the canakinumab development program confirmed the therapeutic potential and mechanism of action of this targeted anti-IL-1 β monoclonal antibody and demonstrated the principal safety characteristics of the molecule.

Given the therapeutic indications, the biology of canakinumab and its classification as a biologic therapeutic, a comprehensive and appropriate preclinical evaluation of pharmacology, pharmacokinetics and safety was performed.

2 Overview of the clinical development program

The clinical development of canakinumab to support the treatment of gouty arthritis was composed of clinical pharmacology and clinical studies in:

- healthy subjects (vaccination study), gouty arthritis and RA patients (PK/PD evaluation)
- gouty arthritis patients for treating acute attacks (claimed indication)
- gouty arthritis patients to prevent attacks when starting urate-lowering therapy (not claimed, contributes to PK/PD and safety data)
- rheumatoid arthritis patients (not claimed, contributes to PK/PD and safety data)
- other indications (not claimed, contribute to the assessment of fatal and non-fatal SAEs)

2.1 Studies with clinical pharmacology assessments

New clinical pharmacology studies consist of a vaccination study [Study A2106] and 16 clinical studies (1411 subjects) which included PK/PD assessments, with data fitted to a dynamic drug-ligand binding and turnover model to generate PK and PD parameters, as indicated in Table 2-1.

Table 2-1 Recent clinical studies added to the PK/PD modeling database

Study	Patient population	No. analyzed	Dose regimen(s)
Gouty arthritis studies			
A2212	Hospitalized patients with acute gout	3	10 mg/kg 2 hr i.v. infusion SD
H2251	Chronic gout patients starting allopurinol	323	25, 50, 100, 200, or 300 mg s.c. SD or 50 mg s.c. on Days 1, 29 + 25 mg s.c. on Days 57, 85
H2251E1	Patients with gout who completed the core study (H2251)		150 mg s.c. SD Redosing upon attack
H2255	Gout patients refractory or contraindicated to NSAIDs and/or colchicine	143	10, 25, 50, 90 or 150 mg s.c. SD
H2356 H2357	Gout patients with frequent attacks in refractory or contraindicated to NSAIDs and/or colchicine	113 + 113	150 mg s.c. SD Redosing upon attack
H2356E1 H2357E1	Gout patients who completed the core study (H2356 or H2357)		150 mg s.c. (dosed upon attack)
RA studies			
A2201	Patients with active RA	262	600 mg i.v. + 300 mg s.c. q 2 wk 300 mg s.c. q 2wk 150 mg s.c. q4wk
A2201E1 A2201E2	Patients with active RA who completed the core study		300 mg s.c. q4wk 300 mg s.c. q2wk (incomplete response) Dose lowered to 150 mg later in study
A2204	Early RA patients	52	600 mg 2 hr i.v. infusion on Days 1, 15 then q4wk up to 26 weeks.
A2206	Adult patients with established RA	12	2 or 10 mg/kg s.c. or 1 or 5 mg/kg i.v. inf. on Days 1 and 15

Study	Patient population	No. analyzed	Dose regimen(s)
A2207	Healthy subjects	60	600 mg i.v. inf. on Day 1
	Adult patients with established RA	115	600 mg i.v. inf. on Days 1, 15, 43
A2211	Patients with RA who completed a core study (A2204, A2206, A2207)	163	600 mg i.v. inf. q6wk
CAPS studies			
D2306	CAPS patients	52	150 or 300 mg s.c. (adults & peds >40 kg) 2 or 4 mg/kg s.c. for peds ≤40 kg q8wk

SD = single dose, inf. = 2 hour i.v. infusion, peds = pediatric patients, qxwk = every x weeks
RA = rheumatoid arthritis, CAPS = Cryopyrin-Associated Periodic Syndromes

2.2 Studies in gouty arthritis

2.2.1 Treating gouty arthritis attacks

There were 3 sets of studies performed in gouty arthritis patients to treat acute attacks, which form the basis for the efficacy claim for treating acute gouty arthritis attacks and are summarized in Table 2-2:

- 1 dose-ranging study of 5 doses against an active control
- 2 adequate and well-controlled trials against an active comparator to show efficacy
- 2 controlled extensions against an active comparator to show longer-term safety / efficacy.

In 2 ongoing open-label extension studies with completed recruitment, canakinumab patients receive the same treatment as previously, and triamcinolone acetonide patients are switched to canakinumab after their second attack.

2.2.2 Preventing acute attacks when starting urate lowering therapy

There were 2 studies performed in gouty arthritis patients to prevent attacks, which did not contribute to the efficacy claim, but were used to assess PK/PD and safety in gouty arthritis patients and are summarized in Table 2-2:

- 1 dose-exploration study of single and multiple doses against an active control
- 1 uncontrolled, open-label extension to the dose-exploration study

Table 2-2 Studies to treat or prevent gouty arthritis attacks

Study	Objectives	Treated	Duration	Treatment
Treating acute attacks and reducing attack rate (claimed)				
Dose-ranging study				
H2255	Dose-ranging / efficacy / safety for acute attacks in patients unable to use NSAIDs / colchicine	200	8 wks	10mg s.c. (n=28) 25mg s.c. (n=29) 50mg s.c. (n=29) 90mg s.c. (n=29) 150mg s.c. (n=28) 40mg i.m. triamcinolone acetonide (n=57)
Pivotal studies and their extensions				
H2356/E1	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine (blinded)	228	12 wks/ +12 wks (24 total)	150mg s.c. (n=113) 40mg i.m. triamcinolone acetonide (n=115)
H2357/E1	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine (blinded)	226	12 wks/ +12 wks (24 total)	150mg s.c. (n=112) 40mg i.m. triamcinolone acetonide (n=114)
Further extension studies (recruitment completed, but studies still ongoing)				
H2356/E2 and H2357/E2	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine (open-label)	271	12 wks/ +12 wks/ +48 wks (72 total)	150mg s.c. (n= 140) 40mg i.m. triamcinolone acetonide (n=131) [2 groups until 24 weeks, after which non-ACZ patients are switched to ACZ]
Preventing attacks when starting uric acid lowering therapy (not claimed)				
Early study				
H2251	Dose finding/ efficacy/safety in gouty arthritis patients starting allopurinol comparing single & multiple doses	431	24 wks	25 or 50mg s.c. Day 1 (n=55, 54) 50mg s.c. D1, 29 & 25mg s.c. D57, 85 (n=53) 100, 200 or 300mg s.c. Day 1 (n=54, 54, 53) 0.5mg colchicine p.o. (n=108)
Uncontrolled, open-label extension				
H2251E1	Safety/efficacy extension in patients continuing allopurinol & treated with canakinumab on demand for acute attack	341 (entered extension)	24 wks	150mg s.c. (n=100) of whom: - 75 took ACZ in the core (Group A), - 25 took colchicine in the core (Group C) No treatment in extension (n=241) of whom: - 181 took ACZ in the core (Group B), - 60 took colchicine in the core (Group D)]

wks = weeks, E = extension study, D = day, ACZ = canakinumab

2.3 Studies in rheumatoid arthritis

There were 8 studies in rheumatoid arthritis patients, which did not contribute to an efficacy claim, but were used to assess PK/PD and safety, and are summarized in Table 2-3:

- 4 double-blind studies against a placebo control
- 4 uncontrolled, open-label studies.

Table 2-3 Studies in rheumatoid arthritis

Study	Objectives	Number	Duration	Treatment
Placebo-controlled, double-blind studies				
A2101	Safety / tolerability / dose escalation / PK/PD in RA patients taking methotrexate	53	17 wks	0.3–10mg i.v. placebo
A2201	Dose finding in RA patients	274	12 wks	150 or 300mg s.c. 600mg .i.v.+ 300mg s.c. placebo
A2204	Efficacy / safety and biomarker profiling in early RA patients taking methotrexate	78	26 wks	600mg .i.v. placebo
A2207	Efficacy / biomarker profiling study in RA patients compared to healthy subjects	60 RA 20 healthy subj.	12 wks	600mg .i.v. placebo
Uncontrolled, open-label studies				
A2206	Exploratory open-label PK/PD, i.v. versus s.c. dosing in established RA patients	13	6 wks	1 or 5mg i.v. 2 or 10mg s.c.
A2201E1	Safety/efficacy in RA patients	227	76 wks	300mg s.c.
A2201E2	Safety/efficacy in RA patients	51	96 wks	300mg s.c.
A2211	Safety/efficacy in RA patients (extension study to studies 22044/6/7)	115	54 wks	600 mg i.v.

RA = rheumatoid arthritis, wks = weeks

2.4 Studies in other indications

There are studies in other indications that contribute key safety information on deaths and non-fatal SAEs. Completed studies have been conducted in CAPS, psoriasis, mild asthmatics and age-related macular degeneration (AMD). Ongoing studies are currently being conducted in: healthy volunteers (1), CAPS (5), systemic juvenile idiopathic arthritis (sJIA) (3), diabetes mellitus (4), chronic obstructive pulmonary disease (COPD) (1), dry eye syndrome (1), osteoarthritis (1), TNF-receptor-associated period syndrome (1), urticarial vasculitis (1), polymyalgia rheumatica (1) and familial Mediterranean fever (2).

3 Clinical Pharmacology

The PK/PD for this application includes studies in healthy volunteers, gouty arthritis patients and patients with rheumatoid arthritis. Population pharmacokinetics was also evaluated, thereby extending the earlier findings from CAPS to include these new populations.

3.1 Pharmacokinetics in gouty arthritis patients

No clinically significant differences (after correction for body weight) in the PK of canakinumab in patients with gouty arthritis compared to patients with CAPS were observed.

In gouty arthritis patients weighing 93 kg, the estimated serum clearance of canakinumab was 0.232 ± 0.012 (mean \pm SEM) L/day, consistent with the clearance values for human IgG molecules, resulting in a half-life ($t_{1/2}$) of 25.6 days. The distribution volume at steady state was 7.92 L, which is above serum volume and characteristic for the distribution of large macromolecules.

The estimated absolute bioavailability of s.c. canakinumab was $62.9 \pm 3.46\%$. For repeated administration of 150 mg s.c. every 12 weeks in adult gout patients, the estimated steady state C_{\max} and AUC (for 12 weeks) were 11.3 $\mu\text{g/mL}$ and 404 $\mu\text{g}\cdot\text{day/mL}$, respectively.

To evaluate the potential accumulation of canakinumab, exposure levels for various dosing intervals were simulated to address different frequencies of retreatment. Following repeated 150 mg s.c. dosing every 2, 4, 8 and 12 weeks, the expected accumulation ratio of canakinumab in gouty arthritis patients was 3.6, 2.0, 1.3 and 1.1-fold respectively. Canakinumab displayed dose independent PK properties, with clearance remaining unchanged within the dose range studied in gouty arthritis patients (10 mg to 300 mg s.c.). There was no indication of changes in PK properties over time.

No clinically significant changes in the PK of canakinumab were observed as a result of differences in gender and age. However, both the serum clearance of canakinumab and its volume of distribution were found to depend upon body weight.

The mean serum clearance of canakinumab in gout patients was 14% and 24% lower with mild (CrCl: 50–80 mL/min) and moderate (CrCl: 30–<50 mL/min) renal impairment, as compared to normal renal function (CrCl >80 mL/min). Relative to the inter-subject variability in the clearance of canakinumab (about 36% CV) across all subjects investigated, there is no clinically relevant impact of renal function on canakinumab clearance, and dose adjustment in patients with mild/moderate renal impairment is not needed.

No formal studies were performed with canakinumab in patients with impaired hepatic function or with more severely impaired renal function, as it is known that the majority of IgG elimination occurs via intracellular catabolism following fluid-phase or receptor-mediated endocytosis and is largely independent of hepatic or renal function. Thus, as with other monoclonal antibodies, no dose adjustment is needed for hepatic or renal impairment.

3.2 Metabolism

The metabolism of canakinumab was not studied, as IgGs are not metabolized in the liver or excreted in bile or urine, but broken down intracellularly in the reticular endothelial system.

3.3 Drug interactions

No specific interaction studies were performed. Clinical data show that canakinumab can be safely administered with urate-lowering therapies and with medications frequently used to treat the common comorbidities occurring in gouty arthritis patients (e.g. hypertension, diabetes, metabolic syndrome, chronic kidney disease, and heart failure).

The use of anakinra with etanercept was reported to worsen the safety profile compared to each drug alone and provided no additional benefit to rheumatoid arthritis patients (Genovese et al 2004). Thus, the use of canakinumab plus a TNF- α inhibitor, although not tested, is also not recommended.

It was reported that the synthesis of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1, IL-6, TNF- α) during chronic inflammation (Sunman et al 2004, Aitken and Morgan 2007, Chaluvadi et al 2009). Anti-cytokine antibodies such as

canakinumab that target and neutralize these proinflammatory cytokines or their receptors are capable of restoring CYP450 enzymes to normal levels (Ashino et al 2007). Thus, a biologic such as canakinumab that reverses inflammation could lead to drug interactions by restoring CYP450s to normal levels and raising the clearance of co-administered drugs metabolized by CYP450. The product information of canakinumab for CAPS patients (Ilaris[®]) mentions the potential pathways of interaction affecting the exposure of concomitant medications by canakinumab.

3.4 Desired pharmacodynamic effect

Canakinumab is targeted to, binds to and inactivates IL-1 β , thereby reducing the effects of IL-1 signaling, which results in a reduction of the signs and symptoms of inflammation. The *in vivo* binding of canakinumab to IL-1 β was confirmed in all gouty arthritis patients, based on the increase in total IL-1 β , similar to that seen in other clinical trial subjects and healthy volunteers.

This phenomenon was seen for all drug forms, including the D form used in pivotal Phase 3 trials and intended for marketing. The population estimate from the PK-binding model of the apparent *in vivo* dissociation constant for the binding of canakinumab to IL-1 β was 1.01 ± 0.124 (mean \pm SEM) nM in gouty arthritis patients.

3.5 Efficacy of vaccination

Study A2106 was an open label, single-center, single dose study to evaluate the efficacy of influenza and meningococcal vaccination in healthy volunteers (HV) exposed to 300 mg canakinumab s.c. A total of 51 HV were randomized (1:1) to a single canakinumab 300 mg s.c. dose (n=25) or no treatment (control group, n=26), followed by inactivated influenza virus (Aggripal[®]) or conjugated meningococcal (Menjugate[®], containing aluminum hydroxide as adjuvant) vaccinations i.m. after 2 weeks.

The primary efficacy variable was the response (≥ 2 fold increase in antibody titer in $\geq 2/3$ serotypes) to vaccination after 4 weeks in subjects treated with canakinumab compared to the control group. Secondary efficacy variables were the response to vaccines at different fold thresholds and time points.

Blockade of IL-1 β by canakinumab did not interfere with the efficacy of influenza and meningococcal vaccinations, as measured by the rise in antibody titers (Chioato et al 2010).

Thus, treatment with canakinumab does not affect the development of a protective response following influenza or meningococcal vaccine as measured by antibody titer. The response to both vaccines was comparable between the canakinumab and placebo groups. Therefore canakinumab does not cause a loss of the effectiveness of vaccination.

The original concern about a possible interference was based on the observation that the adjuvant properties of aluminum salts are mediated by inflammasome activation, which involves IL-1 β . A recent preclinical study has shown that vaccination effectiveness is independent of inflammasome activation (a target of canakinumab inhibition) for alum-based vaccines (Flach et al 2011).

3.6 Immunogenicity

Canakinumab, as a protein, has the potential to induce the formation of anti-canakinumab antibodies. Immunogenicity assessments for anti-canakinumab antibodies were included in all clinical studies. Anti-canakinumab antibodies in serum were measured by surface plasmon resonance spectroscopy using a sensitive and validated Biacore[®] binding assay.

Gouty arthritis

A total of 225 patients were exposed at least once to canakinumab in the gouty arthritis core and extension 1 Phase 3 studies (Studies H2356/2356E1 and H2357/2357E1), 60 of whom were re-treated with canakinumab 150 mg s.c. when they had a new gouty arthritis attack (32 in the core studies and 28 in the extension 1 studies). None of these patients in these studies had positive anti-canakinumab antibodies as determined from the analytical methods used.

In all gouty arthritis studies, of all samples tested for anti-canakinumab antibodies, only 8 patients out of 691 showed a positive immunogenicity response. Of these, 7 patients were treated only once with canakinumab since they did not experience an additional attack and 1 patient was treated twice with canakinumab for a new attack. The presence of anti-canakinumab antibodies had no impact on the PK of, or exposure to, canakinumab and none of these patients reported AEs suggestive of hypersensitivity

The re-treated patient with anti-canakinumab antibodies (patient H2251E1-0058-00002) was randomized to canakinumab in the core study, re-treated with canakinumab in the extension study, and the calculated antibody titers were slightly above the lower limit of quantification of the assay. This patient showed no unexpected change in PK data that would suggest a change in exposure, and no signs of immunogenicity-related AEs were reported. This patient experienced the first post-baseline flare during the extension study at 23:00 on 21-March-2010. He was dosed the day after at 7:36 on 22-March-2010. At the onset of this attack the physician reported a swollen joint with bulging beyond the joint margins. The duration of the flare was 2 days with canakinumab treatment, the patient assessment of response was excellent and the physician assessment was very good. During the attack on 22-March-2010 CRP was 83 mg/L and urate was 5.70 mg/dL. At the follow up visit on 30-March-2010 CRP was 2.9 mg/dL and urate was 6.40 mg/dL demonstrating good response.

RA patients

In the RA program, no patient was found with a positive antibody titer against canakinumab.

4 Efficacy in clinical studies

4.1 Dose selection

For gouty arthritis attacks, a Phase 2 dose-ranging study (Study H2255), summarized in Table 2-2, was performed using a dose range from 10 to 150 mg administered subcutaneously. In this study, each dose of canakinumab was compared with the active comparator, triamcinolone acetonide 40 mg administered intramuscularly. There was a clear superiority in the

incremental improvement, versus the comparator, in efficacy parameters with the highest dose tested. The data are shown in Table 4-1.

In brief, 150 mg canakinumab was confirmed as the most efficacious dose as it provided:

1. faster pain relief than lower canakinumab doses or the triamcinolone acetonide comparator (6 hour pain reduction 8.3 mm better and median time to 50% pain reduction was 1 day less)
2. more pain relief and better treatment response than lower canakinumab doses or triamcinolone acetonide (72 hour pain was significantly less, as well as better patient/physician scores for tenderness)
3. fewer patients using rescue medication than lower canakinumab doses or triamcinolone acetonide (significantly lower overall use in first 7 days, less use of steroids and codeine)

From a safety perspective the 150 mg dose was safe without a dose related safety signal with regard to overall incidence of adverse events and infection adverse events. No SAEs were reported for this dose group in this study. This dose is the same dose approved for the CAPS indication where 150 mg is given every 8 weeks. Thus, there was also supportive safety for carrying this dose forward in gouty arthritis.

Table 4-1 Dose response efficacy and safety data in treating acute attacks

	ACZ885					TA
	10 mg N = 28	25 mg N = 29	50 mg N = 28	90 mg N = 29	150 mg N = 27	40 mg N = 57
Speed of pain relief						
6 hour pain reduction (VAS in mm)	-9.6	-5.1	-13.8	-11.1	-20.2	-11.9
p value (relative to triamcin. ac.)	0.5860	0.1053	0.6489	0.8359	0.0505	-
days to 50% pain reduction	2.9	2.9	1.0	1.0	1.0	2.0
p value (relative to triamcin. ac.)	0.798	0.962	0.379	0.297	0.0006	-
Extent of pain relief at 72 hours						
72 hr pain reduction (VAS in mm)	-48.6	-46.6	-48.6	-52.7	-62.5	-43.3
p value (relative to triamcin. ac.)	0.3311	0.5516	0.3401	0.0815	0.0007	-
72 hr pain decrease (Likert scale)	-1.7	-1.5	-1.5	-1.7	-2.1	-1.4
p value (relative to triamcin. ac.)	0.1395	0.9696	0.7320	0.1792	0.0005	-
Response to treatment						
good/excel patient assess., n (%)	18 (64.3)	18 (62.1)	20 (71.4)	19 (65.5)	24 (88.8)	30 (53.6)
good/v good phys. assess., n (%)	21 (75.0)	18 (62.1)	22 (78.6)	22 (75.9)	25 (92.6)	34 (60.7)
absence of tenderness, n (%)	10 (35.7)	7 (24.1)	9 (32.1)	9 (31.0)	14 (51.9)	16 (28.6)
Use of rescue medication (up to day 7)						
total, n (%)	13 (46.4)	16 (55.2)	16 (57.1)	14 (48.3)	6 (22.2)	31 (55.4)
p value (relative to triamcin. ac.)	0.39	0.93	1.00	0.53	0.01	-
prednisone/prednisolone	5 (17.9)	9 (31.0)	8 (28.6)	6 (20.7)	2 (7.4)	16 (28.6)
codeine	4 (14.3)	6 (20.7)	4 (14.3)	4 (13.8)	1 (3.7)	9 (16.1)
acetaminophen	9 (32.1)	12 (41.4)	15 (53.6)	12 (41.4)	5 (18.5)	23 (41.1)
Safety and tolerability data						
overall rate of AEs	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
Infectious AEs	0	3 (10.3)	3 (10.3)	2 (6.9)	2 (7.1)	4 (7.0)
SAEs*	0	2 (6.9)	2 (6.9)	0	0	1 (1.8)
Safety/tolerability discontinuations	0	0	0	0	0	0

ACZ885 = canakinumab, TA = triamcinolone acetonide, assess. = assessment, **bold** indicates statistically significant p values, good/exc = good or excellent (patient assessment), good/v good = good or very good (physician assessment), * all SAEs were rated as unrelated to study drug by the investigator

4.2 Phase 3 studies

4.2.1 Study design

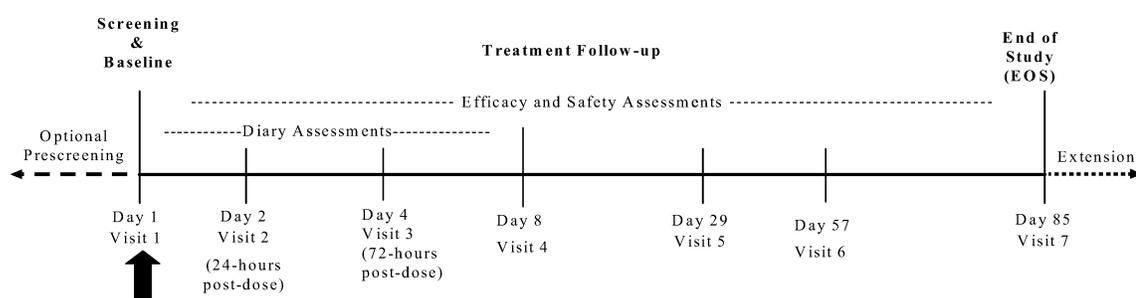
An overview of the 2 pivotal, registration trials is provided in Table 2-2, and illustrated in Figure 4-1. These phase 3 adequate and well-controlled trials were randomized, double-blind trials, designed to support registration. These were superiority designs to demonstrate efficacy of canakinumab, using recognized, validated variables, against an active comparator, a single i.m. dose of 40 mg triamcinolone acetonide.

The effects of treatment and re-treatment, when needed, were followed for 24 weeks (12 weeks in the core studies and an additional 12 weeks in the extension studies, both double-blind).

Study H2356 (primarily in Europe) and Study H2357 (primarily in the US) were identical phase 3, 12-week randomized, double blind, double dummy, active controlled studies of canakinumab for treating acute attacks and reduction in frequency of subsequent attacks in frequently flaring patients for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective. Patients in both trials continued their initial treatment, on demand, in the 2 identical 12-week controlled double-blind extensions (H2356E1 and H2357E1).

In the core study, canakinumab or triamcinolone was given in a double blind fashion (double dummy s.c. and i.m. injections) within 5 days of the first attack. During the core study and the extensions, study drug could be administered again within 5 days of a subsequent attack, provided at least 14 days had elapsed since the prior treatment.

Figure 4-1 Study design (pivotal studies)



4.2.2 Selection of active comparator

The study population was targeted to those patients unable to benefit from NSAIDs or colchicine, so neither of these 2 agents were viable as active controls. Thus, corticosteroids were the only option for an active control.

A systemic, injected corticosteroid was sought, which would allow a single dose to be administered by clinical trial staff, similarly to canakinumab, thus eliminating dosing errors, the need for a tapering regimen and ensuring similar compliance in both treatment groups.

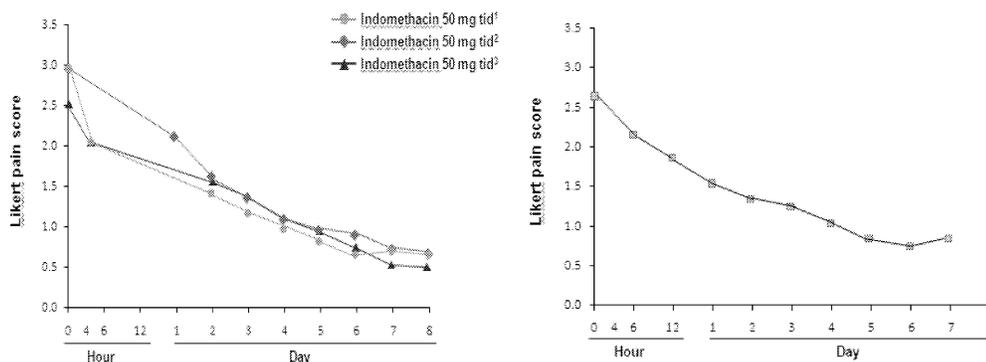
Triamcinolone acetonide i.m. injection was chosen as the control, as it is long-acting, more potent than prednisone/prednisolone, is labeled for use in gout (Kenalog[®] Prescribing Information), and used by rheumatologists to treat attacks (Schlesinger et al 2006).

In the US, the recommended starting dose is 60 mg i.m., however this is not the starting dose in many regions, and a lower starting dose of 40 mg i.m. is more accepted globally. For example, 40 mg is labeled as the initial dose in the UK and Germany, which local investigators favored. Consistent with this, the current US label states that dosage requirements are variable, must be individualized according to the disease and the response of the patient and notes that some patients may be well controlled with doses of 20 mg or less (Kenalog[®] Prescribing Information).

The data from the Phase II dose-finding trial confirms that triamcinolone acetonide is active and a single dose of 40 mg im provides clinically meaningful pain relief (Table 4-1). In that trial there was a mean reduction in VAS pain score of 43.3 mm at 72 hours with 53% of the

patients reporting a good to excellent response in the triamcinolone group. This response in pain relief is similar to that observed in published trials with indomethacin 50 tid (Figure 4-2).

Figure 4-2 Likert pain in published data with 50 mg t.i.d. indomethacin and 40 mg i.m. triamcinolone acetone



left panel redrawn from Schumacher et al 2002, Rubin et al 2004, Willburger et al 2007 (indomethacin 1, 2, 3 respectively) by converting to absolute values and using numerical scores, right panel shows the triamcinolone acetone data from Study H2255

Thus, it is concluded that 40 mg i.m. of triamcinolone acetone is an effective treatment for gouty arthritis attacks and an appropriate comparator for the Phase 3 studies.

4.3 Efficacy Measures

The pivotal studies were designed to show the superiority of 150 mg s.c. canakinumab over 40 mg i.m. triamcinolone acetone for the co-primary efficacy variables of pain intensity (at 72 hours in the most affected joint on VAS scale) and time to first new attack. The pain intensity primary variable was to be analyzed using an analysis of covariance model with treatment as a factor and baseline VAS and baseline BMI as covariates; this is equivalent to an analysis that uses change from baseline VAS pain as the response variable. The time to new attack variable was to be analyzed using a Cox regression model containing treatment and BMI.

The sample size for each pivotal study was determined to be 220 patients (110 per group). This provided overall power of at least 90% for detecting both of the following: 1. a treatment difference in mean pain score (VAS) of 12 mm; and 2. a hazard ratio that would correspond to 12 week incidence of new gout attacks of 0.25 for canakinumab and 0.50 for triamcinolone acetone.

Key secondary efficacy variables were time to 50% reduction in pain, use of rescue medication, time to flare resolution and SF 36 (physical function). A Bonferroni-Holm multiplicity adjustment was used to protect the false positive rate across the key secondary variables. Other secondary variables were patient's assessment of pain in the most affected joint (Likert scale), patient's and physician's global assessment of treatment response (Likert scale), physician's assessment of tenderness, swelling, erythema or range of motion, and inflammatory markers (CRP, SAA). Exploratory variables included disease/flare severity, the treatment response in new flares and assessments of various responses to treatment.

4.3.1 Inclusion criteria

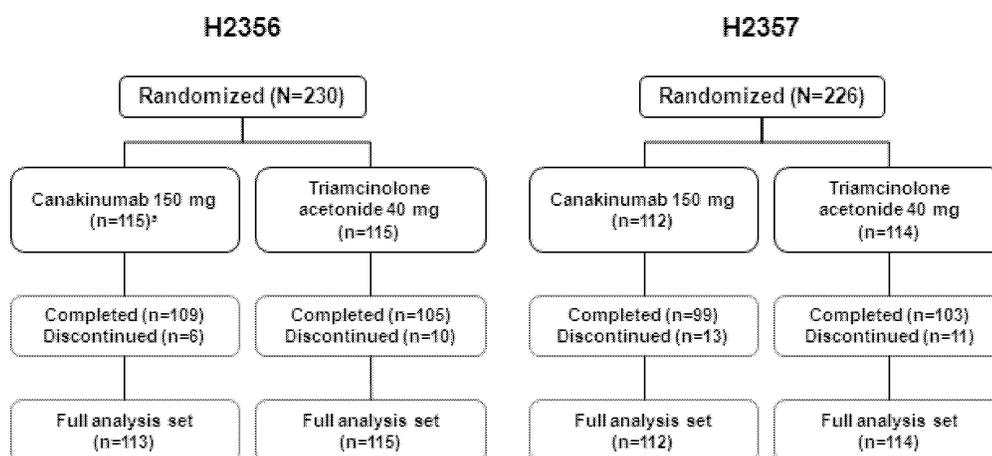
Patients must have met the ACR 1977 preliminary criteria for the classification of acute arthritis of primary gout. They must have had an acute flare (≤ 5 days) with a history of ≥ 3 flares in the last year. Pain intensity needed to be ≥ 50 mm VAS and subjects should have demonstrated contraindication, intolerance or inefficacy to NSAIDs and/or colchicine. A stable dose of urate-lowering drugs (if used) was required and no recent use of certain pain medications (e.g. acetaminophen) or other anti IL-1 drugs was allowed.

There were no major protocol deviations that violated the inclusion criteria. Demographic and baseline characteristics were well balanced. Only a small minority of patients (2 patients (0.9%) in Study H2356 and 7 patients (3.1%) in Study H2357) had no evidence of prior use and of failure with NSAIDs or colchicine, or had no clear contraindications to these agents.

4.3.2 Patient disposition

Patient disposition showed that $>90\%$ of subjects completed each study, as seen in Figure 4-3.

Figure 4-3 Patient disposition in each pivotal trial



*2 patients randomized to canakinumab, who in error received no medication, were not included in the analyses

As seen in Table 4-2, there were few discontinuations for safety reasons (1 death in Study H2356 in the triamcinolone acetonide group due to sudden cardiac death/pulmonary embolism, 1 death in Study H2357 in the canakinumab group due to intracranial hemorrhage, and 2 discontinuations for laboratory abnormalities in Study H2357, 1 in each group).

Table 4-2 Patient disposition in the pivotal trials

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 115	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 n= 225	TA n= 229
Completed, n (%)	109 (94.8)	105 (91.3)	99 (88.4)	103 (90.4)	208 (91.6)	208 (90.8)
Discontinued, n (%)	6 (5.2)	10 (8.7)	13 (11.6)	11 (9.6)	19 (8.4)	21 (9.2)
Withdrawn consent	1 (0.9)	3 (2.6)	6 (5.4)	4 (3.5)	7 (3.1)	7 (3.1)
Lost to follow-up	3 (2.6)	1 (0.9)	5 (4.5)	3 (2.6)	8 (3.5)	4 (1.7)
Admin. Problems	2 (1.7)	1 (0.9)	0	1 (0.9)	2 (0.9)	2 (0.9)
Abnorm. lab. value(s)	0	0	1 (0.9)	1 (0.9)	1 (0.4)	1 (0.4)
Death	0	1 (0.9)	1 (0.9)	0	1 (0.4)	1 (0.4)
Protocol deviation	0	0	0	2 (1.8)	0	2 (0.9)
Unsatisfactory therapeutic effect	0	4 (3.5)	0	0	0	4 (1.7)

ACZ885=canakinumab, TA=triamcinolone acetinide, abnorm lab values=abnormal laboratory values

4.3.3 Patient demographics

The baseline features of patients in each study and pooled data showed that the majority of patients were white, middle aged males who were obese (mean BMI ~32 kg/m²) as seen in Table 4-3.

Table 4-3 Demographics and concomitant conditions at baseline

	Study H2356		Study H2357		pooled data	
	ACZ885 n= 113	TA n= 115	ACZ885 n= 112	TA n= 114	ACZ885 n= 225	TA n= 229
Sex, n (%)						
Male	101 (89.4)	108 (93.9)	100 (89.3)	105 (92.1)	201 (89.3)	213 (93.0)
Female	12 (10.6)	7 (6.1)	12 (10.7)	9 (7.9)	24 (10.7)	16 (7.0)
Age (years), mean (SD)	54 (11.2)	55 (10.7)	51 (12.1)	53 (12.3)	52.3 (11.8)	53.6 (11.5)
Race, n (%)						
Caucasian	93 (82.3)	96 (83.5)	74 (66.1)	80 (70.2)	167 (74.2)	176 (76.9)
Black	0 (0.0)	0 (0.0)	26 (23.2)	24 (21.1)	26 (11.6)	24 (10.5)
Asian	3 (2.7)	3 (2.6)	10 (8.9)	9 (7.9)	13 (5.8)	12 (5.2)
Native American	1 (0.9)	1 (0.9)	0	0	1 (0.4)	1 (0.4)
Pacific Islander	0	0 (0 (0	0	0
Other	16 (14.2)	15 (13.0)	2 (1.8)	1 (0.9)	18 (8.0)	16 (7.0)
Height (cm), mean (SD)	174 (8.2)	175 (8.1)	177 (9.4)	176 (8.6)	175.4 (8.9)	175.7 (8.4)
Weight (kg), mean (SD)	96 (16.3)	97 (18.3)	101 (21.0)	98.3 (19.9)	98.4 (18.9)	97.6 (19.1)
BMI (kg/m²), mean (SD)	32 (4.7)	32 (4.7)	32 (6.0)	32 (5.5)	32.0 (5.4)	31.6 (5.1)

ACZ885 = canakinumab, TA = triamcinolone acetinide, BMI = body mass index

4.3.4 Disease characteristics

A summary of the most relevant features that illustrate the number of flares in the past year, the severity of gouty arthritis, the prevalence of comorbidities, the current use of urate-

lowering therapy and the frequency of patients who had failed on NSAIDs and/or colchicine is shown in Table 4-4.

The disease characteristics in both trials were essentially similar but showed some differences. Patients with tophi and patients using urate lowering drugs were more frequent in Study H2356 than Study H2357. Disease characteristics were mostly well-balanced across treatments, except that chronic kidney disease was more common in the canakinumab group than in the triamcinolone group in both studies.

Table 4-4 Gout severity, comorbidities, use of urate-lowering drugs, NSAIDs/colchicine history

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Flare history, mean (SD)						
flares in past year	6.5 (5.52)	7.0 (5.10)	6.5 (5.75)	5.9 (4.44)	6.5 (5.63)	6.5 (4.80)
Disease severity, n (%)						
oligoarticular gout	37 (32.7)	50 (43.5)	23 (20.5)	28 (24.6)	60 (26.7)	78 (34.1)
polyarticular gout	25 (22.1)	14 (12.2)	23 (20.5)	15 (13.2)	48 (21.3)	29 (12.7)
tophi known	44 (38.9%)	45 (39.1%)	20 (17.9)	23 (20.2)	64 (28.4)	68 (29.7)
Comorbidities, n (%)						
chronic kidney disease	20 (17.7)	13 (11.3)	13 (11.6)	9 (7.9)	33 (14.7)	22 (9.6)
hypertension	78 (69.0)	82 (71.3)	53 (47.3)	57 (50.0)	131 (58.2)	139 (60.7)
coronary artery disease	12 (10.6)	13 (11.3)	11 (9.8)	8 (7.0)	23 (10.2)	21 (9.2)
diabetes	15 (13.3)	11 (9.6)	19 (17.0)	21 (18.4)	34 (15.1)	32 (14.0)
hypercholesterolemia	28 (24.8)	35 (30.4)	27 (24.1)	29 (25.4)	55 (24.4)	64 (27.9)
Taking urate-lowering therapy, (n%)						
all urate-lowering drugs	57 (50.4)	63 (54.8)	32 (28.6)	40 (35.1)	89 (39.6)	103 (45.0)
Contraindicated / intolerant / lack of efficacy, n (%)						
NSAIDs	107 (94.7)	113 (98.3)	97 (86.6)	96 (84.2)	204 (90.7)	209 (91.3)
colchicine	27 (23.9)	39 (33.9)	67 (59.8)	59 (51.8)	94 (41.8)	98 (42.8)
both	22 (19.5)	38 (33.0)	54 (48.2)	46 (40.4)	76 (33.8)	84 (36.7)

ACZ885 = canakinumab, TA = triamcinolone acetonide

4.3.5 Current and prior use of urate-lowering therapy

A detailed review of the current and prior use of ULT is instructive, as it illustrates the real-life clinical experience regarding the challenges in achieving treatment goals for serum urate in general practice, as occurred in the 2 pivotal trials (pooled data) and summarized in Table 4-5.

About one quarter of patients reported no prior use of ULT, for which there was no obvious reason (e.g. contraindication), but it was often recorded that patients did not want to take ULT. Over two thirds of patients reported current or prior use of ULT (mostly allopurinol). Patients who reported prior use of allopurinol discontinued for various reasons, the main one being lack of efficacy (about half of those who had previously taken it).

Table 4-5 Current and prior use of urate-lowering therapy to prevent flares

ULT use	ACZ885 N = 225	TA N = 229
current use of any ULT	89 (39.6)	103 (45.0)
current use of allopurinol	83 (36.9)	95 (41.5)
prior use of any ULT	74 (32.9)	51 (22.3)
prior use of allopurinol	66 (29.3)	50 (21.8)
allopurinol discontinued for:		
lack of efficacy	32 (14.2)	28 (12.2)
hypersensitivity	6 (2.7)	5 (2.2)
moderate/severe renal insufficiency	1 (0.4)	0
other safety/tolerability	0	3 (1.3)
non-compliance	13 (5.8)	5 (2.2)
other	14 (6.2)	9 (3.9)
no prior use of ULT	57 (25.3)	3 (27.5)
contraindicated	1 (0.4)	2 (0.9)
not indicated by local practice	7 (3.1)	5 (2.2)

ACZ885 = canakinumab, TA = triamcinolone acetonide, ULT = urate-lowering therapy

4.3.6 Current and prior use of NSAIDs and colchicine

A detailed review of the current and prior use of NSAIDs and colchicine is similarly instructive, as it also illustrates some of the complexities facing the clinician regarding the treatment of attacks that had preceded enrollment (pooled data), as summarized in Table 4-6.

About 90% of patients were unable to benefit from NSAIDs, due to about 70% inefficacy, 30% contraindications and 25% intolerance. About 40% of patients were unable to benefit from colchicine, due to about 25% inefficacy, 20% intolerance and <10% contraindications.

In addition to these recorded reasons, a subgroup of patients was found to have renal insufficiency at baseline, which constitutes a further contraindication, and some patients did not try colchicine, which is not registered in some countries (e.g. Switzerland, Sweden, Finland), not labeled for use in gout or is rarely used in some countries.

Table 4-6 Prior use of NSAIDs and colchicine to treat previous flares

Reason not to use NSAID and colchicine	ACZ885 N = 225	TA N = 229
NSAIDs – n (%)		
Inefficacy	162 (72.0)	169 (73.8)
contraindication	78 (34.7)	69 (30.1)
Intolerance	61 (27.1)	57 (24.9)
recorded contraindication, intolerance, inefficacy	204 (90.7)	209 (91.3)
colchicine – n (%)		
Inefficacy	58 (25.8)	62 (27.1)
contraindication	22 (9.8)	14 (6.1)
Intolerance	43 (19.1)	45 (19.7)
recorded contraindication, intolerance, inefficacy	94 (41.8)	98 (42.8)
NSAIDs and colchicine – n (%)		
Inefficacy	46 (20.4)	47 (20.5)
contraindication	12 (5.3)	9 (3.9)
Intolerance	15 (6.7)	16 (7.0)
recorded contraindication, intolerance, inefficacy	76 (33.8)	84 (36.7)

ACZ885 = canakinumab, TA = triamcinolone acetonide

4.3.7 Efficacy data from the core, 12 week studies

4.3.7.1 Pain intensity, probability of flare (primary efficacy data)

The 2 co-primary efficacy variables (pain intensity at 72 hours and time to flare, measured as flare probability) both had to be statistically significantly superior to triamcinolone acetonide to confirm the efficacy of canakinumab. These data from each study and pooled data are shown in Table 4-7. Statistically significant efficacy with both variables was demonstrated in both studies, confirming that canakinumab 150 mg s.c. is efficacious in both acute pain reduction and for reducing the risk of a new flare.

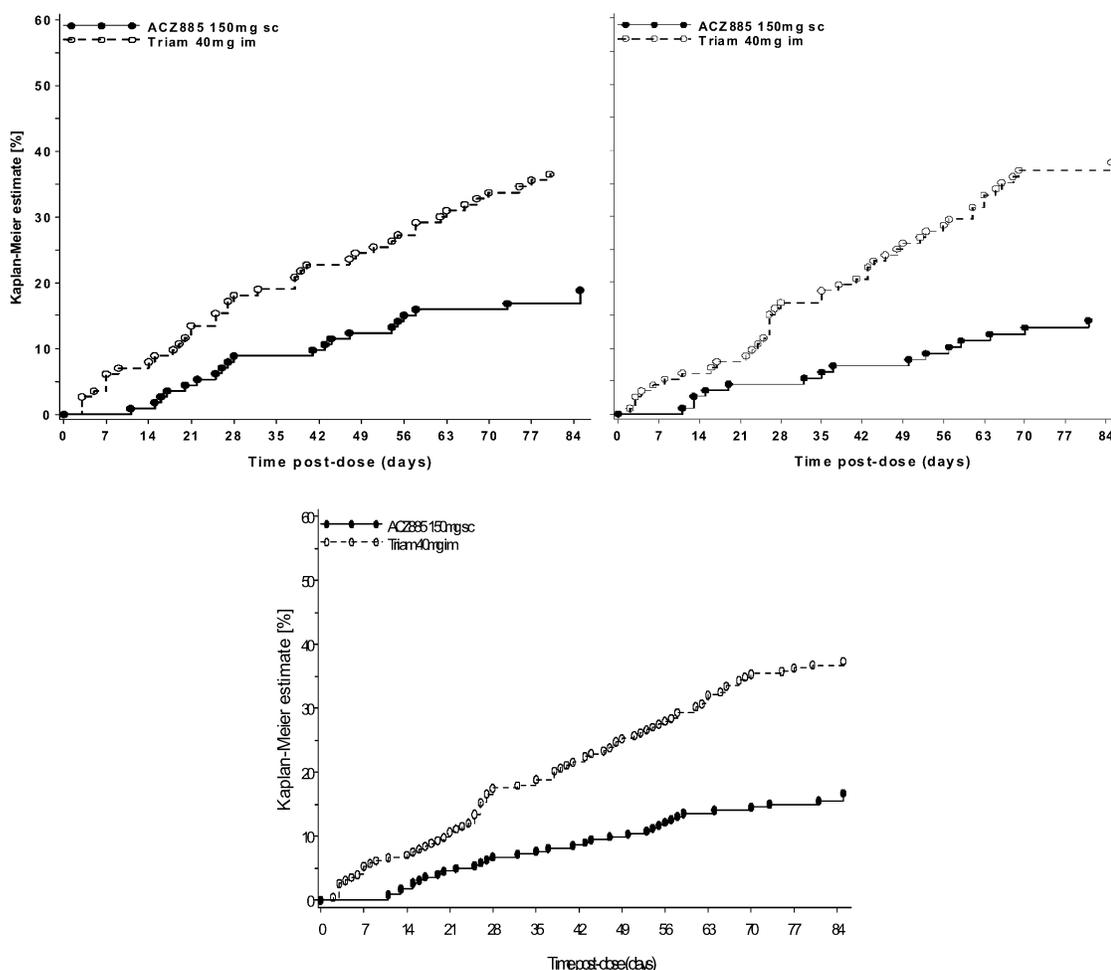
For VAS pain intensity at 72 hours, the treatment differences of about 10 mm in each study and pooled, reach the upper estimate for minimally clinically important change in pain (Wolfe and Michaud 2007). Importantly, the 62% reduced risk of a new flare (hazard ratio of 0.38) in 12 weeks (pooled data) is robust and clinically significant, and reflects the lower cumulative flare rate with canakinumab than with triamcinolone acetonide, seen in Figure 4-4.

Table 4-7 Co-primary efficacy data (pain intensity, probability of flare)

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Pain intensity (mm)						
at baseline (mean±SE)	73.3 ± 1.1	74.8 ± 1.2	74.9 ± 1.3	73.6 ± 1.2	74.1 ± 0.8	74.2 ± 0.9
at 72 hrs (est. mean±SE)	28.1 ± 2.4	39.5 ± 2.4	22.1 ± 2.3	31.9 ± 2.4	25.0 ± 1.7	35.7 ± 1.7
change from baseline at 72 hrs (est. mean±SE)	45.9 ± 2.4	34.5 ± 2.4	52.1 ± 2.3	42.4 ± 2.4	49.1 ± 1.7	38.3 ± 1.7
est. treatment diff. (p value)	-11.4 (p=0.0005)		-9.8 (p=0.0018)		-10.7 (p<0.0001)	
Time to new flare (days)						
median time	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
flare probability (%; CI)	19 (13,27)	36 (28,46)	14 (9,22)	38 (30,48)	16 (12,22)	38 (32,44)
hazard ratio (p value)	0.45 (p=0.0014)		0.32 (p<0.0001)		0.38 (p<0.0001)	

ACZ885 = canakinumab, TA = triamcinolone acetonide, est. mean±SE = model estimates, not raw data, CI = 95% confidence intervals, flare probability = Kaplan Meier cumulative estimates at study end
est. treatment diff. = estimated treatment difference, n.e. = non-estimable until 50% of patients flare

Figure 4-4 Kaplan-Meier cumulative rate of new flares (%) (12 weeks)



Study H2356 (top left), Study H2357 (top right), both studies pooled (lower panel)

4.3.7.2 Efficacy in reducing new flares (secondary data, 12 weeks)

The efficacy in reducing new flares was also assessed by the secondary endpoints of the percentage of patients with a new flare, mean number of flares per patient, and the severity of new flares.

In each study and in the pooled dataset more patients were free of new flares with canakinumab than triamcinolone acetonide (pooled, 84% versus 64%) and fewer had a 2nd, 3rd or 4th new flare (pooled, <3% versus 11%), so there were less mean flares per patient (pooled, 0.2 versus 0.5), as seen in Table 4-8.

Table 4-8 Rate of new flares, mean flares per patient (12 weeks)

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
absence of new flares, n (%)	92 (81.4)	75 (65.2)	97 (86.6)	72 (63.2)	189 (84.0)	147 (64.2)
total with new flares, n (%)	21 (18.6)	40 (34.8)	15 (13.4)	42 (36.8)	36 (16.0)	82 (35.8)
1 new flare, n (%)	18 (15.9)	26 (22.6)	12 (10.7)	30 (26.3)	30 (13.3)	56 (24.4)
2 new flares, n (%)	3 (2.7)	9 (7.8)	2 (1.8)	10 (8.8)	5 (2.2)	19 (8.3)
3 new flares, n (%)	0	4 (3.5)	1 (0.9)	2 (1.8)	1 (0.4)	6 (2.6)
4 new flares, n (%)	0	1 (0.9)	0	0	0	1 (0.4)
mean no. of flares per patient	0.21	0.53	0.17	0.49	0.19	0.51
estimated ratio (p value)	0.40 (p=0.0007)		0.34 (p=0.0003)		n.d	

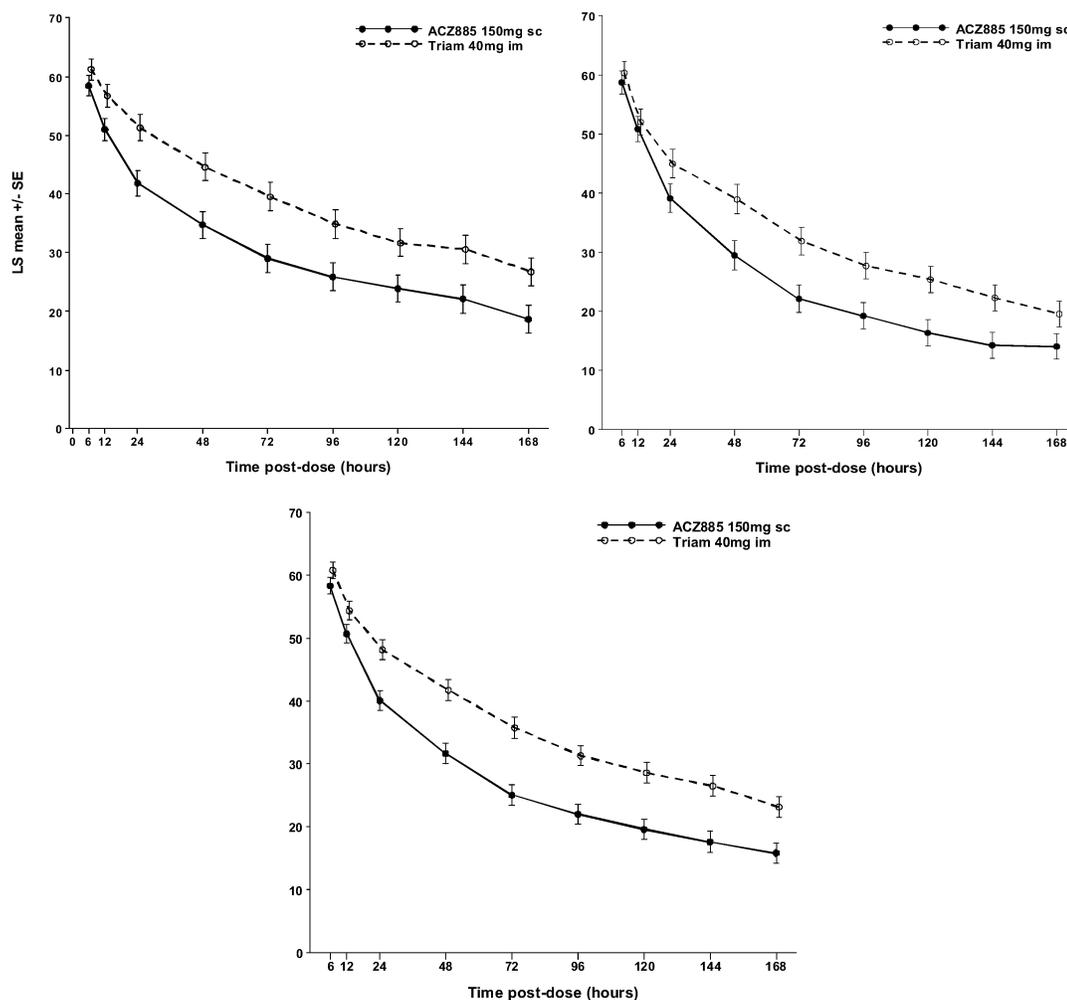
ACZ885 = canakinumab, TA = triamcinolone acetonide, n.d. = not determined
estimated odds ratio >1 indicates less likely with ACZ885

4.3.7.3 Secondary endpoints for acute treatment of the baseline attack

4.3.7.3.1 Signs and symptoms over 7 days

VAS pain assessments over time show that in each study and the pooled dataset VAS pain was less with canakinumab than triamcinolone acetonide, as seen in Figure 4-5, the differences being statistically significant from 24 hours to 7 days in the pooled dataset, indicating greater and faster pain relief with canakinumab than triamcinolone acetonide.

Figure 4-5 VAS pain (mm) over time (baseline flare)



Study H2356 (top left), Study H2357 (top right), both studies pooled (lower panel)
Baseline values of VAS pain are shown in Table 4-2

The values for VAS pain data at the early time points show reductions in pain as early as 6 and 12 hours that are greater with canakinumab; a decrease in baseline pain at 24 hours in the pooled data of 35 mm (i.e. almost 50%), compared to 26 mm with triamcinolone acetone, a treatment difference close to the upper estimate for minimally clinically important change in pain (Wolfe and Michaud 2007), as seen in Table 4-9.

Table 4-9 Mean VAS pain at early times, soon after starting treatment

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
VAS pain reduction (mm)						
at 6 hours	-16.1	-13.1	-16.6	-13.8	-16.3	-13.4
at 12 hours	-23.4	-17.5	-23.9	-22.1	-23.6	-19.8
at 24 hours	-33.3	-23.2	-36.1	-29.0	-34.7	-26.1
at 48 hours	-41.3	-30.4	-46.3	-35.5	-43.8	-32.9
at 72 hours	-45.9	-35.4	-53.4	-42.5	-49.6	-38.9

ACZ885 = canakinumab, TA = triamcinolone acetonide

The median times to at least a 50% reduction in VAS pain were statistically significantly shorter for canakinumab in Study H2356 and the pooled dataset, however not significantly shorter in Study H2357. The proportion of patients responding to treatment in the 7 days after treatment as indicated by the proportion of patients with VAS pain relief of $\geq 50\%$ at 72 hours, and pain relief of $\geq 50\%$ or $\geq 75\%$ at 7 days, was greater with canakinumab than with triamcinolone acetonide, as seen in Table 4-10.

Table 4-10 Degree of VAS pain relief over 7 days

	Study H2356		Study H2357		Pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Patients with pain relief						
$\geq 50\%$ decrease at 72hr, %	63.9%	46.8%	79.4%	61.7%	71.6%	54.2%
$\geq 75\%$ decrease at 72hr, %	38.7%	35.8%	57.0%	42.1%	47.7%	38.9%
$\geq 50\%$ decrease at 7 days, %	86.1%	71.6%	83.5%	82.7%	84.8%	77.0%
$\geq 75\%$ decrease at 7 days, %	69.4%	50.0%	75.7%	68.4%	72.5%	59.0%

ACZ885 = canakinumab, TA = triamcinolone acetonide

The time to complete resolution of pain (Likert pain of none) showed a strong trend ($p=0.013$) favoring canakinumab in H2357, but did not reach statistical significance relative to the Bonferroni-Holm adjusted significance criteria. In H2356 the proportion of patients achieving a complete pain resolutions were lower in both treatment groups and did not reach statistical significance ($p=0.72$). With other pre-specified definitions of substantial resolution (Likert pain of none or mild, VAS pain reduction to <10 mm), improvements were seen in more patients taking canakinumab than triamcinolone acetonide. Likert pain of none or mild was statistically significantly reduced in Study H2356, while other decreases did not reach statistical significance, as seen in Table 4-11.

Table 4-11 Patients with resolution of pain in 7 days using various definitions

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Likert pain of none, %	34.5	31.3	57.1	43.0	45.8**	37.1
Likert pain of none or mild, %	87.6**	78.3	91.1	83.3	n.d.	n.d.
VAS pain <10 mm, %	60.2	45.2	65.2	55.3	n.d.	n.d.

Rates are cumulative Kaplan-Meier estimates , ** statistically significant difference versus triam. ac.
ACZ885 = canakinumab, TA = triamcinolone acetonide, n.d. = not determined

The patient’s global assessment of response to treatment show that in each study patients receiving canakinumab were statistically significantly more likely to have a better response to treatment than those on triamcinolone acetonide, as seen in Table 4-12.

Table 4-12 Patient’s global assessment of response to treatment

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Global assessment, n (%)						
at 72 hrs (good/excellent)	58 (51.3)	46 (41.4)	79 (73.1)	56 (51.8)	137 (62.0)	102 (46.6)
estimated odds ratio (p value)	1.74 (p=0.0245)		2.71 (p<0.0001)		n.d.	
at 7 days (good/excellent)	73 (65.2)	56 (52.4)	88 (80.7)	74 (68.5)	161 (72.9)	130 (60.5)
estimated odds ratio (p value)	1.83 (p=0.0147)		2.14 (p=0.0028)		n.d.	

ACZ885 = canakinumab, TA = triamcinolone acetonide, n.d. = not determined
estimated odds ratio >1 indicates more likely to have a better response with ACZ

The analysis of the physician’s global assessment of response to treatment demonstrated a statistically significantly greatly likelihood for canakinumab patients to have a better response at both 72 hours and 7 days (Table 4-13).

Table 4-13 Physician’s global assessment of response to treatment

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Global assessment, n (%)						
at 72 hrs (good/very good)	73 (64.6)	50 (45.5)	92 (86.0)	67 (61.5)	165 (75.0)	117 (53.4)
estimated odds ratio (p value)	1.96 (p=0.0067)		2.79 (p <0.0001)		n.d.	
at 7 days (good/very good)	88 (78.6)	67 (60.9)	102 (92.7)	87 (79.1)	190 (85.6)	154 (70.0)
estimated odds ratio (p value)	2.50 (p=0.0003)		2.42 (p=0.0008)		n.d.	

ACZ885 = canakinumab, TA = triamcinolone acetonide, n.d. = not determined
estimated odds ratio >1 indicates more likely to have a better response with ACZ

The physician’s assessment of tenderness, swelling and erythema at 72 hours and 7 days show that in each study, patients receiving canakinumab had less tenderness, swelling or erythema than those taking triamcinolone acetonide at both times, not all differences achieved statistical significance, as seen in Table 4-14.

Table 4-14 Physician's assessment of tenderness, swelling and erythema

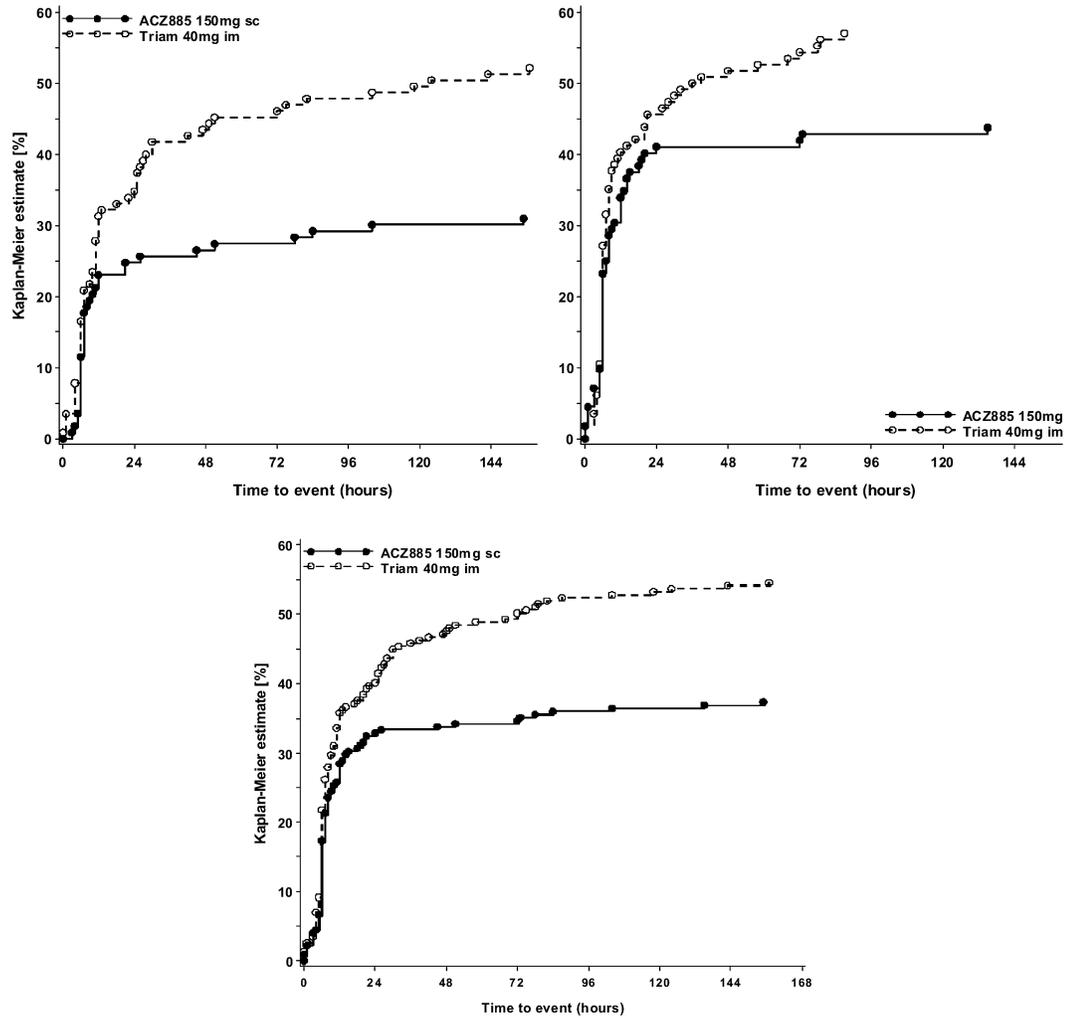
	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
No tenderness						
at 72 hrs, n (%)	38 (33.6)	29 (26.4)	51 (47.7)	33 (30.3)	89 (40.5)	62 (28.3)
est. odds ratio (p value)	2.00 (p= 0.0094)		2.34 (p=0.0014)		n.d.	
at 7 days, n (%)	65 (58.0)	45 (40.9)	79 (47.7)	60 (55.0)	144 (64.9)	105 (47.9)
estimated odds ratio (p value)	2.25 (p=0.0026)		2.07 (p=0.0113)		n.d.	
No swelling						
at 72 hrs, n (%)	43 (38.1)	33 (30.0)	79 (71.8)	39 (35.8)	94 (42.7)	72 (32.9)
est. odds ratio (p value)	1.72 (p=0.0301)		1.76 (p=0.0283)		n.d.	
at 7 days, n (%)	80 (71.4)	62 (56.4)	73 (66.4)	69 (62.7)	153 (68.9)	131 (59.5)
estimated odds ratio (p value)	2.02 (p=0.0116)		1.21 (p=0.5052)		n.d.	
No erythema						
at 72 hrs, n (%)	88 (78.6)	71 (65.1)	80 (74.8)	72 (66.7)	168 (76.7)	143 (65.9)
est. odds ratio (p value)	0.48 (p=0.0199)		0.68 (p=0.2142)		n.d.	
at 7 days, n (%)	107 (95.5)	91 (82.7)	97 (88.2)	95 (87.2)	204 (91.9)	186 (84.9)
estimated odds ratio (p value)	0.21 (p=0.0033)		0.95 (p=0.9091)		n.d.	

ACZ88 = canakinumab, TA = triamcinolone acetonide, n.d. = not determined
estimated odds ratio >1 = less tenderness/swelling with ACZ, <1 = less likely to have erythema with ACZ

4.3.7.3.2 Rescue medication during the baseline attack

The cumulative frequency of patients using rescue medication was lower in patients taking canakinumab than in those taking triamcinolone acetonide, as seen in Figure 4-6 and the mean time to first rescue medication was also significantly longer with canakinumab than triamcinolone acetonide in each study and in the pooled data.

Figure 4-6 Time to first use of rescue medication (baseline flare)



Source: Study H2356- (top left), Study H2357 (top right), both studies pooled (lower)

The proportion of patients using rescue medication shows that in each study and in the pooled dataset patients taking canakinumab were statistically significantly less likely to use rescue medication than those taking triamcinolone acetonide, as seen in Table 4-15.

Table 4-15 Proportion of patients using rescue medication

Type of rescue medication	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
acetaminophen/paracetamol, n (%)	32 (28.3)	52 (45.2)	41 (36.6)	57 (50.0)	73 (32.4)	109 (47.6)
prednisolone/prednisone, n (%)	11 (9.7)	31 (27.0)	14 (12.5)	23 (20.2)	25 (11.1)	54 (23.6)
codeine, n (%)	5 (4.4)	17 (14.8)	21 (18.8)	27 (23.7)	26 (11.6)	44 (19.2)
Patients using rescue, n (%)	35 (31.0)	60 (52.2)	49 (43.8)	65 (57.0)	84 (37.3)	125 (54.6)
estimated odds ratio (p value)	0.42 (p=0.0022)		0.52 (p=0.0214)		0.47 (p=0.0001)	

ACZ885 = canakinumab, TA = triamcinolone acetonide, estimated odds ratio <1 indicates less likely with ACZ885

The amount of rescue medication used (mean total in mg) shows that in each study and in the pooled dataset patients receiving canakinumab took considerably less of each type of medication than those receiving triamcinolone acetonide, as seen in Table 4-16.

Table 4-16 Mean amount of rescue medication taken

	Study H2356		Study H2357		pooled data	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
prednisolone/prednisone (mg)	6.5	24.3	9.2	19.3	7.8	21.8
codeine (mg)	7.7	47.2	27.2	60.6	17.4	53.9
acetaminophen/paracetamol (mg)	1555	2397	1375	2527	1465	2462

ACZ885 = canakinumab, TA = triamcinolone acetonide

4.3.7.3.3 Effect on inflammatory markers (CRP, SAA)

The effect on inflammatory markers at 72 hours and 7 days shows that, in each study, patients receiving canakinumab had statistically significantly lower CRP and SAA values during the flare than those taking triamcinolone acetonide, as seen in Table 4-17.

Table 4-17 C-reactive protein and serum amyloid A protein levels

	Study H2356		Study H2357	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114
CRP				
median at baseline (mg/L)	13.2	9.4	10.2	8.9
median at 72 hrs (mg/L)	4.4	5.2	4.3	7.0
estimated ratio (p value)	0.64 (p ≤ 0.0001)		0.60 (p ≤ 0.0001)	
median at 7 days (mg/L)	2.1	3.6	4.8	7.2
estimated ratio (p value)	0.43 (p < 0.0001)		0.53 (p < 0.0001)	
SAA				
median at baseline (mg/L)	18.0	9.9	11.2	9.8
median at 72 hrs (mg/L)	5.2	10.1	5.1	11.1
estimated ratio (p value)	0.40 (p ≤ 0.0001)		0.40 (p ≤ 0.0001)	
median at 7 days (mg/L)	3.3	7.9	2.9	7.3
estimated ratio (p value)	0.30 (p < 0.0001)		0.39 (p < 0.0001)	

ACZ885 = canakinumab, TA = triamcinolone acetonide, estimated ratio = ratio of ACZ885 to triam. at 72 hr
CRP = C-reactive protein, SAA = serum amyloid A protein, n.d. = not determined

4.3.7.4 Global assessment of treatment (secondary data, 12 weeks)

The physician’s assessment of response to treatment at study end was rated as good or very good in 94% with canakinumab and 82% with triamcinolone acetonide and the patient’s assessment of response to treatment was rated as good or excellent in 80% with canakinumab and 74% with triamcinolone acetonide (pooled).

The SF-36 physical function component score at study end at 12 weeks showed large treatment improvements in both treatment groups and no meaningful treatment differences.

4.3.7.5 Subgroup analyses (12 weeks)

Sub-group assessments were made based on demographics and selected baseline disease characteristics (high and lower flare rates in the past year, in those using or not using urate-lowering therapy) and according to the start of treatment during the baseline attack.

There were no differences in efficacy compared to the overall study population among demographic subgroups (age, sex, race, BMI), or in patients with over or under 6 flares in the past year, and there were no differences in demographic or disease features that correlated with a good or weak response to treatment.

The fall in VAS pain was significantly greater with canakinumab than triamcinolone acetonide with and without urate-lowering drugs. The risk reduction of a new flare was greater with canakinumab in both subgroups, statistically significantly better than that for triamcinolone acetonide without urate-lowering drugs. However, with urate-lowering drugs, a decrease in flare rate with triamcinolone acetonide prevented this comparison (still favoring canakinumab) from reaching statistical significance, as shown in Table 4-18.

Table 4-18 Time to new flare according to use of urate-lowering therapy

pooled data (12 weeks)	All patients		Patients on ULT		Patients NOT on ULT	
	ACZ885 N=225	TA N=229	ACZ885 N=89	TA N=103	ACZ885 N=136	TA N=126
Time to 1st new flare (12 weeks)						
K-M probability (%) (95% CI)	16.4 (12.1,22.1)	37.7 (31.7,44.5)	20.5 (13.5,30.6)	26.5 (19.0,36.2)	13.7 (8.8,20.8)	47.4 (38.9,56.9)
HR to TA (95% CI)	0.38 (0.26, 0.56)		0.73 (0.40, 1.32)		0.23 (0.13, 0.39)	
p-value	p <0.0001		p=0.1492		p <0.0001	

ACZ885 = canakinumab, TA = triamcinolone acetonide, ULT = urate-lowering therapy, HR = hazard ratio

In exploratory analyses, the time of treatment after the start of the flare (0-1, 2, 3, ≥4 days after flare start) was related to the VAS pain response, the frequency of reaching a no pain Likert score (resolution), and the frequency of a new attacks are shown in Table 4-19.

Canakinumab seemed superior to triamcinolone acetonide whenever treatment was given (but this was not formally tested). The greatest pain relief and highest frequency of complete resolution occurred when treatment was given early after flare initiation. With canakinumab and early treatment (0-1 day) the rate of new flare was low (8%), with later treatment (≥2 days) the rate of new flare was higher (≥16%).

Table 4-19 Pain response by time of treatment after the start of the flare

Time after start	ACZ885 (pooled)					
	BL	Day 1	Day 3	Day 7	Resolution (%)	New flare in 12 wks n (%)
	VAS pain (mm), mean (SD)					
0-1 day (n=49)	73.8 (12.9)	33.5 (22.0)	16.0 (19.5)	9.7 (16.7)	71%	4 (8.2)
2 days (n=67)	74.2 (11.7)	41.7 (23.3)	24.6 (20.6)	13.1 (16.7)	37%	11 (16.4)
3 days (n=65)	74.8 (12.2)	40.7 (24.8)	29.3 (24.3)	21.1 (23.6)	32%	14 (21.5)
≥4 days (n=44)	73.1 (13.4)	40.8 (23.1)	24.3 (20.3)	12.8 (18.4)	50%	7 (15.9)
	TA (pooled)					
	BL	Day 1	Day 3	Day 7	Resolution (%)	New flare in 12 wks N (%)
	VAS pain (mm), mean (SD)					
0-1 day (n=64)	73.5 (12.4)	47.6 (28.1)	30.3 (25.6)	15.4 (23.6)	50%	21 (32.8)
2 days (n=72)	75.7 (12.3)	49.3 (27.7)	34.9 (27.8)	22.4 (25.2)	32%	32 (44.4)
3 days (n=51)	73.2 (13.2)	47.9 (24.8)	37.5 (30.8)	27.2 (30.3)	33%	17 (33.3)
≥4 days (n=42)	73.9 (13.3)	46.8 (26.9)	40.1 (29.7)	27.8 (27.1)	31%	13 (31.0)

ACZ885 = canakinumab, TA = triamcinolone acetonide, BL = baseline pain, Resolution = % patients with full resolution of pain at 7 days, SD = standard deviation, n = maximum number of observations at any time point

4.3.8 Efficacy data from the core plus extension studies (24 weeks)

4.3.8.1 Probability of flare (primary efficacy variable)

The probability of flare (or time to new flare), (the co-primary endpoint at 12 weeks), was estimated at 24 weeks as the primary endpoint to assess the durability of effect. The 56% reduced risk of a new flare (hazard ratio of 0.44) in 24 weeks (pooled data), that is seen in

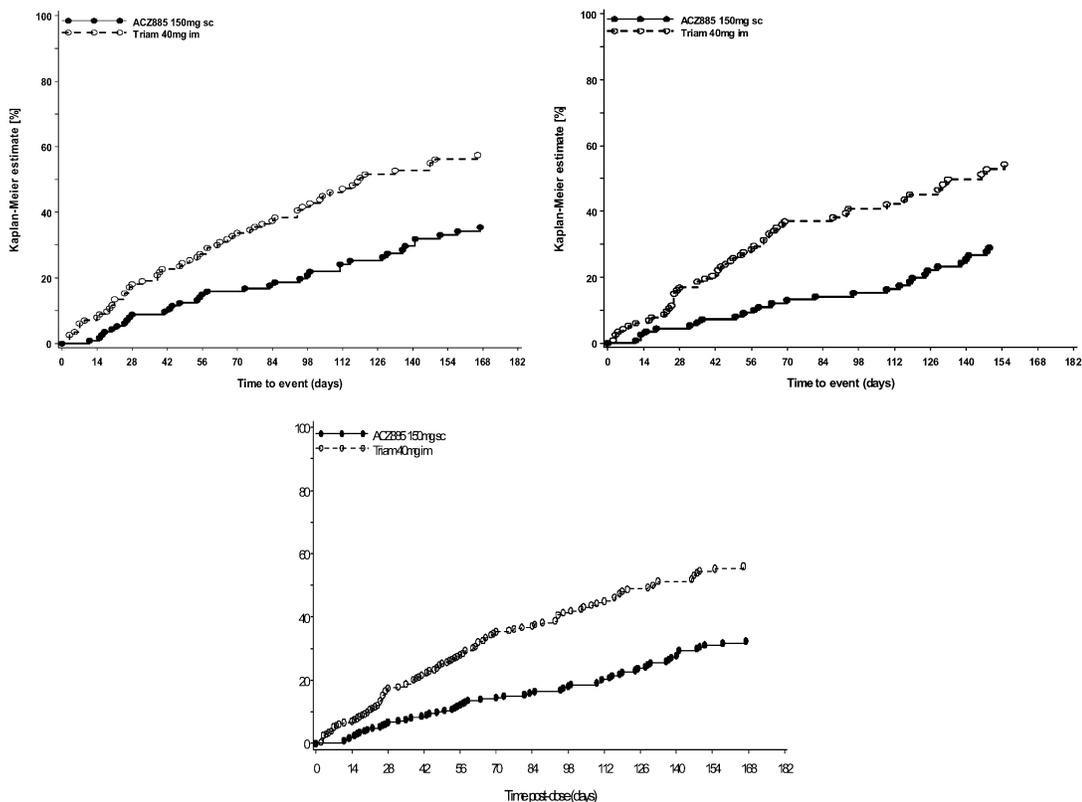
Table 4-20, is robust and clinically significant and reflects the lower cumulative flare rate with canakinumab than with triamcinolone acetonide, as seen in Figure 4-7.

Table 4-20 Time to new flare / probability of flare (24 weeks)

	Study H2356E1 (24 wks)		Study H2357E1 (24 wks)		pooled (24 wks)	
	ACZ885 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
Time to new flare (days)						
median time	n.e.	119	n.e.	146	n.e.	131
flare probability (%; CI)	35 (27, 46)	57 (48, 67)	29 (21,39)	54 (44, 65)	32 (26, 40)	56 (49, 63)
hazard ratio (p value)	0.48 (p=0.0003)		0.40 (p<0.0001)		0.44 (p<0.0001)	

ACZ885 = canakinumab, TA = triamcinolone acetoneide, CI = 95% confidence intervals, flare probability = Kaplan Meier cumulative rates at study end, n.e. = non-estimable until 50% of patients flare

Figure 4-7 Kaplan-Meier cumulative rate of new flares (%) (24 weeks)



Source: Study H2356E1 (top left), Study H2357E1 (top right), both studies pooled (lower)

4.3.8.2 Efficacy in reducing new flares (secondary variable, 24 weeks)

The efficacy in reducing new flares was also assessed by the secondary variables the percentage of patients with a new flare, mean number of flares per patient and the severity of new flares.

In each study and in the pooled dataset more patients were free of new flares with canakinumab than triamcinolone acetonide (pooled, 72% versus 51%) and fewer had a 2 or more flares (pooled, 8% versus 22%), so there were less mean flares per patient (pooled, 0.4 versus 0.8), as seen in Table 4-21.

Table 4-21 Rate of new flares, mean flares per patient (24 weeks)

	Study H2356E1		Study H2357E1		pooled data	
	ACZ88 N = 113	TA N = 115	ACZ885 N = 112	TA N = 114	ACZ885 N = 225	TA N = 229
absence of new-flares, n (%)	77 (68.1)	56 (48.7)	84 (75.0)	61 (53.5)	161 (71.6)	117 (51.1)
total with new-flares, n (%)	36 (31.9)	59 (51.3)	28 (25.0)	53 (46.5)	64 (28.4)	112 (48.9)
1 new flare, n (%)	27 (23.9)	34 (29.6)	20 (17.9)	28 (24.6)	47 (20.9)	62 (27.1)
2 new flares, n (%)	9 (8.0)	14 (12.2)	5 (4.5)	16 (14.0)	14 (6.2)	30 (13.1)
3 new flares, n (%)	0	7 (6.1)	3 (2.7)	8 (7.0)	3 (1.3)	15 (6.6)
≥4 new flares, n (%)	0	4 (3.5)	0	1 (0.9)	0	5 (2.2)
mean flares per patient	0.40	0.87	0.35	0.80	0.37	0.83
estimated rate ratio (p value)	0.45 (p = 0.0001)		0.42 (p<0.0001)		n.d.	

ACZ885 = canakinumab, TA = triamcinolone acetonide
estimated rate ratio >1 indicates higher with ACZ

4.3.8.3 Efficacy in treating new flares (secondary variables, 24 weeks)

Efficacy in treating new flares was assessed by comparing the secondary variables of signs and symptoms over 7 days (mainly patient assessments of pain, patient and physician assessments of pain, inflammation and treatment overall), and rescue medication use.

As re-treated patients showed selection bias from the first treatment because re-treatment was not randomized (resulting in different disease severities and different participation rates), efficacy in re-treatment was mostly assessed by comparing the first and last flares.

Patients in the canakinumab group who re-flared had more polyarticular disease and had a higher mean number of attacks in the year prior to study entry, compared with the triamcinolone patients who were retreated (Table 4-22).

Table 4-22 Pivotal and pooled analysis at 24 weeks: Disease features of patients with new flare or only baseline flare (Safety set)

	Study H2356				Study H2357				pooled data (24 weeks)			
	ACZ885		TA		ACZ885		TA		ACZ885		TA	
	New flare n=36 (%)	No new flare n=77 (%)	New flare n=59 (%)	No new flare n=56 (%)	New flare n=28 (%)	No new flare n=84 (%)	New flare n=53 (%)	No new flare n=61 (%)	New flare n=64 (%)	No new flare n=161 (%)	New flare n=112 (%)	No new flare n=117 (%)
Gout status:												
Monoarticular	31	52	42	46	36	67	62	62	33	60	52	55
Polyarticular	36	16	9	16	32	17	15	12	34	16	12	14
Tophi present	58	30	42	36	32	13	26	15	47	21	35	25
>6 flares/yr	42	18	34	32	54	19	30	13	47	19	32	22
Disability index (mean)	1.9	1.3	1.2	1.4	1.0	0.9	1.1	1.0	1.5	1.1	1.2	1.2
Current flare:												
≤2 joints	50	81	73	75	68	85	85	84	58	83	79	79
≥4 joints	44	13	14	16	18	11	9	13	33	12	12	15

bold highlights values indicating either higher severity in the ACZ new flare group or where values were higher in groups other than in the ACZ new flare group

4.3.8.3.1 Signs and symptoms over 7 days

With canakinumab the VAS pain response of the last flare, shown in Figure 4-8, Table 4-23, was very similar to that of the first flare. However, the pooled data showed that for the new flare, baseline VAS pain was less than for the first flare (68 mm versus 75 mm) with canakinumab but quite similar with triamcinolone acetonide (72 mm versus 75 mm), suggesting that pain intensity for the new flare may be reduced by prior canakinumab treatment.

Figure 4-8 VAS pain (mm) over time (first and last flare) (24 weeks) in the canakinumab group (N=60)

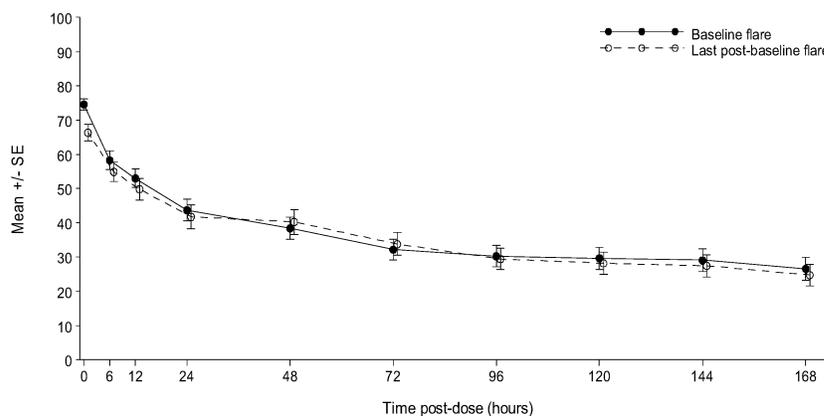


Table 4-23 Mean VAS pain (first and last flare) in the canakinumab group

	Baseline		72 hours		7 days	
	1 st flare	last flare	1 st flare	last flare	1 st flare	last flare
Canakinumab re-treated patients						
Study H2356E1	76.1	65.5	32.4	32.1	25.0	24.6
mean VAS pain, mm (SD), N=35	(12.0)	(17.5)	(22.2)	(23.8)	(24.4)	(23.9)
Study H2357E1	72.6	67.4	31.8	36.2	28.9	25.0
mean VAS pain, mm (SD), N=25	(12.5)	(19.6)	(25.0)	(27.6)	(26.0)	(24.6)
Pooled	74.6	66.3	32.2	33.8	26.6	24.7
mean VAS pain, mm (SD), N=60	(12.3)	(18.3)	(23.2)	(25.3)	(24.9)	(23.9)

VAS = visual analogue scale for pain

The mean (median) duration of the new flare compared to the baseline flare seemed to be reduced with canakinumab in Study H2356E1 and Study H2357E1, whereas with triamcinolone acetonide, mean (median) durations for the new flare showed no sign of any reduction, as seen in Table 4-24.

Table 4-24 Mean/median duration of flare (first and last flare)

Duration of flare	ACZ885				triam.			
	Study H2356/E1		Study H2357/E1		Study H2356/E1		Study H2357/E1	
	1 st flare	last flare						
mean (days)	7.1 (3.5)	6.5 (3.4)	5.5 (3.2)	5.2 (3.5)	7.1 (3.6)	7.0 (3.6)	5.7 (3.6)	6.0 (3.5)
median (days)	7.0	5.0	4.0	4.0	6.0	7.0	4.0	4.5

ACZ8885 = canakinumab, triam. = TA, SD = standard deviation

The percentages of patients with at $\geq 50\%$ or $< 50\%$ reduction in VAS pain by day 7 with the initial treatment relative to the last treatment are shown in Table 4-25. With canakinumab, a strong response ($\geq 50\%$ reduction in VAS pain) predicted a strong response to re-treatment (84%), and a weak response to treatment ($< 50\%$ reduction in VAS pain) predicted a weak response to re-treatment (77%). With triamcinolone acetonide, a good response to treatment predicted a good response to re-treatment (89%), but a weak response to treatment could be followed almost equally by a weak (44%) or strong (56%) response to re-treatment.

Table 4-25 Predictability of VAS pain relief (first and last flare)

pooled data	ACZ885 N = 60	TA N= 89
$\geq 50\%$ VAS pain reduction (baseline flare)	45	64
$\geq 50\%$ re-treatment VAS pain reduction, n (%)	38/45 (84.4%)	57/64 (89.1)
$< 50\%$ re-treatment VAS pain reduction, n (%)	7/45 (15.6%)	7/64 (10.9)
$< 50\%$ VAS pain reduction (baseline flare)	13	16
$\geq 50\%$ re-treatment VAS pain reduction, n (%)	3/13 (23.1%)	9/16 (56.3)
$< 50\%$ re-treatment VAS pain reduction, n (%)	10/13 (76.9%)	7/16 (43.8)

ACZ = canakinumab, TA = triamcinolone acetonide, VAS = visual analogue scale for pain

N = number of patients who had new flares, sub-totals denote re-treated patients who supplied data

The scores for Likert pain, patient and physician global assessments of response, physician assessment of joint tenderness and joint swelling at 72 hours and 7 days confirm the

maintenance of efficacy with canakinumab re-treatment for new flares, as seen in Table 4-26. Similar levels of response were seen during the last flare as in the baseline flare at both times.

Table 4-26 Pain, global assessments, tender/swollen joints (first and last flare)

Canakinumab re-treated patients	72 hours		Day 7	
	1 st flare	last flare	1 st flare	last flare
Study H2356E1, %				
Likert pain (none & mild)	55.9	52.9	72.7	63.6
Patient global (excellent & good)	29.0	45.2	51.5	64.5
Physician global (very good & good)	51.5	66.7	60.6	87.9
Joint tenderness (no pain)	24.2	36.4	36.4	54.5
Joint swelling (no swelling)	30.3	48.5	48.5	63.6
Study H2357E1, %				
Likert pain (none & mild)	66.7	54.2	72.7	81.8
Patient global (excellent & good)	60.0	55.0	63.6	68.2
Physician global (very good & good)	82.6	73.9	88.0	80.0
Joint tenderness (no pain)	43.5	47.8	60.0	64.0
Joint swelling (no swelling)	34.8	60.9	64.0	68.0
Pooled data, %				
Likert pain (none & mild)	60.3	53.4	72.7	70.9
Patient global (excellent & good)	41.2	49.0	56.6	66.0
Physician global (very good & good)	64.3	69.6	72.4	84.5
Joint tenderness (no pain)	32.1	41.1	46.6	58.6
Joint swelling (no swelling)	32.1	53.6	55.2	65.5

4.3.8.4 Rescue medication (last flare)

Although the frequency of patients using any rescue medication or each type of rescue medication and the amounts of acetaminophen/paracetamol or codeine, did not differ between treatments during the last flare, the amount of corticosteroids taken (mean total in mg) was lower with canakinumab than with triamcinolone acetonide, as seen in Table 4-27. These comparisons indicate trends and are not quantitatively reliable, because of the bias in the treatment groups resulting from the first treatment.

Table 4-27 Mean amount of rescue medication taken for last flare (24 weeks)

	Study H2356/E1 (24 weeks)		Study H2357/E1 (24 weeks)	
	ACZ885 N = 35	TA N = 43	ACZ885 N = 25	TA N = 46
prednisolone/prednisone (mg)	4.1	21.6	5.6	18.3
codeine (mg)	7.7	46.0	64.8	65.2
acetaminophen (mg)	1931	2058	2292	1541

ACZ885 = canakinumab, TA = triamcinolone acetonide

Note: Treatment comparisons can only indicate general trends, as a result of selection bias

4.3.8.5 Sub-group analyses (24 weeks)

Sub-group assessments were made on demographic characteristics, in patients with high and lower flare rates in the past year and in those using or not using urate-lowering therapy, to see if these factors affected the efficacy outcome.

There were no differences in efficacy compared to the overall population among demographic subgroups (age, sex, race, BMI), except that there were too few Asians to show a treatment difference. In patients documented as unable to use NSAIDs and colchicine or with over or under 6 flares in the past year the efficacy was similar compared to the overall population, as seen in Table 4-28.

Table 4-28 Efficacy in common subgroups over time

	Estimated % of patients with flare				Hazard ratio relative to triam	
	12 weeks		24 weeks		12 weeks	24 weeks
Subgroup	ACZ885	TA	ACZ885	TA		
Unable to use NSAIDs & colchicine*	13.6	44.5	29.1	63.3	0.25, p<0.0001	0.32, p<0.0001
On ULT	20.5	26.5	33.3	47.9	0.73, p=0.1492	0.64, p=0.0337
≥6 flares in prior yr	26.0	40.5	49.7	58.8	0.54, p=0.0139	0.67, p=0.0340

ACZ885 = canakinumab, TA = triamcinolone acetonide

* = contraindicated, intolerant of, or not responsive to NSAIDs and colchicine

Patients with ≥6 flares in the past year showed a smaller treatment effect at 24 weeks than at 12 weeks, which narrowly missed statistical significance (p=0.034). They had a shorter median time to next flare (approx. 24 weeks, when almost 50% had flared, Table 4-28) than the whole population (32% had flared at 24 weeks, Table 4-28), suggesting that once canakinumab exposure declines, frequently-flaring patients may start to return to higher flare rates and need more frequent treatment.

Patients on urate-lowering drugs, who showed a 27% reduced risk of a new flare with canakinumab at 12 weeks (hazard ratio 0.73, p=0.1492) showed a 36% reduced risk at 24 weeks (hazard ratio 0.64, p=0.0337) as seen in Table 4-29. At both times, the smaller benefit than in the whole group came from lower flare rates with triamcinolone acetonide, not higher rates with canakinumab.

Table 4-29 Time to new flare according to use of urate-lowering therapy

pooled data (24 weeks)	All patients		Patients on ULT		Patients NOT on ULT	
	ACZ885 N=225	TA N=229	ACZ885 N=89	TA N=103	ACZ885 N=136	TA N=126
Time to 1st new flare (24 weeks)						
K-M probability (%) (95% CI)	32.4 (26.2, 39.5)	56.0 (49.0, 63.7)	33.3 (24.0, 44.8)	47.9 (38.0, 58.9)	31.8 (24.0, 41.3)	63.1 (53.5, 72.8)
HR to triam. ac. (95% CI)	0.44 (0.32, 0.60)		0.64 (0.40, 1.03)		0.32 (0.21, 0.48)	
p-value	< 0.0001		0.0337		< 0.0001	

ACZ885 = canakinumab, TA = triamcinolone acetonide, ULT = urate-lowering therapy, HR = hazard ratio

4.4 Efficacy conclusions

Both pivotal efficacy trials provide substantial evidence for the efficacy of 150 mg canakinumab by showing statistically significant and clinically relevant superiority to an active comparator, triamcinolone acetonide, for the 2 co-primary variables (treating the pain and inflammation of an acute gouty arthritis attack and reducing the risk of a new attack) in the targeted patient population (e.g. those unable to obtain adequate response to NSAIDs and/or colchicine whether from intolerance, contraindication or previous lack of efficacy).

Replicate results were seen in the individual 12 week controlled studies for the pre-specified primary variables and were consistent across secondary endpoints. These results were sustained through 24 weeks after initial randomization in the blinded E1 extension studies. All these data support the view that canakinumab provides not only clinically meaningful symptom relief but also significantly reduces the risk and occurrence of new flares.

Efficacy with canakinumab was demonstrated seen in the overall target population and was consistent across various subgroups. Superior efficacy to the active corticosteroid comparator was seen at most intervals between flare onset and start of treatment. Effects were more pronounced when treatment was initiated early after the start of symptoms.

In new flares after canakinumab treatment, efficacy of re-treatment was consistent with the initial treatment and there was no hint of loss of efficacy due to immunogenicity. The degree of response was predictable and generally replicated the response to the baseline flare, with a strong response following an earlier strong response. There was no rebound effect due to prior treatment with canakinumab in that new flares were not more severe or longer lasting than the baseline flare, rather there was a trend for new flares being less severe than the baseline flare.

5 Overall approach to safety evaluation

5.1 Sources of safety data

Safety data for the use of canakinumab for the treatment of gouty arthritis includes data from the clinical studies in patients with gouty arthritis, as well as data from clinical studies in rheumatoid arthritis (RA).

Safety information from the initial BLA for the orphan indication of CAPS was not reported for this application. These considerations were discussed and agreed with FDA at both the End of Phase II meeting on 17-Nov-2009 and again at the pre-sBLA meeting on 08-Jun-2010.

Additional safety information comes from routine pharmacovigilance, spontaneous reports and reports from ongoing studies as presented in the 6 monthly periodic reports in CAPS.

The clinical safety data presented (cut-off date 06-Dec-2010 in the sBLA) includes 1563 patients with gouty arthritis or RA in the pooled datasets.

In the gouty arthritis dataset, 1085 patients were included, with 691 (211.5 patient years of observation) exposed to canakinumab, mostly using on-demand dosing. In the RA datasets, 478 patients were included (465 enrolled in placebo-controlled RA dataset plus 13 from RA

study A2206), and 441 (461.2 patient years) were exposed to canakinumab, given at fixed dosing intervals.

Additional exposure was provided as part of the 120 day Safety Update which include an interim analysis of the extension 2 studies of the pivotal studies H2356 and H2357.

In addition, SAEs and deaths occurring in recently completed and ongoing studies in other indications are presented.

The total number of patients exposed to at least one dose of canakinumab in completed clinical trials in all indications is approximately 2500.

5.2 Safety profile

Relevant safety considerations, including those from prior experience with canakinumab in CAPS, include infections, potential opportunistic infections, neutropenia, thrombocytopenia, hepatic AEs and liver function tests, malignancies, immunogenicity, local injection site reactions, impaired renal function, major adverse cardiac events (MACE), lipid profile, and vertigo.

As patients with gouty arthritis frequently have other concomitant conditions, special attention was paid on the evaluation of safety data in patients with cardiovascular risk factors and those with pre-existing impairment of renal function. As canakinumab is a monoclonal antibody, an evaluation of immunogenicity/allergenicity was made, including the development of antibodies to canakinumab and an evaluation of adverse events that could signal allergic or immunological reactions in patients re-treated for new flares. In addition analysis on uric acid level has been performed.

5.2.1 Organization of the safety presentation

The safety presentation starts with the general safety profile observed in the individual trials providing the efficacy data that support the proposed indication in gouty arthritis. The safety of re-treatment in gouty arthritis provides a specific assessment of safety in patients who receive re-treatment for new flares.

An integrated safety presentation follows, which includes data from the controlled, pooled datasets in gouty arthritis and RA. For each of these, adverse events (AEs) including serious events (SAEs) and deaths as well as laboratory abnormalities are presented.

Long term safety with scheduled dosing is shown for the controlled and uncontrolled studies in the all RA dataset, as this dataset has the longest period of follow-up. In addition longer-term data is shown for the gouty arthritis population.

6 Safety in the studies for treating acute gouty arthritis flares

The following studies have been conducted for treating acute gout flares and presented in detail below, i.e. dose-ranging study for treating flares (H2255), pivotal studies (H2356 and H2357) and the extension E1, as well as the second open-label extension E2.

An additional Phase II dose-ranging study was performed for prevention of flares in gouty arthritis patients initiating urate lowering therapy with allopurinol.

6.1 Dose-ranging studies in gouty arthritis

In gouty arthritis, a dose ranging study was performed in the target population for treating flares in patients with acute gouty arthritis (H2255). A further dose ranging study in gouty arthritis was performed for prevention of flares in patients initiating urate lowering therapy with allopurinol (H2251).

6.1.1 Dose ranging study in gouty arthritis patients for treating flares

Two hundred subjects, who were refractory or contraindicated to treatment with NSAIDs and/or colchicine, were randomized to one of 5 single doses of canakinumab (10, 25, 50, 90 or 150 mg s.c.) or 1 single dose of triamcinolone acetonide (40 mg i.m.) in the Phase II dose-ranging study for gouty arthritis attacks. Subjects were followed for 8 weeks.

The adverse event (AE) profile across all canakinumab doses was similar, with no apparent dose relationship in any single system organ class (SOC). At least one AE was reported in 42% of the triamcinolone acetonide-treated patients and 32-52% of the canakinumab-treated patients (Table 6-1).

Table 6-1 Frequency of common AEs by SOC ($\geq 5\%$ in any group) (Study H2255)

	ACZ885 10 mg N = 28 n (%)	ACZ885 25 mg N = 29 n (%)	ACZ885 50 mg N = 29 n (%)	ACZ885 90 mg N = 29 n (%)	ACZ885 150 mg N = 28 n (%)	TA 40 mg N = 57 n (%)
Total with AE(s)	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
Cardiac disorders	1 (3.6)	0	1 (3.4)	0	1 (3.6)	3 (5.3)
Gastrointestinal disorders	4 (14.3)	2 (6.9)	1 (3.4)	2 (6.9)	0	2 (3.5)
General dis & admin. site	1 (3.6)	2 (6.9)	1 (3.4)	1 (3.4)	1 (3.6)	2 (3.5)
Infections & infestations	1 (3.6)	4 (13.8)	5 (17.2)	3 (10.3)	3 (10.7)	9 (15.8)
Injury, poisoning & proc. compl.	1 (3.6)	3 (10.3)	1 (3.4)	0	1 (3.6)	3 (5.3)
Investigations	2 (7.1)	0	1 (3.4)	3 (10.3)	2 (7.1)	2 (3.5)
Metabolism & nutrition disorders	2 (7.1)	1 (3.4)	1 (3.4)	0	2 (7.1)	0
Musculoskel. & connective tiss.	1 (3.6)	2 (6.9)	5 (17.2)	2 (6.9)	1 (3.6)	6 (10.5)
Nervous system disorders	2 (7.1)	4 (13.8)	4 (13.8)	2 (6.9)	1 (3.6)	5 (8.8)
Respiratory, thoracic & med.	1 (3.6)	0	2 (6.9)	3 (10.3)	1 (3.6)	1 (1.8)
Skin & subcutaneous tissue dis.	1 (3.6)	3 (10.3)	1 (3.4)	0	1 (3.6)	1 (1.8)

Primary system organ classes (SOCs) are sorted alphabetically
ACZ885 = canakinumab, TA = triamcinolone acetonide

The most frequent of the individual AEs ($>5\%$ in any group) are shown in Table 6-2. Most were assessed as mild or moderate in severity without a clear dose response.

No patient in either group discontinued the study for any AE.

Table 6-2 Frequency of AEs by preferred term ($\geq 5\%$ in any group) (study H2255)

	ACZ885 10 mg N = 28 n (%)	ACZ885 25 mg N = 29 n (%)	ACZ885 50 mg N = 29 n (%)	ACZ885 90 mg N = 29 n (%)	ACZ885 150 mg N = 28 n (%)	Triam 40 mg N = 57 n (%)
Total with AE(s)	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
Headache	1 (3.6)	3 (10.3)	1 (3.4)	2 (6.9)	1 (3.6)	4 (7.0)
Nasopharyngitis	1 (3.6)	1 (3.4)	2 (6.9)	0	1 (3.6)	2 (3.5)
Pain in extremity	0	1 (3.4)	1 (3.4)	0	0	3 (5.3)
Urinary tract infection	0	0	0	1 (3.4)	0	3 (5.3)
AST increased	0	0	0	2 (6.9)	1 (3.6)	0
Blood uric acid increased	0	0	0	2 (6.9)	1 (3.6)	0
Oropharyngeal pain	0	0	0	2 (6.9)	1 (3.6)	0
ALT increased	0	0	0	2 (6.9)	0	0
Bone pain	0	0	2 (6.9)	0	0	0
Hyperhidrosis	0	2 (6.9)	0	0	0	0

Preferred terms are sorted by descending frequency in the 150 mg ACZ group
ACZ885 = canakinumab, TA = triamcinolone acetonide

SAEs were experienced by 5 patients: 1 (1.8%) on triamcinolone acetonide, 4 (2.8%) on canakinumab), none reported related to the study drug. These were 2 patients on 25 mg canakinumab (appendicitis in one, bronchitis in one), 2 patients on 50 mg canakinumab (appendicitis in one and coronary artery stenosis in one) and 1 patient on triamcinolone acetonide (cerebrovascular disorder).

6.1.2 Dose ranging study in gouty arthritis patients for prevention of flares

Approximately half of patients in all treatment groups experienced at least one AE during the study and most frequent AEs are presented by SOC (Table 6-3) and preferred term (Table 6-4). The overall incidence of AEs was similar across all treatment groups (51.9% to 58.5% in the canakinumab groups and 53.7% in the colchicine group).

SAEs were infrequent, occurring in 20 patients overall (1-3 patients in any canakinumab group and 6 patients in the colchicine group). There were no meaningful differences between the treatment groups in the type and frequency of SAEs reported. The most common SAEs by primary SOC were gastrointestinal disorders and infections and infestations (both 4 patients in total). All SAEs by preferred term were single occurrences, except for hematuria which occurred in 2 patients (one on canakinumab 100 mg and another on canakinumab 200 mg). Infection SAEs were reported in 4 patients in 3 canakinumab groups (25 mg, 200 mg and repeated dose regimen), with no suggestion of dose-related effects. A total of 6 patients, 4 treated with canakinumab and 2 treated with colchicine, discontinued due to SAEs.

Table 6-3 Frequency of common AEs by SOC ($\geq 5\%$ in any group) (Study H2251)

	ACZ 25 mg N=55 n (%)	ACZ 50 mg N=54 n (%)	ACZ 100 mg N=54 n (%)	ACZ 200 mg N=54 n (%)	ACZ 300 mg N=53 n (%)	ACZ q4wk N=53 n (%)	Colch 0.5 mg N=108 n (%)
No. of patients with AE(s)	29 (52.7)	30 (55.6)	28 (51.9)	28 (51.9)	29 (54.7)	31 (58.5)	58 (53.7)
Cardiac disorders	1 (1.8)	1 (1.9)	1 (1.9)	4 (7.4)	3 (5.7)	0	2 (1.9)
Gastrointestinal disorders	6 (10.9)	5 (9.3)	6 (11.1)	5 (9.3)	5 (9.4)	4 (7.5)	10 (9.3)
General disorders and administration site conditions	3 (5.5)	2 (3.7)	3 (5.6)	2 (3.7)	0	0	4 (3.7)
Infections and infestations	11 (20.0)	8 (14.8)	10 (18.5)	11 (20.4)	8 (15.1)	10 (18.9)	13 (12.0)
Injury, poisoning and procedural complications	2 (3.6)	2 (3.7)	5 (9.3)	1 (1.9)	4 (7.5)	2 (3.8)	6 (5.6)
Investigations	9 (16.4)	4 (7.4)	0	5 (9.3)	3 (5.7)	1 (1.9)	10 (9.3)
Metabolism and nutrition disorders	4 (7.3)	5 (9.3)	3 (5.6)	4 (7.4)	2 (3.8)	3 (5.7)	4 (3.7)
Musculoskeletal and connective tissue disorders	11 (20.0)	10 (18.5)	10 (18.5)	10 (18.5)	8 (15.1)	5 (9.4)	18 (16.7)
Nervous system disorders	6 (10.9)	5 (9.3)	4 (7.4)	3 (5.6)	8 (15.1)	5 (9.4)	7 (6.5)
Psychiatric disorders	3 (5.5)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	0	1 (0.9)
Renal and urinary disorders	1 (1.8)	3 (5.6)	2 (3.7)	2 (3.7)	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	1 (1.8)	2 (3.7)	3 (5.6)	2 (3.7)	5 (9.4)	1 (1.9)	4 (3.7)
Skin and subcutaneous tissue disorders	3 (5.5)	5 (9.3)	3 (5.6)	2 (3.7)	4 (7.5)	7 (13.2)	6 (5.6)
Vascular disorders	6 (10.9)	2 (3.7)	2 (3.7)	7 (13.0)	4 (7.5)	2 (3.8)	1 (0.9)

Primary system organ classes are sorted alphabetically.

A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

Table 6-4 Frequency of AEs by preferred term (>= 5% in any group) (study H2251)

	ACZ 25 mg N=55 n (%)	ACZ 50 mg N=54 n (%)	ACZ 100 mg N=54 n (%)	ACZ 200 mg N=54 n (%)	ACZ 300 mg N=53 n (%)	ACZ q4wk N=53 n (%)	Colch 0.5 mg N=108 n (%)
No. of patients with AE(s)	29 (52.7)	30 (55.6)	28 (51.9)	28 (51.9)	29 (54.7)	31 (58.5)	58 (53.7)
Headache	4 (7.3)	3 (5.6)	1 (1.9)	2 (3.7)	6 (11.3)	3 (5.7)	6 (5.6)
Arthralgia	4 (7.3)	5 (9.3)	4 (7.4)	2 (3.7)	3 (5.7)	2 (3.8)	3 (2.8)
Hypertension	6 (10.9)	2 (3.7)	2 (3.7)	5 (9.3)	4 (7.5)	2 (3.8)	1 (0.9)
Upper respiratory tract infection	2 (3.6)	1 (1.9)	2 (3.7)	3 (5.6)	1 (1.9)	3 (5.7)	4 (3.7)
Back pain	3 (5.5)	3 (5.6)	1 (1.9)	3 (5.6)	0	0	4 (3.7)
Nasopharyngitis	5 (9.1)	2 (3.7)	2 (3.7)	0	0	3 (5.7)	1 (0.9)
Diarrhea	3 (5.5)	1 (1.9)	2 (3.7)	3 (5.6)	1 (1.9)	0	2 (1.9)
Nausea	2 (3.6)	1 (1.9)	3 (5.6)	0	0	1 (1.9)	1 (0.9)
Alanine aminotransferase increased	3 (5.5)	1 (1.9)	0	1 (1.9)	0	0	1 (0.9)
Aspartate aminotransferase increased	3 (5.5)	1 (1.9)	0	1 (1.9)	0	0	1 (0.9)
Rash	1 (1.8)	1 (1.9)	0	0	0	3 (5.7)	1 (0.9)
Sinus congestion	0	0	0	0	3 (5.7)	0	1 (0.9)

Preferred terms are sorted by descending frequency of the total numbers observed for all patients (not shown). A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

6.2 Pivotal studies for treating acute gout flares

As described in Section 4, two identically designed Phase 3 studies (H2356 and H2357) compared canakinumab 150 mg s.c. with triamcinolone acetonide 40 mg i.m to treat acute gout flares and delay recurrence of new flares. The studies consisted of a 12 week core study and a blinded extension of an additional 12 weeks. The minimum time allowed for re-dosing for an occurrence of a new flare was 14 days after the prior dose. A total of 456 patients with gouty arthritis (meeting the ACR 1977 preliminary criteria) with acute flares were randomized in both core studies (227 to canakinumab and 229 to triamcinolone acetonide).

Since the original sBLA, which included analyses of patient who completed the core studies (Studies H2356 and H2357) and the first extensions studies (Studies H2356E1 and H2357E1), interim analyses (i.a.) have been performed of the second extensions studies (Studies H2356E2 i.a. and H2357E2 i.a.), to maximize the re-treatment data for analysis.

Patients originally assigned to canakinumab continued on their assigned therapy. Patients on triamcinolone acetonide continued on their assigned therapy throughout E1. However, when suffering a re-flare in E2, they were switched to canakinumab. To avoid possible bias, comparisons were not made across the original treatment groups, but were made only in the patients re-treated for new flares, by comparing the frequency that patients experienced AEs before and after re-treatment and in the 4 week period after each new treatment.

The baseline demographics and disease characteristics of the patients included in each study are summarized in Table 4-3 and Table 4-4.

6.2.1 Patient disposition in the core and extension studies

Nearly 90% or more of the patients randomized to either treatment in both studies completed the core study and approximately 67-78% entered the double blind 12 week extension studies. The most common reason for study discontinuation in both the core and extension studies and in both the canakinumab and triamcinolone acetonide groups was withdrawal of consent. One patient in each group died prior to study completion (further details on these two patients are provided in section 6.2.3) (Table 6-5).

Table 6-5 Patient disposition by treatment

	Study H2356 Core			Study H2357 Core		
	ACZ885 150 mg sc N=115 n (%)	TA 40 mg i.m. N=115 n (%)	Total N=230 n (%)	ACZ885 150 mg sc N=112 n (%)	TA 40 mg im N=114 n (%)	Total N=226 n (%)
Completed	109 (94.8)	105 (91.3)	214 (93.0)	99 (88.4)	103 (90.4)	202 (89.4)
Discontinued	6 (5.2)	10 (8.7)	16 (7.0)	13 (11.6)	11 (9.6)	24 (10.6)
Reason for discontinuation						
Adverse event(s)	0	0	0	0	0	0
Abnormal laboratory value(s)	0	0	0	1 (0.9)	1 (0.9)	2 (0.9)
Abnormal test procedure result(s)	0	0	0	0	0	0
Unsatisfactory therapeutic effect	0	4 (3.5)	4 (1.7)	0	0	0
Patient no longer needs study drug	0	0	0	0	0	0
Patient withdrew consent	1 (0.9)	3 (2.6)	4 (1.7)	6 (5.4)	4 (3.5)	10 (4.4)
Lost to follow-up	3 (2.6)	1 (0.9)	4 (1.7)	5 (4.5)	3 (2.6)	8 (3.5)
Administrative problems	2 (1.7)	1 (0.9)	3 (1.3)	0	1 (0.9)	1 (0.4)
Death	0	1 (0.9)	1 (0.4)	1 (0.9)	0	1 (0.4)
Protocol deviation	0	0	0	0	2 (1.8)	2 (0.9)
	H2356 Extension 1*			H2357 Extension 1*		
Completed the core phase	109 (94.8)	105 (91.3)	214 (93.0)	99 (88.4)	103 (90.4)	202 (89.4)
Entered the extension 1 phase	90 (78.3)	85 (73.9)	175 (76.1)	84 (75.0)	76 (66.7)	160 (70.8)
Completed the extension 1 phase	87 (75.7)	80 (69.6)	167 (72.6)	78 (69.6)	72 (63.2)	150 (66.4)
Discontinued (core and extension)	9 (7.8)	15 (13.0)	24 (10.4)	19 (17.0)	15 (13.2)	34 (15.0)
Reason for discontinuation						
Adverse event(s)	0	0	0	1 (0.9)	0	1 (0.4)
Abnormal laboratory value(s)	0	0	0	1 (0.9)	1 (0.9)	2 (0.9)
Abnormal test procedure result(s)	0	0	0	0	0	0
Unsatisfactory therapeutic effect	0	5 (4.3)	5 (2.2)	0	1 (0.9)	1 (0.4)
Patient no longer needs study drug	0	0	0	0	0	0
Patient withdrew consent	1 (0.9)	4 (3.5)	5 (2.2)	10 (8.9)	7 (6.1)	17 (7.5)
Lost to follow-up	5 (4.3)	4 (3.5)	9 (3.9)	6 (5.4)	3 (2.6)	9 (4.0)
Administrative problems	2 (1.7)	1 (0.9)	3 (1.3)	0 (0.0)	1 (0.9)	1 (0.4)
Death	0	1 (0.9)	1 (0.4)	1 (0.9)	0	1 (0.4)
Protocol deviation	1 (0.9)	0	1 (0.4)	0 (0.0)	2 (1.8)	2 (0.9)

* data are cumulative for core and extension studies
ACZ885 = canakinumab, TA = triamcinolone acetonide

6.2.2 Adverse events in the pivotal core and extension studies

The AEs by primary SOC are displayed for both pivotal studies, cumulative for the core and extension studies (Table 6-6). Overall, more patients treated with canakinumab reported at least one adverse event, compared with triamcinolone treated patients. In both studies there was a higher incidence of infections with canakinumab especially of upper respiratory tract infections, mostly mild and self-limiting.

Table 6-6 AEs by primary system organ class

	Study H2356 core + E1		Study H2357 core + E1	
	ACZ885 150 mg s.c. N=113 n (%)	TA 40 mg i.m. N=115 n (%)	ACZ885 150 mg sc N=112 n (%)	TA 40 mg im N=114 n (%)
Total with AE(s)	71 (62.8)	56 (48.7)	78 (69.6)	65 (57.0)
Infections and infestations	25 (22.1)	18 (15.7)	21 (18.8)	10 (8.8)
Musculoskeletal & connective tissue	19 (16.8)	11 (9.6)	21 (18.8)	27 (23.7)
Nervous system disorders	17 (15.0)	6 (5.2)	10 (8.9)	13 (11.4)
Investigations	16 (14.2)	9 (7.8)	13 (11.6)	16 (14.0)
Metabolism and nutrition disorders	16 (14.2)	11 (9.6)	12 (10.7)	13 (11.4)
Vascular disorders	12 (10.6)	10 (8.7)	6 (5.4)	6 (5.3)
Gastrointestinal disorders	9 (8.0)	8 (7.0)	18 (16.1)	10 (8.8)
Cardiac disorders	8 (7.1)	6 (5.2)	4 (3.6)	5 (4.4)
Skin & subcutaneous tissue disorders	7 (6.2)	3 (2.6)	2 (1.8)	8 (7.0)
Blood & lymphatic system disorders	6 (5.3)	3 (2.6)	4 (3.6)	1 (0.9)
Renal & urinary disorders	6 (5.3)	3 (2.6)	3 (2.7)	3 (2.6)
General disorders & admin. site	5 (4.4)	4 (3.5)	12 (10.7)	6 (5.3)
Eye disorders	4 (3.5)	0	1 (0.9)	1 (0.9)
Psychiatric disorders	4 (3.5)	2 (1.7)	4 (3.6)	5 (4.4)
Injury, poisoning & procedural compl.	3 (2.7)	6 (5.2)	7 (6.3)	9 (7.9)
Ear & labyrinth disorders	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Hepatobiliary disorders	2 (1.8)	1 (0.9)	3 (2.7)	1 (0.9)
Respiratory, thoracic & mediastinal	2 (1.8)	2 (1.7)	8 (7.1)	5 (4.4)
Social circumstances	0	1 (0.9)	0	0
Neoplasms benign, malignant & unsp.	0	0	2 (1.8)	0
Immune system disorders	0	0	1 (0.9)	1 (0.9)
Congenital, familial & genetic dis.	0	0	0	1 (0.9)
Endocrine disorders	0	0	0	1 (0.9)

Primary system organ classes (SOCs) sorted by descending frequency for ACZ885 in Study H2356 core+E1
ACZ885 = canakinumab, TA = triamcinolone acetonide

The most common AEs in both studies that occurred with a frequency of > 3% in any treatment group are summarized in Table 6-7. Most AEs were mild or moderate in severity and not reported to be related to study drug.

Table 6-7 Most frequent AEs by preferred term (greater than 3 percent in any group)

	Study H2356 core + E1		Study H2357 core + E1	
	ACZ885 150 mg s.c. N=113 n (%)	TA 40 mg i.m. N=115 n (%)	ACZ885 150 mg sc N=112 n (%)	TA 40 mg im N=114 n (%)
Total with AE(s)	71 (62.8)	56 (48.7)	78 (69.6)	65 (57.0)
Headache	7 (6.2)	2 (1.7)	4 (3.6)	6 (5.3)
Hypertension	7 (6.2)	8 (7.0)	5 (4.5)	5 (4.4)
GGT increased	6 (5.3)	2 (1.7)	0	0
Arthralgia	5 (4.4)	1 (0.9)	4 (3.6)	9 (7.9)
Back pain	5 (4.4)	0	8 (7.1)	2 (1.8)
Hypertriglyceridemia	5 (4.4)	0	4 (3.6)	2 (1.8)
Nasopharyngitis	5 (4.4)	1 (0.9)	0	4 (3.5)
Osteoarthritis	5 (4.4)	1 (0.9)	0	0
Gout	0	5 (4.3)	1 (0.9)	4 (3.5)
Rash	0	0	0	4 (3.5)
Muscle spasms	0	0	3 (2.7)	6 (5.3)
Pain in extremity	0	0	2 (1.8)	5 (4.4)
Blood CPK increased	0	0	1 (0.9)	4 (3.5)
Fatigue	0	0	5 (4.5)	1 (0.9)
Diarrhoea	0	0	4 (3.6)	3 (2.6)

Preferred terms are sorted by descending frequency for ACZ885 in Study H2356E1
ACZ885 = canakinumab, TA = triamcinolone acetonide

6.2.3 Deaths and SAEs

Deaths and serious adverse events from the pivotal core studies and their extensions are summarized in Table 6-8.

Table 6-8 Deaths and SAEs

	H2356 (core + E1)		H2357 (core +E1)	
	ACZ885 150 mg s.c. N=113 n (%)	TA 40 mg i.m. N=115 n (%)	ACZ885 150 mg s.c. N=112 n (%)	TA 40 mg i.m. N=114 n (%)
Death(s)	0	0	1 (0.9)	0
Patient with SAE(s)	11 (9.7)*	6 (5.2)	7 (6.3)	2(1.8)

ACZ885 = canakinumab, TA = triamcinolone acetonide
*Patient 0013/00001 with SAE of pneumonia died during E2

Deaths were balanced between the 2 treatments and neither of the 2 deaths was reported related to study drug. One patient in the triamcinolone acetonide group of Study H2356 core experienced an SAE of pulmonary embolism on Day 10, and died the same day from sudden cardiovascular death. One patient in the canakinumab group of Study H2357 core experienced an intracranial hemorrhage on Day 57 after start of study medication and died 10 days later. The last and only dose of canakinumab 150 mg was administered on Day 1. This patient has a

medical history of a prior cerebrovascular accident and active medical conditions of hypertension and obesity. SAE were more frequently reported in canakinumab treated patient than in triamcinolone acetonide.

There were 18 patients in the canakinumab treatment groups who reported 24 SAEs (11 with 15 events and 7 with 9 events for Studies H2356+E1 and H2357+E1, respectively) and 8 patients in the triamcinolone acetonide group reported 13 SAEs (6 with 6 SAEs and 2 with 7 SAEs in Studies H2356+E1 and H2357+E1, respectively).

An overview of all patients who experienced SAEs is provided in [Table 6-9](#). All SAEs were associated with hospitalization. None were suspected to be related to study drug by the investigator.

Based on its mechanism of action and potent anti-inflammatory effect, there is an increased risk of infections with canakinumab, which is discussed further in the Safety Topics of Special Interest (Section 9.1). This increased risk of infections was also observed in CAPS and is included as a Warning in current product labeling. In the pivotal gouty arthritis trials, including the extensions, 4 subjects had infections (jaw abscess, limb abscess, pneumonia and gastroenteritis) and were hospitalized during the initial 24 weeks of the core and E1 extensions. They recovered with standard care and continued the study. Two subjects receiving triamcinolone acetonide were hospitalized for acute gout attacks. None receiving canakinumab required hospitalization for gout.

Table 6-9 Overview of patients with SAEs

Patient ID	Age/ sex/ race	SAE(s) (preferred term)	Severity	Comments
Canakinumab				
H2356 (core and extension)				
BEL/0030/00005	79/F/Ca	Angina pectoris	Moderate	History of cardiac failure, hypertension (active)
BEL/0030/00007	39/M/Ca	Glaucoma	Severe	History of glaucoma (active)
DEU/0082/00011	73/F/Ca	Gastritis Chronic renal failure	Moderate Severe	History of chronic renal failure (active)
LTU/0020/00009	47/M/Ca	Spondylolisthesis Spinal cord ischemia Lumbar spinal stenosis	Moderate Moderate Moderate	History of radiculopathy, spondylolisthesis, osteochondrosis, spinal osteoarthritis (active)
LTU/0022/00005	55/M/Ca	Arrhythmia	Moderate	History of arrhythmia (past)
LTU/0023/00005	53/M/Ca	Renal artery occlusion Myocardial ischemia	Moderate Mild	History of hypertension, left ventricular hypertrophy, diabetes mellitus (active)
POL/0121/00001	52/M/Ca	Abscess jaw	Severe	Resolved with standard of care
RUS/0132/00006	52/M/Ot	Prostatic specific antigen increased	Moderate	Patient was hospitalized
SGP/0160/00003	71/M/As	Hyperglycemia	Mild	History of diabetes mellitus (active). Event was due to omission of insulin.
UKR/0197/00003	56/M/Ca	Device dislocation	Moderate	Hip endoprosthesis issues led to surgery

Patient ID	Age/ sex/ race	SAE(s) (preferred term)	Severity	Comments
LVA/0013/00001	74/M/Ca	Pneumonia	Mild	History of nephrosclerosis, CHF and obesity, died about 3 months after last study drug administration during E2
H2357 (core and extension)				
0527/00001	51/M/As	Convulsion	Moderate	The event occurred on Day 37 and resolved on the same day. The patient received 2 doses of study drug, the first on Day 1 and the second on Day 16. The investigator reported that the convulsion was due to a space-occupying lesion.
0540/00006	26/M/Ca	Abscess limb	Moderate	Medical history included cellulitis.
0547/00002	60/M/Ca	Atrial fibrillation	Moderate	No related medical history.
0548/00005	67/M/BI	Pancreatitis	Moderate	No related medical history.
0558/00003	52/M/Ca	Gastroenteritis	Severe	The event occurred on Day 27 and resolved the next day. The patient received only one dose of study drug on Day 1. No relevant medical history.
0580/00004	63/M/Ca	Cerebrovascular accident Hemorrhage intracranial	Mild Severe	The cerebrovascular accident occurred on Day 56, followed by the fatal intracranial hemorrhage on Day 67. The patient received only one dose of study drug on Day 1. Medical history included a prior cerebrovascular accident and active hypertension and obesity.
0588/00003	65/M/Ca	Back pain Intervertebral disc protrusion*	Severe Severe	Medical history included intervertebral disc operation, osteoarthritis in knees, and bilateral knee arthroscopy.
Triamcinolone acetonide				
H2356 (core and extension)				
EST/0008/00004	41/M/Ca	Meniscus lesion	Moderate	Past history of meniscus lesion, and meniscus removal
LTU/0024/00002	54/M/Ca	Vertebrobasilar insufficiency	Moderate	Past history of transient ischemic attack
NOR/0101/00001	59/M/Ca	Pulmonary embolism	Severe	Patient died. History of hypertension, atrial dilation (active)
RUS/0135/00003	74/M/Ca	Ischemic stroke	Severe	History of hypertension (active). Past history of chronic cardiac failure
SGP/0160/00002	39/M/As	Gout	Severe	Patient was hospitalized due to severe pain from gout attack
UKR/0197/00002	55/M/Ca	Gout	Moderate	Hospitalized for SAE during E1

Patient ID	Age/ sex/ race	SAE(s) (preferred term)	Severity	Comments
H2357 (core and extension)				
0571/00004	63/F/ Black	Vomiting Diarrhea Nausea	Severe Severe Severe	The 3 events started on Day 67 and resolved 4 days later on Day 70. The patient received 2 doses of study drug, the first on Day 1 and the second on Day 15.
0591/00002	56/M/Ca	(Worsening) aortic valve incompetence Aortic stenosis (Worsening) bicuspid aortic valve Cardiomyopathy	Moderate Moderate Moderate Moderate	No relevant medical history. Medical history included heart valve incompetence, ECG poor R-wave progression, and myocardial infarction (all active at core study entry). The patient also had active hypertension, type I diabetes, hypertriglyceridemia and obesity.

6.2.4 Safety profile with re-treatment

6.2.4.1 AEs and SAEs in re-treated patients

6.2.4.1.1 Adverse events

AEs were analyzed in re-treated patients (35 and 25 patients on canakinumab and 43 and 46 patients on triamcinolone acetonide H2356 core+E1 and H2357 core+E1, respectively), as shown in Table 6-10.

Table 6-10 AEs by SOC in patients re-treated and not re-treated

	H2356 core+E1						H2357 core+E1					
	Retreated			Not re-treated			Retreated			Not re-treated		
	ACZ885 150 mg N=35 n (%)	TA 40 mg N=43 n (%)	Total N=78 n (%)	ACZ 150 mg N=78 n (%)	TA 40 mg N=72 n (%)	Total N=150 n (%)	ACZ 150 mg N=25 n (%)	TA 40 mg N=46 n (%)	Total N=71 n (%)	ACZ 150 mg N=87 n (%)	TA 40 mg N=68 n (%)	Total N=155 n (%)
Any AE	25 (71.4)	21 (48.8)	46 (59.0)	46 (59.0)	35 (48.6)	81 (54.0)	23 (92.0)	30 (65.2)	53 (74.6)	55 (63.2)	35 (51.5)	90 (58.1)
Blood & lymphatic syst.	2 (5.7)	2 (4.7)	4 (5.1)	4 (5.1)	1 (1.4)	5 (3.3)	0	1 (2.2)	1 (1.4)	4 (4.6)	0	4 (2.6)
Cardiac disorders	3 (8.6)	1 (2.3)	4 (5.1)	5 (6.4)	5 (6.9)	10 (6.7)	1 (4.0)	3 (6.5)	4 (5.6)	3 (3.4)	2 (2.9)	5 (3.2)
Congenital, familial	0	0	0	0	0	0	0	1 (2.2)	1 (1.4)	0	0	0
Ear & labyrinth dis.	1 (2.9)	1 (2.3)	2 (2.6)	1 (1.3)	0	1 (0.7)	0	0 (0.0)	0	1 (1.1)	1 (1.5)	2 (1.3)
Endocrine disorders	0	0	0	0	0	0	0	0 (0.0)	0	0	1 (1.5)	1 (0.6)
Eye disorders	3 (8.6)	0 (0.0)	3 (3.8)	1 (1.3)	0	1 (0.7)	0	1 (2.2)	1 (1.4)	1 (1.1)	0	1 (0.6)
Gastrointestinal dis.	2 (5.7)	4 (9.3)	6 (7.7)	7 (9.0)	4 (5.6)	11 (7.3)	7 (28.0)	6 (13.0)	13 (18.3)	11 (12.6)	4 (5.9)	15 (9.7)
General disorders	3 (8.6)	3 (7.0)	6 (7.7)	2 (2.6)	1 (1.4)	3 (2.0)	3 (12.0)	4 (8.7)	7 (9.9)	9 (10.3)	2 (2.9)	11 (7.1)
Hepatobiliary disorders	1 (2.9)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.4)	2 (1.3)	2 (8.0)	1 (2.2)	3 (4.2)	1 (1.1)	0	1 (0.6)
Immune System dis.	0	0	0	0	0	0	0	1 (2.2)	1 (1.4)	1 (1.1)	0	1 (0.6)
Infections & infest.	8 (22.9)	9 (20.9)	17 (21.8)	17 (21.8)	9 (12.5)	26 (17.3)	7 (28.0)	4 (8.7)	11 (15.5)	14 (16.1)	6 (8.8)	20 (12.9)
Injury, poison, & proc.	1 (2.9)	3 (7.0)	4 (5.1)	2 (2.6)	3 (4.2)	5 (3.3)	3 (12.0)	5 (10.9)	8 (11.3)	4 (4.6)	4 (5.9)	8 (5.2)
Investigations	8 (22.9)	1 (2.3)	9 (11.5)	8 (10.3)	8 (11.1)	16 (10.7)	6 (24.0)	8 (17.4)	14 (19.7)	7 (8.0)	8 (11.8)	15 (9.7)
Metabolism & nutrition	8 (22.9)	3 (7.0)	11 (14.1)	8 (10.3)	8 (11.1)	16 (10.7)	5 (20.0)	8 (17.4)	13 (18.3)	7 (8.0)	5 (7.4)	12 (7.7)
Muskuloskel. & conn.	8 (22.9)	5 (11.6)	13 (16.7)	11 (14.1)	6 (8.3)	17 (11.3)	5 (20.0)	10 (21.7)	15 (21.1)	16 (18.4)	17 (25.0)	33 (21.3)
Neoplasms benign	0	0	0	0	0	0	0	0	0	2 (2.3)	0	2 (1.3)
Nervous system dis.	6 (17.1)	3 (7.0)	9 (11.5)	11 (14.1)	3 (4.2)	14 (9.3)	4 (16.0)	8 (17.4)	12 (16.9)	6 (6.9)	5 (7.4)	11 (7.1)
Psychiatric disorders	1 (2.9)	1 (2.3)	2 (2.6)	3 (3.8)	1 (1.4)	4 (2.7)	2 (8.0)	2 (4.3)	4 (5.6)	2 (2.3)	3 (4.4)	5 (3.2)
Renal urinary disorders	2 (5.7)	1 (2.3)	3 (3.8)	4 (5.1)	2 (2.8)	6 (4.0)	2 (8.0)	1 (2.2)	3 (4.2)	1 (1.1)	2 (2.9)	3 (1.9)

	H2356 core+E1					H2357 core+E1						
	Retreated			Not re-treated		Retreated			Not re-treated			
	ACZ885 150 mg N=35 n (%)	TA 40 mg N=43 n (%)	Total N=78 n (%)	ACZ 150 mg N=78 n (%)	TA 40 mg N=72 n (%)	Total N=150 n (%)	ACZ 150 mg N=25 n (%)	TA 40 mg N=46 n (%)	Total N=71 n (%)	ACZ 150 mg N=87 n (%)	TA 40 mg N=68 n (%)	Total N=155 n (%)
Respir., thor. & med.	1 (2.9)	1 (2.3)	2 (2.6)	1 (1.3)	1 (1.4)	2 (1.3)	5 (20.0)	3 (6.5)	8 (11.3)	3 (3.4)	2 (2.9)	5 (3.2)
Skin & subcut. tiss. dis.	4 (11.4)	3 (7.0)	7 (9.0)	3 (3.8)	0	3 (2.0)	2 (8.0)	4 (8.7)	6 (8.5)	0	4 (5.9)	4 (2.6)
Social circumstances	0	0	0	0	1 (1.4)	1 (0.7)	0	0	0	0	0	0
Vascular disorders	7 (20.0)	6 (14.0)	13 (16.7)	5 (6.4)	4 (5.6)	9 (6.0)	3 (12.0)	4 (8.7)	7 (9.9)	3 (3.4)	2 (2.9)	5 (3.2)

ACZ885=canakinumab, TA=triamcinolone acetonide

Overall, there was a higher incidence of subjects reporting AEs seen in the re-treated versus non-re-treated canakinumab patients (71.4% and 92.0% for re-treated canakinumab patients vs. 59.0% and 63.2% for not re-treated canakinumab patients in H2356E1 and H2357E1, respectively). Among the 60 patients retreated in the canakinumab, these tended to be more severe gouty arthritis patients compared with the 89 retreated with triamcinolone. The canakinumab group vs triamcinolone acetonide group had more polyarticular involvement (31.7% vs. 13.5%), presence of tophi (46.7 vs. 33.7) and historical flare frequency (mean of 8.1 flares/year vs. 6.3 flares per year).

No difference was seen between the re-treated and not re-treated triamcinolone acetonide patients (48.8% vs. 48.6%) in H2356, a slightly higher incidence of patients with AEs were reported in H2357 among re-treated triamcinolone acetonide patients (65.2% vs. 51.5%).

SOCs with a >10% higher proportion of patients with AEs in re-treated versus non-re-treated canakinumab patients were investigations (22.9% vs. 10.3%), metabolism and nutrition disorders (22.9% vs. 10.3%) and vascular disorders (20.0% vs. 6.4%) in H2356E1. In H2357E1, gastrointestinal disorders (28.0% vs. 12.6%), infections and infestations (28.0% vs. 16.1%), and investigations (24.0% vs. 8.0%) were reported more in the retreated canakinumab group than the non-retreated canakinumab group. The frequencies of other SOC's were comparable between the re-treated and non-re-treated canakinumab patients.

Despite the observation that a greater percentage of patients re-treated with canakinumab reported AEs, compared to those patients not re-treated in both studies, the increased rate did not appear to be related to the re-treatment itself. Of the 35 patients in H2356E1 and 25 patients in H2357E1, who received more than one dose of canakinumab, the incidence of AEs within the first 4 weeks of the first dose was comparable to the first 4 weeks after the second dose. In H2356E1, 15 (42.9%) had AEs within 4 weeks of the first dose and 12 (34.3%) had AEs within 4 weeks of the second dose and in H2357E1, 11 (44%) were reported in the same period after the first dose and 10 (40%) after the second dose, showing that the proportion of patients reporting AEs did not rise after re-treatment.

6.2.4.1.2 Serious Adverse Events

The frequency of SAEs in re-treated patients was low overall: 2 patients or 5.7% on canakinumab and 1 patient or 2.3% on triamcinolone acetonide in H2356E1 and 1 patient or 4.0% on canakinumab and 2 or 4.3% patients on triamcinolone acetonide in H2357E1. The SAEs included glaucoma (1 patient) and myocardial ischemia and retinal artery occlusion (both in 1 patient) and convulsions (1 patient) with canakinumab re-treatment, and gout (1 patient) and vomiting, diarrhea and nausea (3 events in 1 patient after the first dose), and aortic valve incompetence, cardiomyopathy, bicuspid aortic valve and aortic stenosis (1 patient after the second dose) in triamcinolone acetonide re-treated patients.

6.2.4.2 Safety profile in patients re-treated in 2356/E2 and 2357/E2

New flares were infrequent with canakinumab and data from the second extension provides more data on the safety of retreatment. As described above, patients with new flares in the canakinumab group tended to have more severe gouty arthritis. The adverse event profile after

the first dose in these patients did not appear to be different from patients who received second or subsequent re-treatments. The data is presented as the frequency of events before and after canakinumab re-treatment in patients treated only with canakinumab, and in patients originally treated with triamcinolone acetonide and then switched to canakinumab in E2 and thus, newly exposed to canakinumab. Overall, the review of the safety data in patients re-treated with canakinumab in the Phase 3 program demonstrates no relevant new safety findings associated with receiving a second dose of canakinumab.

Adverse events

The frequencies of patient with AEs in SOCs are shown for Study H2356E2 i.a. and Study H2357E2 i.a. in Table 6-11 and Table 6-12, respectively. Whereas the overall rate of AEs was higher in patients with new flares treated with canakinumab than in those treated with triamcinolone acetonide, it did not rise in either study after canakinumab re-treatment compared to before canakinumab re-treatment or after starting canakinumab treatment in patients previously treated with triamcinolone acetonide.

After canakinumab re-treatment, the frequency of patients with SOCs of infections, investigations, metabolic disorders and musculoskeletal disorders were generally lower than before re-treatment, and rates did not rise after the initiation of canakinumab treatment in patients previously treated with triamcinolone acetonide.

Table 6-11 AEs by primary SOC (>5% in any group) (Study H2356E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=113 n (%)	Before ACZ Re-treatment N=64 n (%)	After ACZ Re-treatment N=64 n (%)	All TA N=115 n (%)	Before ACZ treatment N=35 n (%)	After ACZ treatment N=35 n (%)
Total with any AE	75 (66.4)	39 (60.9)	33 (51.6)	60(52.2)	18 (51.4)	14 (40.0)
Blood & lymphatic syst.	7 (6.2)	3 (4.7)	1 (1.6)	3 (2.6)	1 (2.9)	0
Cardiac disorders	10(8.8)	4 (6.3)	2 (3.1)	8 (7.0)	2 (5.7)	1 (2.9)
Gastrointestinal dis.	11 (9.7)	6 (9.4)	3 (4.7)	9 (7.8)	1 (2.9)	2 (5.7)
Infections & infestations	33 (29.2)	16 (25.0)	12 (18.8)	20(17.4)	6 (17.1)	8 (22.9)
Injury, poison. & proc.	5 (4.4)	3 (4.7)	1 (1.6)	7 (6.1)	4 (11.4)	0
Investigations	16 (14.2)	8 (12.5)	4 (6.3)	12 (10.4)	3 (8.6)	0
Metabolism & nutrition	17 (15.0)	10(15.6)	3 (4.7)	12 (10.4)	2 (5.7)	2 (5.7)
Musculoskel. & conn.	22 (19.5)	10(15.6)	6 (9.4)	12 (10.4)	2 (5.7)	2 (5.7)
Nervous system dis.	20(17.7)	8 (12.5)	6 (9.4)	6 (5.2)	1 (2.9)	1 (2.9)
Psychiatric disorders	6 (5.3)	1 (1.6)	2 (3.1)	3 (2.6)	2 (5.7)	0
Renal & urinary dis.	10(8.8)	6 (9.4)	3 (4.7)	5 (4.3)	1 (2.9)	0
Respiratory., thoracic	2 (1.8)	1 (1.6)	1 (1.6)	6 (5.2)	1 (2.9)	1 (2.9)
Skin & subcutan. tiss.	9 (8.0)	5 (7.8)	4 (6.3)	3 (2.6)	1 (2.9)	0
Vascular disorders	18 (15.9)	8 (12.5)	9 (14.1)	12 (10.4)	3 (8.6)	2 (5.7)

ACZ = canakinumab, TA = triamcinolone acetonide

Table 6-12 AEs by primary SOC (>5% in any group) (Study H2357E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=112 n (%)	Before ACZ Re-treatment N=54 (%)	After ACZ Re-treatment N=54 n (%)	All TA N=114 n (%)	Before ACZ treatment N=32 n (%)	After ACZ treatment N=32 n (%)
Total with any AE	78 (69.6)	38 (70.4)	23 (42.6)	68 (59.6)	22 (68.8)	12 (37.5)
Blood & lymphatic system	4 (3.6)	0	0	1 (0.9)	1 (3.1)	3 (9.4)
Gastrointestinal disorders	19 (17.0)	7 (13.0)	3 (5.6)	10(8.8)	2 (6.3)	3 (9.4)
General dis. & admin. site	12 (10.7)	4 (7.4)	2 (3.7)	7 (6.1)	2 (6.3)	0
Hepatobiliary disorders	4 (3.6)	3 (5.6)	1 (1.9)	1 (0.9)	0	1 (3.1)
Infections & infestations	29 (25.9)	13 (24.1)	10 (18.5)	14 (12.3)	7 (21.9)	2 (6.3)
Injury, poison. & proc.	7 (6.3)	2 (3.7)	2 (3.7)	9 (7.9)	6 (18.8)	0
Investigations	14 (12.5)	4 (7.4)	7 (13.0)	18 (15.8)	4 (12.5)	0
Metabolism & nutrition	15 (13.4)	5 (9.3)	4 (7.4)	13 (11.4)	4 (12.5)	1 (3.1)
Musculoskeletal & conn.	25 (22.3)	7 (13.0)	7 (13.0)	27 (23.7)	9 (28.1)	2 (6.3)
Nervous system dis.	10(8.9)	4 (7.4)	3 (5.6)	13 (11.4)	3 (9.4)	2 (6.3)
Psychiatric disorders	4 (3.6)	4 (7.4)	1 (1.9)	5 (4.4)	0	1 (3.1)
Renal & urinary disorders	5 (4.5)	1 (1.9)	3 (5.6)	5 (4.4)	2 (6.3)	1 (3.1)
Respiratory, thor. & med.	10(8.9)	4 (7.4)	4 (7.4)	5 (4.4)	2 (6.3)	3 (9.4)
Skin & subcutan. tissue	4 (3.6)	2 (3.7)	0	9 (7.9)	3 (9.4)	0
Vascular disorders	9 (8.0)	3 (5.6)	3 (5.6)	6 (5.3)	1 (3.1)	2 (6.3)

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

The frequencies of common i.e. >5% AEs by preferred term for both studies are shown in Tables 6-13 and Table 6-14, respectively. The rates of many AEs were higher in patients with new flares treated with canakinumab than in those treated with triamcinolone acetonide but did not rise in either study after canakinumab re-treatment compared to before canakinumab re-treatment, or after starting canakinumab treatment in patients previously treated with triamcinolone acetonide.

Table 6-13 Common AEs by preferred term (>5% in any group) (Study H2356E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=113 n (%)	Before ACZ Re-treatment N=64 n (%)	After ACZ Re-treatment N=64 n (%)	All Triam N=115 n (%)	Before ACZ treatment N=35 n (%)	After ACZ treatment N=35 n (%)
Total with any AE	75 (66.4)	39 (60.9)	33 (51.6)	60 (52.2)	18 (51.4)	14 (40.0)
Hypertension	12 (10.6)	5 (7.8)	6 (9.4)	10 (8.7)	3 (8.6)	2 (5.7)
Headache	8 (7.1)	3 (4.7)	2 (3.1)	2 (1.7)	0	1 (2.9)
Nasopharyngitis	8 (7.1)	3 (4.7)	2 (3.1)	2 (1.7)	0	1 (2.9)
Gamma-GT increased	6 (5.3)	3 (4.7)	1 (1.6)	4 (3.5)	0	0
Arthralgia	6 (5.3)	2 (3.1)	3 (4.7)	2 (1.7)	1 (2.9)	1 (2.9)
Bronchitis	3 (2.7)	1 (1.6)	1 (1.6)	3 (2.6)	2 (5.7)	3 (8.6)
Osteoarthritis	7 (6.2)	1 (1.6)	2 (3.1)	1 (0.9)	0	0
Back pain	6 (5.3)	4 (6.3)	2 (3.1)	0	0	1 (2.9)
Hypertriglyceridaemia	5 (4.4)	4 (6.3)	0	0	0	1 (2.9)
Upper resp. tract inf.	2 (1.8)	2 (3.1)	0	3 (2.6)	2 (5.7)	0
Hyperlipidaemia	0	0	0	1 (0.9)	0	2 (5.7)

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

Table 6-14 Common AEs by preferred term (>5% in any group) (Study H2357E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=112 n (%)	Before ACZ Re treatment N=54 n (%)	After ACZ Re treatment N=54 n (%)	All Triam N=114 n (%)	Before ACZ treatment N=32 n (%)	After ACZ treatment N=32 n (%)
Total with any AE	78 (69.6)	38 (70.4)	23 (42.6)	68 (59.6)	22 (68.8)	12 (37.5)
Arthralgia	4 (3.6)	1 (1.9)	1 (1.9)	9 (7.9)	3 (9.4)	0
Hypertension	7 (6.3)	2 (3.7)	3 (5.6)	5 (4.4)	1 (3.1)	1 (3.1)
Headache	4 (3.6)	3 (5.6)	1 (1.9)	6 (5.3)	2 (6.3)	1 (3.1)
Muscle spasms	4 (3.6)	2 (3.7)	1 (1.9)	7 (6.1)	2 (6.3)	0
Back pain	8 (7.1)	2 (3.7)	2 (3.7)	2 (1.8)	1 (3.1)	0
Pain in extremity	3 (2.7)	2 (3.7)	0	6 (5.3)	3 (9.4)	0
Upper resp tract inf.	7 (6.3)	4 (7.4)	4 (7.4)	2 (1.8)	1 (3.1)	0
Nasopharyngitis	0	0	0	5 (4.4)	4 (12.5)	2 (6.3)
Oedema peripheral	2 (1.8)	0	0	4 (3.5)	2 (6.3)	0
Insomnia	3 (2.7)	3 (5.6)	1 (1.9)	2 (1.8)	0	0
Muscle strain	1 (0.9)	0	0	2 (1.8)	2 (6.3)	0
Sinus congestion	1 (0.9)	1 (1.9)	0	0	0	2 (6.3)
Dermal cyst	0	0	0	2 (1.8)	2 (6.3)	0
Limb injury	0	0	0	2 (1.8)	2 (6.3)	0
Proteinuria	0	0	0	2 (1.8)	2 (6.3)	0

ACZ = canakinumab, TA = triamcinolone acetoneide, i.a. = interim analysis

The frequencies of patients with AEs by SOC within 4 weeks after 1st or 2nd dosing are shown for Study H2356E2 i.a. and Study H2357E2 i.a. in Table 6-15 and Table 6-16,

respectively. The frequencies of AEs in the 4 weeks after dosing in either study did not rise after a 2nd compared to the 1st canakinumab dose, and did not rise after starting canakinumab treatment in patients previously treated with triamcinolone acetonide.

Table 6-15 AEs within 4 weeks of dosing by primary SOC (Study H2356E2 i.a.)

	ACZ885 150 mg s.c. re-treated with ACZ885, N = 64		TA 40 mg i.m. treated with ACZ885, N = 35	
	within 4 wks after 1st dose of ACZ n (%)	within 4 wks after 2nd dose of ACZ n (%)	within 4 wks after 1st dose of TA n (%)	within 4 wks after 1st dose of ACZ n (%)
Total with any AE	19 (29.7)	19 (29.7)	5 (14.3)	6 (17.1)
Blood & lymphatic system disorders	2 (3.1)	0	1 (2.9)	0
Cardiac disorders	1 (1.6)	0	0	0
Ear & labyrinth disorders	0	1 (1.6)	1 (2.9)	0
Eye disorders	0	1 (1.6)	0	0
Gastrointestinal disorders	4 (6.3)	1 (1.6)	0	1 (2.9)
General disorders & administr. site cond.	3 (4.7)	1 (1.6)	1 (2.9)	0
Immune system disorders	0	1 (1.6)	0	0
Infections & infestations	5 (7.8)	4 (6.3)	1 (2.9)	3 (8.6)
Injury, poisoning & procedural compl.	1 (1.6)	0	0	0
Investigations	4 (6.3)	3 (4.7)	0	0
Metabolism & nutrition disorders	6 (9.4)	1 (1.6)	0	0
Musculoskeletal & conn. tissue dis.s	3 (4.7)	1 (1.6)	1 (2.9)	1 (2.9)
Nervous system disorders	6 (9.4)	3 (4.7)	0	1 (2.9)
Renal & urinary disorders	2 (3.1)	0	1 (2.9)	0
Respiratory, thoracic & mediastinal dis.	1 (1.6)	1 (1.6)	0	1 (2.9)
Skin and subcutaneous tissue disorders	1 (1.6)	3 (4.7)	0	0
Vascular disorders	1 (1.6)	3 (4.7)	1 (2.9)	1 (2.9)

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

Table 6-16 AEs within 4 weeks of dosing by primary SOC (Study H2357E2 i.a.)

	ACZ885 150 mg s.c. re-treated with ACZ885, N = 54		TA 40 mg i.m. treated with ACZ885, N = 32	
	within 4 wks after 1st dose of ACZ n (%)	within 4 wks after 2nd dose of ACZ n (%)	within 4 wks after 1st dose of TA n (%)	within 4 wks after 1st dose of ACZ n (%)
Total with any AE	22 (40.7)	14 (25.9)	13 (40.6)	6 (18.8)
Blood & lymphatic system disorders	0	0	1 (3.1)	3 (9.4)
Gastrointestinal disorders	5 (9.3)	3 (5.6)	1 (3.1)	2 (6.3)
General disorders & admin. site cond.	2 (3.7)	1 (1.9)	0	0
Hepatobiliary disorders	2 (3.7)	0	0	1 (3.1)
Infections & infestations	3 (5.6)	2 (3.7)	0	1 (3.1)
Injury, poisoning & procedural comp.	0	1 (1.9)	2 (6.3)	0
Investigations	3 (5.6)	4 (7.4)	2 (6.3)	0
Metabolism & nutrition disorders	2 (3.7)	2 (3.7)	2 (6.3)	0
Musculoskeletal & conn. tissue disorders	4 (7.4)	3 (5.6)	6 (18.8)	0
Neoplasms benign, malignant & unsp.	1 (1.9)	0	0	0
Nervous system disorders	2 (3.7)	1 (1.9)	2 (6.3)	1 (3.1)
Psychiatric disorders	3 (5.6)	1 (1.9)	0	0
Renal & urinary disorders	0	1 (1.9)	1 (3.1)	1 (3.1)
Respiratory, thoracic & mediastin. dis.	1 (1.9)	2 (3.7)	2 (6.3)	1 (3.1)
Skin & subcutaneous tissue disorders	2 (3.7)	0	1 (3.1)	0
Vascular disorders	0	1 (1.9)	0	1 (3.1)

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

Serious adverse events

The frequencies of patient with SAEs by SOCs are shown for Study H2356E2 i.a. and Study H2357E2 i.a. in Table 6-17 and Table 6-18, respectively. The overall rate of SAEs in both studies was higher in patients with new flares treated with canakinumab than in those treated with triamcinolone acetonide. One canakinumab patient died due to pneumonia in the second extension (patient H2356E2-0013-00001). This 74 year old, male Caucasian received canakinumab on day 1 and day 214. He had pneumonia reported as an SAE on days 161-172 in E1, and again from days 262-323 when he died. Coexisting conditions were chronic heart failure and nephrosclerosis. One patient who had an SAE of worsening of anemia (patient H2357E2-0523-00002), reported after switching from triamcinolone acetonide to canakinumab, discontinued because of this event.

Table 6-17 Frequency of SAEs (Study H2356E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=113 n (%)	Before ACZ Re treatment N=64 n (%)	After ACZ Re treatment N=64 n (%)	All TA N=115 n (%)	Before ACZ treatment N=35 n (%)	After ACZ treatment N=35 n (%)
with any SAE	18 (15.9)	6 (9.4)	7 (10.9)	10 (8.7)	1 (2.9)	0
Cardiac disorders	5 (4.4)	1 (1.6)	2 (3.1)	2 (1.7)	0	0
Eye disorders	2 (1.8)	2 (3.1)	0	0	0	0
Gastrointestinal dis.	2 (1.8)	0	1 (1.6)	0	0	0
General disorders	1 (0.9)	0	0	0	0	0
Infections & infestat.	2 (1.8)	2 (3.1)	1 (1.6)	1 (0.9)	0	0
Injury, poisoning	1 (0.9)	0	0	1 (0.9)	0	0
Investigations	1 (0.9)	0	0	0	0	0
Metabolism & nutr.	1 (0.9)	1 (1.6)	1 (1.6)	2 (1.7)	1 (2.9)	0
Musculoskel. & conn.	1 (0.9)	1 (1.6)	0	0	0	0
Neopl. malign. benign	0	0	0	1 (0.9)	0	0
Nervous system dis.	3 (2.7)	1 (1.6)	2 (3.1)	2 (1.7)	0	0
Renal & urinary dis.	4 (3.5)	1 (1.6)	2 (3.1)	1 (0.9)	0	0
Respirat., thor. & med.	0	0	0	1 (0.9)	0	0
Vascular disorders	1 (0.9)	0	0	0	0	0

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

Table 6-18 Frequency of SAEs (Study H2357E2 i.a.)

	ACZ885 150 mg s.c.			TA 40 mg i.m.		
	All ACZ N=112 n (%)	Before ACZ Re treatment N=54 n (%)	After ACZ Re treatment N=54 n (%)	All TA N=114 n (%)	Before ACZ treatment N=32 n (%)	After ACZ treatment N=32 n (%)
with any SAE	8 (7.1)	0	1 (1.9)	2 (1.8)	0	2 (6.3)
Blood & lymphatic	0	0	0	0	0	2 (6.3)
Cardiac disorders	1 (0.9)	0	0	1 (0.9)	0	0
Congenital, familial	0	0	0	1 (0.9)	0	0
Gastrointestinal dis.	1 (0.9)	0	0	1 (0.9)	0	1 (3.1)
General disorders	1 (0.9)	0	0	0	0	0
Infections & infestat.	3 (2.7)	0	0	0	0	0
Musculoskel & conn.	1 (0.9)	0	0	0	0	0
Nervous system dis.	2 (1.8)	0	1 (1.9)	0	0	0
Vascular disorders	0	0	0	1 (0.9)	0	0

ACZ = canakinumab, TA = triamcinolone acetonide, i.a. = interim analysis

7 Integrated data in controlled trials of different indications

Integrated data from studies in 2 indications was used to further analyze AE and SAE frequencies, laboratory results, as well as long-term safety experience in an extended dataset.

7.1 Description of the safety datasets in different indications

The evaluation of safety data across the programs has to consider the dosage used and the regimens (single doses, on demand or scheduled dosing), routes of administration (s.c. or i.v.) and various duration and periods of exposure and/or observation.

Separate datasets were created for the indications of gouty arthritis and RA. Studies similar in design, duration and indication were pooled to maximize the amount of information (Table 7-1).

Table 7-1 Study groupings and safety assessments in pooled datasets

Dataset	Studies	Number	Safety topics, Subgroup analyses
Dataset: gouty arthritis (all active-controlled, 8-24 weeks): 3 double-blind core studies, 2 double-blind extensions, 1 single-blind study	H2251, H2255 H2356, H2356E1, H2357, H2357E1	1085 (691 ACZ)c	<i>Topics:</i> deaths, SAEs, significant AEs, all AEs, laboratory data, vital signs, immunogenicity AEs <i>Subgroups:</i> - age, gender, race, BMI - NSAIDs & colchicine ineffective, contraindicated or not tolerated* - comorbidities* -re-treated patients*
[1 study (H2251) to prevent flares 5 studies in treatment of flares]			
Dataset: placebo-controlled RA (4 double-blind, placebo-controlled studies, 12-26 weeks duration)	A2101, A2201 A2204, A2207	465 (344 ACZ, 121 PBO)	<i>Topics:</i> deaths, SAEs, significant AEs, all AEs, laboratory data, vital signs, immunogenicity AEs, dose dependency of safety
Dataset: all RA (8 controlled & uncontrolled studies, 6-104 weeks)	A2101, A2201/E1/E2, A2204, A2207, A2206, A2211	441 (all ACZ)	<i>Topics:</i> deaths, SAEs, significant AEs, all AEs, laboratory data, vital signs, immunogenicity AEs, long-term safety

* subgroups from Studies H2356/E1 and H2357/E1 only, PBO = placebo

7.2 Population characteristics

7.2.1 Gouty arthritis (active controlled studies)

7.2.1.1 Dataset and evaluations

Most of the data in this dataset is derived from the phase 2 and phase 3 studies (including extension phases) already described. The pooled dataset also includes an additional Phase 2 study that evaluated a wider dose range in patient treated prophylactically to prevent paradoxical flare when starting allopurinol. Patients were grouped into separate dose exposure categories: ≤ 100 mg, 150 mg split dose, 150 mg and ≥ 200 mg.

Phase 2 study H2251, was a double-blind, dose-ranging study to evaluate the efficacy of canakinumab in the prevention of acute gouty flares in patients initiating urate-lowering therapy. In this 24 week long study, 432 patients were randomized to receive a single dose of canakinumab, 25, 50, 100, 200, or 300 mg s.c.; or 4 doses of canakinumab administered every 4 weeks (50+50+25+25 for a total 150 mg, referred to as 'split dose'); or daily colchicine 0.5 mg over 16 weeks.

The pooled safety dataset was evaluated for AEs, SAEs and clinical laboratory tests. Besides standard safety evaluations, there was an evaluation of safety topics relevant to this class of immune modulator including experience with canakinumab in the CAPS population and analyses especially relevant for the target population (i.e. infections, opportunistic infections, malignancies, vertigo, severe injection site reactions, hematological changes such as neutropenia and thrombocytopenia, dyslipidemia, hepatic transaminase and bilirubin elevations, autoimmune reactions, immunogenicity/allergenicity, cardiovascular risk factors, pre-existing impairment of renal function, uric acid level).

7.2.1.2 Extent of Exposure

For gouty arthritis, a summary of the overall number of patients exposed, the duration of observation and the frequencies of patients receiving 1, 2, 3, 4 or ≥ 5 drug injections for the gouty arthritis, active-controlled dataset is presented in Table 7-2. Most subjects required only a single injection for the treatment of acute gouty arthritis attacks. Multiple injections in the canakinumab split 150 mg group reflect the design of that study in which subjects received 50 mg injections for Weeks 1 and 2 and 25 mg injections for weeks 3 and 4 such that most (96%) received the full 4 injections.

Table 7-2 Duration of observation, number of drug injections (gouty arthritis)

	ACZ885 ≤100 mg N=278	ACZ885 split 150mg N=53	ACZ885 150 mg N=253	ACZ885 ≥200 mg N=107	TA N=286	colch. N=108
Duration (days)						
Mean (SD)	87.1 (30.3)	113.4 (8.0)	139.3 (48.6)	110.0 (19.3)	124.3 (54.7)	106.7 (23.6)
Median	111.0	113.0	168.0	113.0	165.0	113.0
Min – max	1 – 128	63 - 128	4 - 192	1 – 180	2 - 197	4 – 135
Patient years	66.3	16.5	96.5	32.2	97.3	31.5
Duration - n (%)						
≥1 day	278 (100)	53 (100)	253 (100)	107 (100)	286 (100)	108 (100)
≥4 wks	270 (97.1)	53 (100.0)	248 (98.0)	104 (97.2)	274 (95.8)	105 (97.2)
≥8 wks	260 (93.5)	53 (100.0)	243 (96.0)	104 (97.2)	270 (94.4)	100 (92.6)
≥12 wks	153 (55.0)	52 (98.1)	211 (83.4)	101 (94.4)	209 (73.1)	100 (92.6)
≥16 wks	132 (47.5)	47 (88.7)	175 (69.2)	93 (86.9)	161 (56.3)	88 (81.5)
≥20 wks	0	0	172 (68.0)	1 (0.9)	155 (54.2)	0
≥24 wks	0	0	140 (55.3)	1 (0.9)	129 (45.1)	0
No. of injections						
1	278 (100)	0	193 (76.3)	107 (100)	197 (68.9)	-
2	0	0	47 (18.6)	0	55 (19.2)	-
3	0	2 (3.8)	11 (4.3)	0	26 (9.1)	-
4	0	51 (96.2)	2 (0.8)	0	6 (2.1)	-
≥5	0	0	0	0	2 (0.7)	-

ACZ 885 = canakinumab, TA = triamcinolone acetoneide, colch. = colchicine, SD = standard deviation
No. of injections = number of injections (for ACZ885 and TA)

7.2.1.3 Demographics and disease characteristics

In the gouty arthritis dataset, patients were predominantly male, middle-aged, overweight and had one or more comorbidities reflecting the typical gouty arthritis population.

The demographic features of the patients are shown in Table 7-3.

Table 7-3 Patient demographics by treatment group (gouty arthritis)

	ACZ885 ≤100 mg N=278 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA 40 mg N=286 n (%)	colch. 0.5 mg od N=108 n (%)
Demographics					
Male, n (%)	257 (92.4)	229 (90.5)	101 (94.4)	268 (93.7)	101 (93.5)
Age, mean years (SD)	52.0 (11.4)	52.1 (12.2)	52.5 (11.0)	53.4 (11.5)	52.4 (10.7)
Caucasian, n (%)	223 (80.2)	191 (75.5)	75 (70.1)	230 (80.4)	86 (80.6)
Black, n (%)	13 (4.7)	27 (10.7)	5 (4.7)	27 (9.4)	4 (3.7)
Asian, n (%)	19 (6.8)	15 (5.9)	9 (8.4)	12 (4.2)	5 (4.6)
BMI, mean kg/m ² (SD)	30.9 (4.7)	31.8 (5.3)	30.6 (4.4)	31.4 (4.9)	30.3 (4.7)

ACZ885 = canakinumab, TA = triamcinolone acetoneide, colch. = colchicine

7.2.1.4 Patient disposition

Across all dose groups the vast majority (89.3–98.1%) of subjects treated with canakinumab completed the studies in which they participated (Table 7-4).

Table 7-4 Patient disposition by treatment group (gouty arthritis)

	ACZ885 ≤100 mg N=278 n (%)	ACZ885 spl. 150 mg N=53 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA 40 mg N=286 n (%)	colch. 0.5 mg od N=108 n (%)
Total completed	255 (91.7)	52 (98.1)	226 (89.3)	99 (92.5)	253 (88.5)	95 (88.0)
Total discontinued	23 (8.3)	1 (1.9)	27 (10.7)	8 (7.5)	33 (11.5) ¹	13 (12.0)
Primary reason for discontinuation:						
<i>Safety reasons:</i>						
Abnormal laboratory value(s)	2 (0.7)	0	1 (0.4)	0	1 (0.3)	0
AE(s)	4 (1.4)	0	1 (0.4)	5 (4.7)	0	2 (1.9)
Death	0	0	1 (0.4)	0	1 (0.3)	1 (0.9)
<i>Other reasons:</i>						
Administrative problems	0	0	0	0	3 (1.0)	2 (1.9)
Lost to follow-up	8 (2.9)	1 (1.9)	12 (4.7)	1 (0.9)	7 (2.4)	1 (0.9)
Protocol deviation	1 (0.4)	0	1 (0.4)	0	2 (0.7)	3 (2.8)
No longer requires study drug	0	0	0	1 (0.9)	0	0
Withdrawn consent	7 (2.5)	0	11 (4.3)	1 (0.9)	13 (4.5)	3 (2.8)
Unsatisfactory therapeutic effect	1 (0.4)	0	0	0	6 (2.1)	1 (0.9)

ACZ885 = canakinumab, TA = triamcinolone acetonide, colch. = colchicine

7.2.2 Rheumatoid arthritis (placebo-controlled studies)

7.2.2.1 Dataset and evaluations

Safety data from 4 completed placebo-controlled studies (Studies A2101, A 2201, A2204 and A2207) were pooled for the dataset referenced as the “placebo-controlled RA” dataset. The placebo-controlled RA dataset allows direct comparison to placebo treatment in the rheumatoid arthritis population.

The studies used regular periodic dosing of canakinumab (i.v. or s.c.), almost all on a background of 7.5–15 mg of methotrexate. In 3 of the 4 studies i.v. dosing was used, mostly with higher doses leading to higher exposures than with the target dose of 150 mg s.c.

As different doses, dosing schedules and administration sites were used, data was clustered into 3 canakinumab treatment groups according to the corresponding s.c. dose (based on the equivalence of 150 mg s.c. to 1.4 mg/kg i.v. in a 75 kg subject with approximately 60% s.c. bioavailability). The groupings are summarized in Table 7-5.

Table 7-5 Summary of studies in the placebo-controlled RA safety dataset

ACZ Dose Grouping	Study A2101 (dose-ranging) Stable MTX ≥ 15 mg	Study A2201 (dose-ranging) MTX ≥7.5 mg	Study A2204 (early RA) +7.5-15 mg MTX	Study A2207 (PK/PD Study) (± MTX)
<150 mg	0.3 mg/kg i.v. Days 1 & 15 (N=6) 1.0 mg/kg i.v., Days 1 & 15 (N=6)	-	-	-
150 mg	-	150 mg s.c. q4wks (N=69)	-	-
>50 mg	3.0 mg/kg i.v. Days 1 & 15 (N=6) 10 mg/kg i.v. Day 1 & 15 (N=6 +14)	300 mg s.c. q2wks (N=64) 600 mg i.v. induction 300 mg s.c. q2wks (N=71)	600 mg i.v. Days 1, & 15 & monthly for 26 wks (N=52)	600 mg i.v. Days 1, 15 & 43 (N=50)
Placebo	Placebo N=8+7	Placebo N = 70	Placebo N=26	Placebo N=10

MTX = methotrexate, ACZ = canakinumab

Of the 3 canakinumab dose groupings, only 12 RA patients received the <150 mg dose and do not contribute sufficient information for inclusion. Therefore, most of the displays and discussion will focus only the higher 150 mg and > 150 mg dose groupings.

7.2.2.2 Extent of Exposure

For the placebo-controlled RA, a summary of the number of patients exposed and the duration of exposure to canakinumab is shown in Table 7-6. The mean duration of exposure was highest in the >150mg group. Most patients in all treatment groups had ≥12 weeks of exposure.

Table 7-6 Duration of exposure by treatment group (placebo-controlled RA)

	ACZ885 <150 mg N=12	ACZ885 150 mg N=69	ACZ885 >150 mg N=263	placebo N=121
Exposure (days)				
Mean (SD)	114.9 (6.5)	83.8 (11.4)	134.0 (71.9)	122.6 (63.9)
Median	113.0	85.0	93.0	87.0
Min – Max	110 - 135	15 - 100	15 – 301	15 – 294
Patient years	3.8	15.8	96.5	40.6
Exposure - n (%)				
≥1 day	12 (100.0)	69 (100.0)	263 (100.0)	121 (100.0)
≥ 6 wks	12 (100.0)	67 (97.1)	254 (96.6)	118 (97.5)
≥12 wks	12 (100.0)	63 (91.3)	237 (90.1)	105 (86.8)
≥24 wks	0	0	80 (30.4)	30 (24.8)

ACZ885 = canakinumab, SD = standard deviation

7.2.2.3 Demographics and disease characteristics

Patients were mostly female, Caucasian and middle aged, as seen in Table 7-7. Patient characteristics were distributed evenly across all groups.

Table 7-7 Patient demographics by treatment group (placebo-controlled RA)

	ACZ885 <150 mg N=12	ACZ885 150 mg N=69	ACZ885 >150 mg N=263	Placebo N=121
Demographics				
Female, n (%)	10 (83.3)	56 (81.2)	224 (85.2)	89 (73.6)
Age, mean years(SD)	57.1 (10.99)	57.1 (11.9)	55.5 (12.6)	54.5 (12.9)
Caucasian	10 (83.3)	67 (97.1)	250 (95.1)	114 (94.2)
Black	0	1 (1.4)	2 (0.8)	4 (3.3)
Asian	2 (16.7)	0	3 (1.1)	1 (0.8)
BMI mean kg/m ² (SD)	28.7 (4.4)	27.6 (4.0)	27.4 (4.5)	27.1 (4.5)

ACZ885 = canakinumab

7.2.2.4 Patient Disposition

The patient disposition for the placebo-controlled RA dataset of double-blind, placebo-controlled studies are shown in Table 7-8.

Table 7-8 Patient disposition by treatment groups (placebo-controlled RA)

	ACZ885 <150 mg N=12 n (%)	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	Placebo N=121 n (%)
Total completed	12 (100.0)	65 (94.2)	239 (90.9)	107 (88.4)
Total discontinued	0	4 (5.8)	24 (9.1)	14 (11.6)
Primary reason for discontinuation :				
Safety reasons:				
AE(s)	0	1 (1.4)	10 (3.8)	3 (2.5)
Abnormal laboratory value(s)	0	0	1 (0.4)	0
Other reasons:				
Administrative problems	0	1 (1.4)	1 (0.4)	0
Lost to follow-up	0	0	3 (1.1)	0
Protocol deviation	0	2 (2.9)	1 (0.4)	1 (0.8)
Subject withdrew consent	0	0	2 (0.8)	5 (4.1)
Unsatisfactory therapeutic effect	0	0	6 (2.3)	5 (4.1)

ACZ885 = canakinumab

7.2.3 All RA dataset

Data from additional 4 studies, 3 of which are open-label extensions to studies in the placebo-controlled group, were pooled with the placebo-controlled studies to create the "All RA". This dataset provides safety for longer term scheduled dosing with doses of either 150 mg or 300 mg s.c. every 2 or 4 weeks or 600 mg i.v. every 6 weeks.

7.3 Safety Profile

7.3.1 Adverse events by system organ class (SOC)

Adverse events by SOC in each of the 2 indications during controlled studies are shown in Table 7-9. The groups with the highest frequencies of AEs in each SOC are bolded.

Because IL-1 blockade may interfere with the immune response to infection, a higher rate of infections is not unexpected as a class effect. A higher incidence of infection was observed in the previously approved CAPS population and appeared to be dose-related. Most of the RA population received i.v. induction doses of 600 mg followed by either continued i.v. or s.c. administration of canakinumab in doses of 150 or 300 mg, resulting in exposure to substantially more canakinumab than the dose targeted for gouty arthritis (150 mg). Additionally, in the RA program, the higher doses were to be given on a regular schedule, generally every 2 or 4 weeks, compared with the on demand dosing proposed in gouty arthritis. While there is a slightly greater incidence of infections in the canakinumab group in the RA dataset, the incidence of infections in the placebo group is also greater than the incidence of infections in the gouty arthritis dataset. It is not unexpected that the patients in this dataset would have a higher incidence of AEs, particularly infections, given the population and that methotrexate was administered as background therapy.

In the gouty arthritis population there is a higher incidence of total AEs in the canakinumab 150mg dose group than in active controls, which is driven primarily by an imbalance in infections, metabolism and nutritional disorders and investigations.

The higher incidence in the adverse event, “Investigations”, was primarily due to hematology changes (e.g. decreased platelet, neutrophil or lymphocyte counts). The higher rate of the adverse event, “Metabolism and nutrition disorders”, was mostly due to raised lipid parameters (i.e. hypertriglyceridemia, hypercholesterolemia or dyslipidemia). No additional pattern or cluster of increased AEs has been observed.

For vascular and cardiac disorders, a higher incidence of adverse events was observed in the canakinumab ≥ 200 mg group for the gouty arthritis dataset compared to the lower dose group and the canakinumab dose groups in the RA dataset. However, in the more specific evaluation of potential extended MACE, described in Safety topics of Special Interest (Section 9.9), no evidence of dose response was found.

Table 7-9 Adverse Events by system organ class, by indication and dose grouping

	Gouty Arthritis (active controlled studies)				RA (placebo-controlled studies)									
	ACZ885 150 mg N=253		ACZ885 ≥200 mg N=107		TA N=286		colch. N=108		ACZ885 150 mg N=69		ACZ885 >150 mg N=263		placebo N=121	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary SOCs														
any AE	158 (62.5)	57 (53.3)	145 (50.7)	58 (53.7)	32 (46.4)	165 (62.7)	82 (67.8)							
Infections & infestations	49 (19.4)	19 (17.8)	37 (12.9)	13 (12.0)	11 (15.9)	82 (31.2)	43 (35.5)							
Musculosk. & conn. tissue	41 (16.2)	18 (16.8)	44 (15.4)	18 (16.7)	10 (14.5)	58 (22.1)	35 (28.9)							
Investigations	31 (12.3)	8 (7.5)	27 (9.4)	10 (9.3)	2 (2.9)	23 (8.7)	8 (6.6)							
Metabolism & nutrition dis.	30 (11.9)	6 (5.6)	24 (8.4)	4 (3.7)	1 (1.4)	12 (4.6)	3 (2.5)							
Nervous system disorders	28 (11.1)	11 (10.3)	24 (8.4)	7 (6.5)	4 (5.8)	43 (16.3)	24 (19.8)							
Gastrointestinal disorders	27 (10.7)	10 (9.3)	20 (7.0)	10 (9.3)	6 (8.7)	51 (19.4)	43 (35.5)							
Vascular disorders	18 (7.1)	11 (10.3)	16 (5.6)	1 (0.9)	1 (1.4)	20 (7.6)	10 (8.3)							
General dis. & admin. site	18 (7.1)	2 (1.9)	12 (4.2)	4 (3.7)	8 (11.6)	45 (17.1)	19 (15.7)							
Cardiac disorders	13 (5.1)	7 (6.5)	14 (4.9)	2 (1.9)	2 (2.9)	10 (3.8)	7 (5.8)							
Respiratory, thor. & med.	11 (4.3)	7 (6.5)	8 (2.8)	4 (3.7)	5 (7.2)	19 (7.2)	10 (8.3)							
Injury, poison. & procedural	11 (4.3)	5 (4.7)	18 (6.3)	6 (5.6)	4 (5.8)	17 (6.5)	9 (7.4)							
Skin & subcut. tissue dis.	10 (4.0)	6 (5.6)	12 (4.2)	6 (5.6)	4 (5.8)	39 (14.8)	16 (13.2)							
Blood & lymphatic system	10 (4.0)	2 (1.9)	6 (2.1)	3 (2.8)	1 (1.4)	7 (2.7)	2 (1.7)							
Renal & urinary disorders	9 (3.6)	2 (1.9)	8 (2.8)	1 (0.9)	1 (1.4)	7 (2.7)	4 (3.3)							
Psychiatric disorders	8 (3.2)	2 (1.9)	8 (2.8)	1 (0.9)	4 (5.8)	15 (5.7)	5 (4.1)							
Hepatobiliary disorders	6 (2.4)	2 (1.9)	2 (0.7)	1 (0.9)	0	2 (0.8)	1 (0.8)							
Eye disorders	5 (2.0)	0	2 (0.7)	0	1 (1.4)	6 (2.3)	3 (2.5)							
Ear & labyrinth disorders	3 (1.2)	2 (1.9)	2 (0.7)	0	1 (1.4)	11 (4.2)	4 (3.3)							
Neoplasms ben., malign.	2 (0.8)	1 (0.9)	0	1 (0.9)	0	2 (0.8)	0							
Immune system disorders	1 (0.4)	1 (0.9)	1 (0.3)	0	0	2 (0.8)	2 (1.7)							
Reproductive syst.	0	3 (2.8)	0	0	0	9 (3.4)	2 (1.7)							

	Gouty Arthritis (active controlled studies)			RA (placebo-controlled studies)			
	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA N=286 n (%)	colch. N=108 n (%)	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	placebo N=121 n (%)
Primary SOCs							
Congenital, familial	0	0	1 (0.3)	1 (0.9)	0	0	0
Endocrine disorders	0	0	1 (0.3)	0	0	0	0
Social circumstances	0	0	1 (0.3)	0	0	0	0
Surgical & medical proc.	0	0	0	1 (0.9)	0	2 (0.8)	2 (1.7)

Only most relevant dosages are included. Primary SOCs sorted in descending order in the ACZ885 150 mg GA group. ACZ885 = canakinumab, RA = rheumatoid arthritis

7.3.2 Adverse events occurring in ≥3% in any gouty arthritis group

Table 7-10 AEs ≥3% in any gouty arthritis group by preferred term, indication and by dose grouping

Adverse Events	Gouty Arthritis (active controlled studies)				RA (placebo-controlled studies)			
	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA N=286 n (%)	colch. N=108 n (%)	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	placebo N=121 n (%)	
any AE	158 (62.5)	57 (53.3)	145 (50.7)	58 (53.7)	32 (46.4)	165 (62.7)	82 (67.8)	
Back pain	13 (5.1)	3 (2.8)	2 (0.7)	4 (3.7)	1 (1.4)	12 (4.6)	6 (5.0)	
Hypertension	12 (4.7)	9 (8.4)	13 (4.5)	1 (0.9)	1 (1.4)	10 (3.8)	8 (6.6)	
Headache	12 (4.7)	8 (7.5)	12 (4.2)	6 (5.6)	0	24 (9.1)	11 (9.1)	
Arthralgia	10 (4.0)	5 (4.7)	11 (3.8)	3 (2.8)	1 (1.4)	8 (3.0)	6 (5.0)	
Hypertriglyceridemia	9 (3.6)	3 (2.8)	2 (0.7)	0	0	0	0	
GGT increased	8 (3.2)	1 (0.9)	5 (1.7)	2 (1.9)	0	0	0	
Diarrhea	5 (2.0)	4 (3.7)	6 (2.1)	2 (1.9)	1 (1.4)	13 (4.9)	12 (9.9)	
Upper RTI	5 (2.0)	4 (3.7)	4 (1.4)	4 (3.7)	3 (4.3)	11 (4.2)	5 (4.1)	
Pain in extremity	3 (1.2)	2 (1.9)	11 (3.8)	0	1 (1.4)	5 (1.9)	2 (1.7)	
Gout	1 (0.4)	0	9 (3.1)	0	0	0	0	

Only most relevant dosages are included. ACZ885 = canakinumab, TA = triamcinolone acetonide, colch. = colchicine, RA = rheumatoid arthritis

7.3.3 Gouty arthritis (active controlled studies)

7.3.3.1 AE Severity (gouty arthritis)

The severity of all AEs is summarized in Table 7-11. Total AEs were mostly mild or moderate.

Table 7-11 Severity of total AEs (24 weeks)

Severity	ACZ885 ≤100 mg N = 278 n (%)	ACZ885 150 mg N = 253 n (%)	ACZ885 ≥200 mg N = 107 n (%)	TA N = 286 n (%)	colch. N = 108 n (%)
Total AEs					
Mild	68 (24.5)	88 (34.8)	32 (29.9)	81 (28.3)	32 (29.6)
Moderate	57 (20.5)	57 (22.5)	20 (18.7)	54 (18.9)	19 (17.6)
Severe	12 (4.3)	13 (5.1)	4 (3.7)	10 (3.5)	6 (5.6)

ACZ885 = canakinumab, TA = triamcinolone acetone, colch. = colchicine

7.3.3.2 Serious adverse events

Frequencies of patients with SAEs by primary system organ class and preferred term in the gouty arthritis dataset of active-controlled studies are shown Table 7-12.

Table 7-12 SAEs by primary SOC and preferred term (gouty arthritis)

Primary SOC Preferred term	ACZ885 ≤100 mg N=278 n (%)	ACZ885 split 150mg N=53 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA N=286 n (%)	colch N=108 n (%)
Total with SAE (s)	11 (4.0)	1 (1.9)	18 (7.1)	6 (5.6)	9 (3.1)	6 (5.6)
Cardiac disorders	0	0	4 (1.6)	1 (0.9)	1 (0.3)	2 (1.9)
Angina pectoris	0	0	1 (0.4)	0	0	1 (0.9)
Arrhythmia	0	0	1 (0.4)	0	0	0
Atrial fibrillation	0	0	1 (0.4)	0	0	0
Myocardial ischemia	0	0	1 (0.4)	0	0	0
Acute myocardial infarction	0	0	0	1 (0.9)	0	0
Aortic valve incompetence	0	0	0	0	1 (0.3)	0
Cardiomyopathy	0	0	0	0	1 (0.3)	0
Myocardial infarction	0	0	0	0	0	1 (0.9)
Congenital, familial & genetic dis.	0	0	0	0	1 (0.3)	0
Bicuspid aortic valve	0	0	0	0	1 (0.3)	0
Eye disorders	0	0	2 (0.8)	0	0	0
Glaucoma	0	0	1 (0.4)	0	0	0
Retinal artery occlusion	0	0	1 (0.4)	0	0	0
Gastrointestinal disorders	1 (0.4)	0	2 (0.8)	2 (1.9)	1 (0.3)	1 (0.9)
Gastritis	0	0	1 (0.4)	1 (0.9)	0	0
Pancreatitis	0	0	1 (0.4)	0	0	0
Abdominal pain	0	0	0	0	0	1 (0.9)
Colitis ulcerative	0	0	0	1 (0.9)	0	0
Diarrhea	0	0	0	0	1 (0.3)	0
Hemorrhoidal hemorrhage	1 (0.4)	0	0	0	0	0
Nausea	0	0	0	0	1 (0.3)	0
Umbilical hernia	0	0	0	0	0	1 (0.9)
Vomiting	0	0	0	0	1 (0.3)	0
General dis. & admin. site cond.	0	0	1 (0.4)	0	0	0
Device dislocation	0	0	1 (0.4)	0	0	0
Hepatobiliary disorders	0	0	0	0	0	1 (0.9)
Cholelithiasis	0	0	0	0	0	1 (0.9)
Infections and infestations	4 (1.4)	1 (1.9)	4 (1.6)	2 (1.9)	0	0
Abscess jaw	0	0	1 (0.4)	0	0	0
Abscess limb	0	0	1 (0.4)	0	0	0
Gastroenteritis	0	0	1 (0.4)	0	0	0
Pneumonia	0	1 (1.9)	1 (0.4)	0	0	0
Appendicitis	2 (0.7)	0	0	0	0	0
Bronchitis	1 (0.4)	0	0	0	0	0
Ear infection	0	1 (1.9)	0	0	0	0
Erysipelas	1 (0.4)	0	0	0	0	0
Gangrene	0	0	0	1 (0.9)	0	0
Sepsis	0	0	0	1 (0.9)	0	0
Tonsillitis	0	0	0	1 (0.9)	0	0
Injury, poisoning & procedural compl.	1 (0.4)	0	0	1 (0.9)	1 (0.3)	1 (0.9)

Primary SOC Preferred term	ACZ885 ≤100 mg N=278 n (%)	ACZ885 split 150mg N=53 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA N=286 n (%)	colch N=108 n (%)
Femur fracture	0	0	0	0	0	1 (0.9)
Hand fracture	0	0	0	0	0	1 (0.9)
Ligament rupture	0	0	0	1 (0.9)	0	0
Meniscus lesion	0	0	0	0	1 (0.3)	0
Radius fracture	0	0	0	0	0	1 (0.9)
Tibia fracture	1 (0.4)	0	0	0	0	0
Ulna fracture	0	0	0	0	0	1 (0.9)
Investigations	0	0	1 (0.4)	0	0	0
Prostatic specific antigen incr.	0	0	1 (0.4)	0	0	0
Metabolism & nutrition disorders	0	0	1 (0.4)	0	2 (0.7)	0
Hyperglycemia	0	0	1 (0.4)	0	0	0
Gout	0	0	0	0	2 (0.7)	0
Musculoskeletal & conn. tissue dis.	1 (0.4)	0	2 (0.8)	0	0	1 (0.9)
Back pain	0	0	1 (0.4)	0	0	0
Intervertebral disc protrusion	0	0	1 (0.4)	0	0	0
Lumbar spinal stenosis	0	0	1 (0.4)	0	0	0
Spondylolisthesis	0	0	1 (0.4)	0	0	0
Osteoarthritis	1 (0.4)	0	0	0	0	0
Tendonitis	0	0	0	0	0	1 (0.9)
Neoplasms benign, malign. & unsp.	0	0	0	1 (0.9)	0	1 (0.9)
Prostate cancer	0	0	0	1 (0.9)	0	0
Renal cancer	0	0	0	0	0	1 (0.9)
Nervous system disorders	2 (0.7)	0	3 (1.2)	0	3 (1.0)	0
Cerebrovascular accident	0	0	1 (0.4)	0	0	0
Convulsion	0	0	1 (0.4)	0	0	0
Hemorrhage intracranial	0	0	1 (0.4)	0	0	0
Spinal cord ischemia	0	0	1 (0.4)	0	0	0
Carotid artery stenosis	1 (0.4)	0	0	0	0	0
Cerebrovascular disorder	0	0	0	0	1 (0.3)	0
Ischemic stroke	0	0	0	0	1 (0.3)	0
Stupor	1 (0.4)	0	0	0	0	0
Vertebrobasilar insufficiency	0	0	0	0	1 (0.3)	0
Renal and urinary disorders	2 (0.7)	0	1 (0.4)	1 (0.9)	0	0
Renal failure chronic	0	0	1 (0.4)	0	0	0
Hematuria	1 (0.4)	0	0	1 (0.9)	0	0
Nephrolithiasis	1 (0.4)	0	0	0	0	0
Nephrotic syndrome	0	0	0	1 (0.9)	0	0
Renal failure	0	0	0	1 (0.9)	0	0
Respiratory, thoracic & mediast. dis.	0	0	0	0	1 (0.3)	0
Pulmonary embolism	0	0	0	0	1 (0.3)	0
Vascular disorders	0	0	0	0	1 (0.3)	0
Aortic stenosis	0	0	0	0	1 (0.3)	0

ACZ885 = canakinumab, TA = triamcinolone acetonide, colch. = colchicine

Infections and infestations were the most frequent SAEs across the canakinumab groups affecting 1.4 to 1.9% of patients. Cardiac disorders were reported in a similar proportion of patients in the colchicine (1.9%, 2 patients) and canakinumab 150 mg (1.6%, 4 patients) groups, 0.9% (1 patient) in the canakinumab ≥ 200 mg group, 0.3% (1 patient) in the triamcinolone acetonide group and none in the lower dose canakinumab groups.

All but 2 of the SAEs were reported not suspected to be related to study drug according to the investigator. One case of erysipelas in a canakinumab-treated patient and one case of renal cancer in a colchicine-treated patient were reported suspected to be study drug-related.

7.3.3.3 Deaths

There were 5 deaths in completed gouty arthritis studies, 3 in the studies included in the gouty arthritis dataset and 2 in long-term extension study H2251E1. One other death in gouty arthritis study H2251 occurred in the screening phase (myocardial infarction). None were considered related to study drug as reported by the investigator.

A summary of the deaths and a brief account of the relevant circumstances, together with the investigator's assessment of relationship to study drug are provided in Table 7-13.

Table 7-13 Overview of deaths in completed gouty arthritis studies

Dataset PID (age/sex/race)	Study drug	Cause of death (Preferred term)	Day of death	Day of last dose of study drug	Study drug relationship
Gouty arthritis					
[H2251-0508-00005] (54/M/Ca)	colchicine	Myocardial infarction (Myocardial infarction)	42	31	not suspected
[H2251E1-0074- 00004] (67/M/Ca)	ACZ885 split 150 mg in core, none in E1	Myocardial ischemia (Myocardial fibrosis)	195 (from core BL)	114 (core)	not suspected
[H2251E1-0514- 00005] (35/M/Black)	ACZ885 100 mg in core, none in E1	Gun shot wound to head (Gun shot wound)	223 (from core BL)	118 (core)	not suspected
[H2356-0101-00001] (59/M/Ca)	TA	Sudden cardiac death/ Pulmonary embolism (Sudden cardiac death)	10	1	not suspected
[H2357-0580-00004] (63/M/Ca)	ACZ885 150 mg	Intracranial hemorrhage (Haemorrhage intracranial)	67	1	not suspected

M = male, F = female, Ca = Caucasian, ACZ885 = canakinumab, TA = triamcinolone acetonide

7.3.3.4 Subgroup analyses

AEs were evaluated in 150 mg canakinumab or triamcinolone acetonide groups with gouty arthritis in demographic sub-groups (age, sex, race, BMI), and in patients with or without contraindications, intolerance or lack of efficacy to NSAIDs and colchicine, and there were no consistent or clinically relevant differences.

Relevant laboratory and vital sign variables were also explored in comorbidity sub-groups. For hypertensive patients at baseline, there were modest improvements with 150 mg canakinumab compared to triamcinolone acetonide in blood pressure (BP). A similar modest improvement of systolic BP has been observed in patients with metabolic syndrome. Total cholesterol and lipoprotein A improved in patients with hypercholesterolemia. Those suffering from chronic kidney disease showed improvement in BP, GFR and microalbuminuria (Table 7-14).

Table 7-14 Selected laboratory/vital sign data in comorbid subgroups (24weeks)

Co-morbidity subgroup	Canakinumab difference (baseline, EOS)	TA difference (baseline, EOS)
Hypertension (ACZ885=58%, TA=61%)		
systolic BP (mmHg)	- 5.4 (142, 137)	- 4.2 (140, 136)
diastolic BP (mmHg)	- 2.0 (86, 84)	- 0.6 (86, 85)
Metabolic syndrome (ACZ885=36%, TA=29%)		
systolic BP (mmHg)	- 3.9 (138, 134)	- 2.7 (137, 135)
diastolic BP (mmHg)	- 1.0 (83, 82)	- 0.2 (84, 84)
triglycerides (mmol/L)	+ 0.28 (2.58, 2.86)	+ 0.10 (2.62, 2.72)
total cholesterol (mmol/L)	- 0.02 (5.18, 5.16)	- 0.07 (5.38, 5.31)
Hypercholesterolemia (ACZ885=24%, TA=28%)		
triglycerides (mmol/L)	+ 0.16 (2.99, 3.15)	- 0.18 (2.69, 2.51)
total cholesterol (mmol/L)	- 0.26 (5.67, 5.42)	- 0.19 (5.83, 5.65)
apolipoprotein B (g/L)	-0.07 (1.08, 0.99)	- 0.06 (1.14, 1.08)
lipoprotein A (mg/L)	- 74 (417, 330)	- 29 (438, 422)
Chronic kidney disease (ACZ885=15%, TA=10%)		
systolic BP (mmHg)	- 3.3 (137, 134)	+0.0 (137, 137)
diastolic BP (mmHg)	- 0.3 (83, 82)	+ 0.6 (82, 83)
GFR (by MDRD ml/min/m ²)	+ 3.2 (45, 48)	+1.2 (45, 46)
microalbuminuria (mg/L)	- 147 (408, 262)	+ 45 (433, 478)

ACZ885 = canakinumab, TA = triamcinolone acetonide, BP = blood pressure, EOS = end of study
GFR = glomerular filtration rate, MDRD = Modification of diet in renal disease study
% denotes the frequency of each comorbidity in the pivotal trial population

7.3.3.5 Clinical chemistry changes

Notable changes in clinical chemistry were infrequent with 150 mg canakinumab, and if they arose, were generally within the range of the controls. Additional discussion is found in Safety topics of special interest (Section 9.12.1).

Urate levels in the pivotal trials, which were raised at baseline, showed a small rise after canakinumab and a smaller rise after triamcinolone acetonide at 12 weeks, but the effect had diminished at 24 weeks (Table 7-15). Urate levels rise after a flare (Logan et al 1997, Urano et al 2002), when inflammatory markers rise (Urano et al 2002), suggesting that the greater rise in urate with canakinumab than triamcinolone acetonide may reflect a greater anti-inflammatory effect.

Another explanation for the increased serum urate levels is the reduction in fractional urate excretion in inflammatory states which has been seen in patients with acute gout flares (Urano

et al 2002). It has also been detected in patients with other acute inflammatory conditions (Sivera et al 2010) and suggests that increased serum urate after an inflammatory attack may be a general feature of many types of inflammation.

Table 7-15 Changes in urate levels at weeks 12 and 24 (pivotal gout trials)

	Baseline	12 weeks	24 weeks
Overall population			
ACZ885 150 mg (N=253)	485 ±122 µmol/L (8.1 ± 2.0 mg/dL)	+ 42 ±123 µmol/L (+ 0.7 ± 2.1 mg/dL)	+ 32 ± 119 µmol/L (+ 0.5 ± 2.0 mg/dL)
TA (N=286)	488 ± 122 µmol/L (8.2 ± 2.0 mg/dL)	+ 7 ± 110 µmol/L (+ 0.1 ± 1.8 mg/dL)	- 9 ± 105 µmol/L (- 0.2 ± 1.8 mg/dL)

Data shown as mean ± standard deviation, triam = triamcinolone acetoneide
1 mg/dL = 59.48 µmol/L, ACZ885 = canakinumab, TA = triamcinolone acetoneide

7.3.3.6 Hematology changes

Mean decreases in white cell, absolute neutrophil and platelet counts were seen with 150 mg canakinumab to a greater extent than with the controls. Additional discussion is found in Safety topics of Special Interest (Section 9.3.1 and Section 9.4.1).

7.3.4 Rheumatoid arthritis (placebo-controlled studies)

7.3.4.1 Adverse events

Refer to Table 7-9 and Table 7-10 for AEs in placebo-controlled RA.

7.3.4.2 Serious adverse events

A summary of SAEs by primary SOC and preferred term in the placebo-controlled RA dataset is shown in Table 7-16.

Infections and infestations were the most frequent SAEs occurring in 7 (2.7%) patients (single cases of various infections). However, 3 of the 12 patients in the <150 mg group had 4 SAEs: angina pectoris, lung infection with pyrexia, and erysipelas.

In the placebo group, SAEs were mostly GI disorders (2 cases of GI hemorrhage, 1 abdominal hernia obstructive) and musculoskeletal disorders (3 cases of worsening of RA).

A total of 7 SAEs reports were assessed as potentially related to study drug by the investigators, 2 events in patients in the canakinumab <150 mg group and 5 in the canakinumab >150 mg group. In the lower dose group, both events were infections (1 erysipelas of the leg and 1 lung infection). Both patients recovered and completed the study. In the higher dose group 1 event of lip edema was suspected of relationship to the methotrexate background therapy. Three patients all in the canakinumab > 150 mg group discontinued the study (1 event of gastritis, 1 event of cellulitis with abscess formation and 1 event of urosepsis). One patient had an event of appendicitis; this patient completed the study.

Table 7-16 Frequency of SAEs by primary SOC and preferred term (placebo-controlled RA)

Primary SOC Preferred terms	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	Placebo N=121 n (%)
Total number SAE(s)	1 (1.4)	12 (4.6)	9 (7.4)
Cardiac disorders	0	0	1 (0.8)
Atrial fibrillation	0	0	1 (0.8)
Ear and labyrinth disorders	0	1 (0.4)	0
Deafness neurosensory	0	1 (0.4)	0
Gastrointestinal disorders	0	2 (0.8)	3 (2.5)
Gastritis	0	1 (0.4)	0
Lip edema	0	1 (0.4)	0
Abdominal hernia obstructive	0	0	1 (0.8)
Gastric ulcer hemorrhage	0	0	1 (0.8)
Upper gastrointestinal hemorrhage	0	0	1 (0.8)
General disorders & administration site conditions	0	0	1 (0.8)
Non cardiac chest pain	0	0	1 (0.8)
Infections and infestations	0	7 (2.7)	0
Abscess limb	0	1 (0.4)	0
Appendicitis	0	1 (0.4)	0
Cellulitis	0	1 (0.4)	0
Diverticulitis	0	1 (0.4)	0
Ear infection	0	1 (0.4)	0
Sinusitis	0	1 (0.4)	0
Soft tissue infection	0	1 (0.4)	0
Tracheobronchitis	0	1 (0.4)	0
Urosepsis	0	1 (0.4)	0
Injury, poisoning & procedural complications	1 (1.4)	2 (0.8)	0
Femur fracture	0	1 (0.4)	0
Pelvic fracture	0	1 (0.4)	0
Radius fracture	0	1 (0.4)	0
Thoracic vertebral fracture	1 (1.4)	0	0
Musculoskeletal & connective tissue disorders	0	1 (0.4)	3 (2.5)
Musculoskeletal chest pain	0	1 (0.4)	0
Rheumatoid arthritis	0	0	3 (2.5)
Reproductive system & breast disorders	0	1 (0.4)	0
Ovarian cyst	0	1 (0.4)	0
Surgical & medical procedures	0	0	1 (0.8)
Arthrodesis	0	0	1 (0.8)

ACZ885 = canakinumab

7.3.4.3 Deaths

There were 3 deaths in the entire RA program, all in single-blind extensions to the placebo controlled trials (i.e. there were none in the placebo-controlled RA dataset, all were in the All

RA dataset). These events are described in Table 7-17. All deaths were considered not related to study drug.

Table 7-17 Deaths in the entire RA dataset

Dataset PID (age/sex/race)	Study drug	Cause of death (Preferred term)	Day of death	Day of last dose of study drug	Study drug relationship†
Rheumatoid arthritis [A2201E2-0002- 00015] (60/F/Ca)	ACZ885 (last dose 150 mg s.c. cumulative dose 6450 mg)	Wound infection due to intestinal rupture 12 days before (Wound infection)	630	586	not suspected
[A2211-0051-05179] (56/M/Ca)	ACZ885 (last dose 600 mg i.v. cumulative dose 3600 mg)	Femoral neck fracture of right hip 10 days before, autopsy showed disseminated intravascular clotting as final cause of death (Hip fracture)	433	407	not suspected
[A2201E1-0074- 00008] (70/M/Ca) ‡ Argus case no: PHHO2009ES07028	ACZ885 (last dose 300 mg s.c. cumulative dose 5100 mg)	Multi-organ metastases from lung adenocarcinoma (not in deaths listing ‡)	26-Aug- 2009 (after DBL)	4-May-2009 (day 337 in A2201E1, day 421 of ACZ885 treatment)	not suspected

PID = patient identification, DBL = database lock, BL = baseline, M = male, F = female, Ca = Caucasian, ACZ885 = canakinumab

† Investigator's assessment, ‡ Death after DBL, thus reported in the Argus database, not in the study report

7.3.4.4 Clinical chemistry changes

Discussion of clinical chemistry changes is found in Safety topics of Special Interest (Section 9.12.2).

7.3.4.5 Hematology changes

Discussion of hematology changes is found in Safety topics of Special Interest (Section 9.3.2, Section 9.4.2).

8 Safety over time

8.1 Longer-term safety in the gouty arthritis dataset

8.1.1 Adverse events by onset period

The incidence of AEs by primary system organ class and onset period (0-12 weeks, >12 weeks) in the gouty arthritis dataset is presented in Table 8-1.

Table 8-1 Frequency of AEs by primary SOC and onset period (gouty arthritis)

Primary SOC	Onset period	ACZ885 ≤100 mg n/N (%)	ACZ885 split 150mg n/N (%)	ACZ885 150 mg n/N (%)	ACZ885 ≥200 mg n/N (%)	TA n/N (%)	colch n/N (%)
Total with any AE(s)	0-12 wks	114/278 (41.0)	24/53 (45.3)	130/253 (51.4)	44/107 (41.1)	123/286 (43.0)	46/108 (42.6)
	>12 wks	57/153 (37.3)	13/52 (25.0)	80/208 (38.5)	32/101 (31.7)	55/205 (26.8)	29/99 (29.3)
Infections & infestations	0-12 wks	31 (11.2)	7 (13.2)	29 (11.5)	11 (10.3)	26 (9.1)	8 (7.4)
	>12 wks	16 (10.5)	4 (7.7)	23 (11.1)	8 (7.9)	13 (6.3)	6 (6.1)
Musculoskeletal. & connective tissue dis.	0-12 wks	23 (8.3)	5 (9.4)	28 (11.1)	12 (11.2)	39 (13.6)	13 (12.0)
	>12 wks	22 (14.4)	0	20 (9.6)	7 (6.9)	10 (4.9)	7 (7.1)
Investigations	0-12 wks	17 (6.1)	0	24 (9.5)	5 (4.7)	21 (7.3)	7 (6.5)
	>12 wks	4 (2.6)	1 (1.9)	10 (4.8)	3 (3.0)	10 (4.9)	4 (4.0)
Metabolism & nutrition disorders	0-12 wks	10 (3.6)	1 (1.9)	23 (9.1)	2 (1.9)	19 (6.6)	3 (2.8)
	>12 wks	6 (3.9)	2 (3.8)	7 (3.4)	4 (4.0)	8 (3.9)	1 (1.0)
Nervous system disorders	0-12 wks	23 (8.3)	4 (7.5)	22 (8.7)	9 (8.4)	21 (7.3)	4 (3.7)
	>12 wks	7 (4.6)	1 (1.9)	10 (4.8)	2 (2.0)	4 (2.0)	4 (4.0)
Gastrointestinal disorders	0-12 wks	23 (8.3)	3 (5.7)	23 (9.1)	9 (8.4)	16 (5.6)	7 (6.5)
	>12 wks	3 (2.0)	1 (1.9)	5 (2.4)	5 (5.0)	5 (2.4)	4 (4.0)
Vascular disorders	0-12 wks	8 (2.9)	1 (1.9)	14 (5.5)	5 (4.7)	12 (4.2)	1 (0.9)
	>12 wks	3 (2.0)	1 (1.9)	5 (2.4)	7 (6.9)	6 (2.9)	0
General disorders & admin. site cond.	0-12 wks	10 (3.6)	0	13 (5.1)	2 (1.9)	9 (3.1)	1 (0.9)
	>12 wks	3 (2.0)	0	9 (4.3)	0	3 (1.5)	3 (3.0)
Cardiac disorders	0-12 wks	3 (1.1)	0	5 (2.0)	4 (3.7)	7 (2.4)	2 (1.9)
	>12 wks	2 (1.3)	0	8 (3.8)	3 (3.0)	8 (3.9)	0
Respiratory, thoracic & mediastinal dis.	0-12 wks	10 (3.6)	1 (1.9)	5 (2.0)	3 (2.8)	8 (2.8)	1 (0.9)
	>12 wks	3 (2.0)	0	7 (3.4)	4 (4.0)	0	3 (3.0)
Injury, poisoning & procedural complic.	0-12 wks	11 (4.0)	1 (1.9)	6 (2.4)	3 (2.8)	11 (3.8)	4 (3.7)
	>12 wks	4 (2.6)	1 (1.9)	5 (2.4)	2 (2.0)	7 (3.4)	2 (2.0)
Skin & subcutaneous tissue disorders	0-12 wks	12 (4.3)	5 (9.4)	9 (3.6)	3 (2.8)	8 (2.8)	4 (3.7)
	>12 wks	4 (2.6)	2 (3.8)	3 (1.4)	3 (3.0)	4 (2.0)	2 (2.0)
Blood & lymphatic system disorders	0-12 wks	4 (1.4)	1 (1.9)	9 (3.6)	0	6 (2.1)	2 (1.9)
	>12 wks	2 (1.3)	0	2 (1.0)	2 (2.0)	0	3 (3.0)
Renal and urinary disorders	0-12 wks	6 (2.2)	0	6 (2.4)	1 (0.9)	8 (2.8)	1 (0.9)
	>12 wks	1 (0.7)	0	3 (1.4)	1 (1.0)	0	0
Psychiatric disorders	0-12 wks	6 (2.2)	0	6 (2.4)	2 (1.9)	6 (2.1)	1 (0.9)
	>12 wks	2 (1.3)	0	2 (1.0)	0	2 (1.0)	0
Hepatobiliary disorders	0-12 wks	1 (0.4)	0	5 (2.0)	2 (1.9)	1 (0.3)	1 (0.9)
	>12 wks	2 (1.3)	0	1 (0.5)	0	1 (0.5)	0
Eye disorders	0-12 wks	3 (1.1)	1 (1.9)	3 (1.2)	0	2 (0.7)	0
	>12 wks	1 (0.7)	0	3 (1.4)	0	0	0
Ear & labyrinth disorders	0-12 wks	2 (0.7)	0	1 (0.4)	1 (0.9)	2 (0.7)	0
	>12 wks	2 (1.3)	1 (1.9)	2 (1.0)	1 (1.0)	0	0
Neoplasms benign, malignant & unspec.	0-12 wks	0	0	1 (0.4)	0	0	0
	>12 wks	0	0	1 (0.5)	1 (1.0)	0	1 (1.0)
Immune system	0-12 wks	0	0	1 (0.4)	0	1 (0.3)	0

Primary SOC	Onset period	ACZ885 ≤100 mg n/N (%)	ACZ885 split 150mg n/N (%)	ACZ885 150 mg n/N (%)	ACZ885 ≥200 mg n/N (%)	TA n/N (%)	colch n/N (%)
disorders	>12 wks	1 (0.7)	0	0	1 (1.0)	0	0
Reproductive system & breast disorders	0-12 wks	3 (1.1)	0	0	1 (0.9)	0	0
	>12 wks	1 (0.7)	1 (1.9)	0	2 (2.0)	0	0
Congenital, familial & genetic disorders	0-12 wks	0	0	0	0	1 (0.3)	1 (0.9)
	>12 wks	0	0	0	0	1 (0.5)	0
Endocrine disorders	0-12 wks	0	0	0	0	1 (0.3)	0
	>12 wks	0	0	0	0	0	0
Social circumstances	0-12 wks	0	0	0	0	1 (0.3)	0
	>12 wks	0	0	0	0	0	0
Surgical & medical procedures	0-12 wks	0	0	0	0	0	0
	>12 wks	0	0	0	0	0	1 (1.0)

ACZ885 = canakinumab, TA = triamcinolone acetonide, colch. – colchicine

Overall, the incidence of AEs with onset in the second 12 weeks of observation (i.e. AE start day on or after day 85) was lower than the first 12 weeks (i.e. AE start day prior to day 85).

In the canakinumab and comparator groups, infections and infestations did not increase over time, as was the case for the frequencies of AEs in the majority of primary SOCs. In both the canakinumab 150 mg and triamcinolone acetonide groups, the frequency of cardiac disorders with onset in the >12 week period was higher than in the 0-12 week period with no relevant difference between the treatments by onset of cardiac disorders (canakinumab 150 mg 0-12 weeks: 5/253 patients, 2.0%, >12 weeks: 8/208 patients, 3.8%; triamcinolone acetonide 0-12 weeks: 7/286 patients, 2.4%, >12 weeks: 8/205 patients, 3.9%). This increase in the incidence of cardiac disorders by onset period was not seen in the other treatment groups.

8.1.1.1 Common AEs by onset period

In the canakinumab 150 mg and triamcinolone acetonide groups, there was no increase in the incidence of common AEs during the >12 week onset period versus the 0-12 week period, except for upper respiratory tract infection which increased in the canakinumab 150 mg group whereas nasopharyngitis and bronchitis increased in the triamcinolone acetonide group. As these are related medical conditions, there is unlikely to be any clinically relevant differences between canakinumab 150 mg and triamcinolone acetonide treatment in the frequencies of these types of AEs by onset period. Ear infection increased in the canakinumab 150 mg group, although it occurred in only one patient (0.4%) in the 0-12 week period and 2 patients (1.0%) in the >12 week onset period (Table 8-2).

Table 8-2 Common AEs (≥3.0% in any group) by preferred term and onset period (gouty arthritis)

Preferred term	Onset	ACZ885 ≤100 mg n/N (%)	ACZ885 split 150mg n/N (%)	ACZ885 150 mg n/N (%)	ACZ885 ≥200 mg n/N (%)	TA n/N (%)	colch n/N (%)
Total with AE(s)	0-12 wks	114/278 (41.0)	24/53 (45.3)	130/253 (51.4)	44/107 (41.1)	123/286 (43.0)	46/108 (42.6)
	>12 wks	57/153 (37.3)	13/52 (25.0)	80/208 (38.5)	32/101 (31.7)	55/205 (26.8)	29/99 (29.3)
Back pain	0-12 wks	4 (1.4)	0	9 (3.6)	3 (2.8)	1 (0.3)	2 (1.9)
	>12 wks	6 (3.9)	0	5 (2.4)	0	1 (0.5)	2 (2.0)
Hypertension	0-12 wks	7 (2.5)	1 (1.9)	9 (3.6)	3 (2.8)	9 (3.1)	1 (0.9)
	>12 wks	3 (2.0)	1 (1.9)	4 (1.9)	6 (5.9)	5 (2.4)	0
Headache	0-12 wks	15 (5.4)	2 (3.8)	8 (3.2)	7 (6.5)	10 (3.5)	4 (3.7)
	>12 wks	2 (1.3)	1 (1.9)	6 (2.9)	1 (1.0)	3 (1.5)	3 (3.0)
Arthralgia	0-12 wks	9 (3.2)	2 (3.8)	6 (2.4)	3 (2.8)	9 (3.1)	3 (2.8)
	>12 wks	8 (5.2)	0	6 (2.9)	2 (2.0)	3 (1.5)	1 (1.0)
Hypertriglyceridemia	0-12 wks	2 (0.7)	0	7 (2.8)	1 (0.9)	1 (0.3)	0
	>12 wks	0	0	2 (1.0)	2 (2.0)	1 (0.5)	0
GGT increased	0-12 wks	4 (1.4)	0	6 (2.4)	1 (0.9)	4 (1.4)	2 (1.9)
	>12 wks	0	0	3 (1.4)	0	1 (0.5)	0
Nasopharyngitis	0-12 wks	11 (4.0)	2 (3.8)	4 (1.6)	0	3 (1.0)	0
	>12 wks	3 (2.0)	1 (1.9)	2 (1.0)	0	5 (2.4)	1 (1.0)
Diarrhea	0-12 wks	7 (2.5)	0	5 (2.0)	4 (3.7)	6 (2.1)	2 (1.9)
	>12 wks	1 (0.7)	0	0	1 (1.0)	1 (0.5)	0
Upper RTI	0-12 wks	3 (1.1)	2 (3.8)	2 (0.8)	3 (2.8)	2 (0.7)	2 (1.9)
	>12 wks	3 (2.0)	1 (1.9)	4 (1.9)	1 (1.0)	2 (1.0)	2 (2.0)
Nausea	0-12 wks	8 (2.9)	1 (1.9)	2 (0.8)	0	5 (1.7)	1 (0.9)
	>12 wks	1 (0.7)	0	2 (1.0)	0	0	0
Bronchitis	0-12 wks	1 (0.4)	0	2 (0.8)	0	0	0
	>12 wks	1 (0.7)	2 (3.8)	2 (1.0)	0	2 (1.0)	0
Pain in extremity	0-12 wks	4 (1.4)	2 (3.8)	2 (0.8)	2 (1.9)	7 (2.4)	0
	>12 wks	4 (2.6)	0	1 (0.5)	0	5 (2.4)	0
Ear infection	0-12 wks	0	0	1 (0.4)	0	0	0
	>12 wks	0	2 (3.8)	2 (1.0)	0	0	0
Pruritus	0-12 wks	3 (1.1)	1 (1.9)	2 (0.8)	1 (0.9)	0	0
	>12 wks	1 (0.7)	1 (1.9)	0	0	0	1 (1.0)
Gout	0-12 wks	1 (0.4)	0	1 (0.4)	0	7 (2.4)	0
	>12 wks	0	0	0	0	3 (1.5)	0
Rash	0-12 wks	1 (0.4)	2 (3.8)	0	0	3 (1.0)	1 (0.9)
	>12 wks	1 (0.7)	1 (1.9)	0	0	1 (0.5)	0

ACZ885 = canakinumab, TA = triamcinolone acetonide, colch. – colchicine

8.2 Long-term safety from the all RA dataset

The larger all RA dataset includes subjects from open-label extension studies who were switched from placebo and focuses on long-term safety of canakinumab over time.

For the all RA dataset, a summary of the number of patients exposed and the duration of exposure to canakinumab is shown in Table 8-3 where the canakinumab data are pooled and are presented over time.

Table 8-3 Duration of exposure by onset period (all RA)

	ACZ885 overall N=441	ACZ885 0-24wks N=441	ACZ885 >24-48wks N=332	ACZ885 >48-72wks N=255	ACZ885 >72-96wks N=149	ACZ885 >96-144wks N=37
Exposure (days)						
Mean	382.0	382.0	476.2	542.7	626.3	749.1
SD	218.09	218.09	163.53	122.35	85.84	54.39
Median	400.0	400.0	477.0	535.0	616.0	746.0
Min - max	8 - 886	8 - 886	169 - 886	337 - 886	505 - 886	673 - 886
Patient years	461.2	-	-	-	-	-
Exposure - n (%)						
≥1 day	441 (100.0)	-	-	-	-	-
≥12 weeks	411 (93.2)	-	-	-	-	-
≥24 weeks	332 (75.3)	-	-	-	-	-
≥36 weeks	301 (68.3)	-	-	-	-	-
≥48 weeks	255 (57.8)	-	-	-	-	-
≥72 weeks	150 (34.0)	-	-	-	-	-
≥96 weeks	38 (8.6)	-	-	-	-	-
Cumulative dose (mg)						
Mean	4826.5	-	-	-	-	-
SD	2985.92	-	-	-	-	-
Median	4800.0	-	-	-	-	-
Min	40.8	-	-	-	-	-
Max	18300.0	-	-	-	-	-

ACZ885 = canakinumab, SD = standard deviation

Of the 441 canakinumab-treated patients (placebo patients are not shown) 75% were exposed for ≥24 weeks, 50% for ≥57.1 weeks (i.e. the median duration of 400 days), and >7,5% were exposed for ≥96 weeks. The median cumulative dose of canakinumab at 4800 mg was 32 times that for 150 mg canakinumab in gouty arthritis, allowing the safety of canakinumab to be examined at exposures much higher than those expected. In the target dose group, 69 patients were exposed for a total of >15 patient years.

Frequencies of canakinumab patients with treatment emergent SAEs were analysed by 24 and 48 week time periods.

Primary SOC in which more than 1% of patients in the ACZ885 overall group had SAEs included infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders, injury, poisoning and procedural complications and vascular disorders. RA (worsening of RA in 5 patients) and osteoarthritis (4 patients) were the most frequent SAEs, erysipelas SAEs affected 3 patients.

Over time, the proportions of canakinumab-treated patients with any SAE varied from 6.6% in the first 24 week period to 3.1% in the last period, >96 to 144 weeks. Infections tended to

occur slightly more often in the first 24 weeks of treatment: 2.5% of patients compared to 0.8-2.3% of patients in longer periods, whereas there was a small increase over time in the incidence of musculoskeletal disorders (primarily (worsening of) RA and osteoarthritis): 0.7% of patients in the first 24 week period versus 1.4-2.9% in the subsequent 3 periods (but none in the last 48 week period). Otherwise, the frequencies of SAEs over time were unremarkable given the low incidence and decreasing numbers of patients contributing to the longer time periods.

9 Safety topics of special interest

Safety topics of special interest have been identified since canakinumab is a monoclonal antibody and acts as an immuno modulator. In addition, patients with gouty arthritis frequently have other concomitant conditions thus the following topics are presented in greater detail: Infections, potential opportunistic infections, neutropenia, thrombocytopenia, hepatic AEs and liver function tests, malignancies, immunogenicity, local injection site reactions. AEs related to impaired renal function, major adverse cardiac events (MACE), blood pressure, lipid profile, uric acid levels and vertigo.

9.1 Infections

The overall rate and severity of infections and infestations (primary SOC) and the common infections by preferred term were examined.

9.1.1 Gouty arthritis dataset

The numbers of subjects from the gouty arthritis safety set with at least one infection AE or SAEs are displayed in Table 9-1.

Table 9-1 Frequency of infection AEs and SAEs (gouty arthritis)

	≤100mg ACZ885 N=278	Split 150mg ACZ885 N=53	150mg ACZ885 N=253	≥200mg ACZ885 N=107	All ACZ885 N=691	TA N=286	colch N=108
with at least 1 AE of infection, n (%)	42 (15.1)	10 (18.9)	49 (19.9)	19 (17.8)	120 (17.4)	37 (12.9)	13 (12.0)
SAE of Infections, n(%)	4 (1.4)	1(1.9)	4 (1.6)	2(1.9)	11 (1.6)	0	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine

The percentages of subjects with at least 1 AE of infection were similar across the doses of canakinumab studied, ranging from 15.1 to 19.9%. These percentages were smaller in the triamcinolone (12.9%) and colchine (12.0%) groups.

The proportions of patients with SAEs of infections were similar across the doses of canakinumab studied, and ranged from 1.4 to 1.9%. There was no clustering of events around a particular type of infection, and there was no suggestion of a dose response.

Any infection SAE suspected to be drug related in the gouty arthritis program was reviewed by an external committee and adjudicated for drug relationship. All but 1 of the infection SAEs were not suspected to be related to study drug according to the investigator. One case of

erysipelas in a canakinumab-treated patient was suspected to be study drug-related; in this case, the adjudication category of causality was Possible B (i.e. weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship). The adjudication category, if applicable, is provided in Table 9-2.

Table 9-2 Overview of infections and infestations SAEs (gouty arthritis)

Patient ID (Age/sex/race)	Treatment	Description / Action taken	Study drug relationship † Severity	Adjudication category *
[H2251-0015-00004] (53/M/Ca)	ACZ885 ≤100 mg	Erysipelas of left leg / hospitalized, co-med taken, discontinued study drug	Suspected Severe	Possible B (infection) *
[H2255-0091-00005] (76/F/Ca)	ACZ885 ≤100 mg	Bronchitis / hospitalized, co-med taken	Not suspected Severe	NA
[H2255-0106-00006] (63/M/Ca)	ACZ885 ≤100 mg	Appendicitis / hospitalized	Not suspected Moderate	NA
[H2255-0542-00001] (36/M/Ca)	ACZ885 ≤100 mg	Appendicitis / hospitalized, non-drug therapy	Not suspected Moderate	NA
[H2251-0070-00006] (59/M/Ca) ‡	ACZ885 split 150mg	Ear infection, Pneumonia / hospitalized, co-med taken	Not suspected Moderate	NA
[H2356-0013-00001] (74/M/Ca) ‡	ACZ885 150 mg	Pneumonia / hospitalized, co-med taken	Not suspected Mild	NA
[H2356-0121-00001] (52/M/Ca)	ACZ885 150 mg	Jaw abscess / hospitalized, co-med taken	Not suspected Severe	NA
[H2357-0540-00006] (26/M/Ca) ‡	ACZ885 150 mg	Abcess left forearm / hospitalized, co-med taken, non-drug therapy	Not suspected Moderate	NA
[H2357-0558-00003] 52/M/Ca	ACZ885 150 mg	Gastroenteritis / hospitalized, co-med taken	Not suspected Severe	NA
[H2251-0080-00007] 54/F/As ‡	ACZ885 ≥200 mg	Tonsillitis, gastritis / hospitalized, co-med taken	Not suspected Severe	NA
[H2251-0080-00008] 59/M/As	ACZ885 ≥200 mg	Gangrene, Sepsis / hospitalized, co-med taken, discontinued study drug	Not suspected Severe	NA

M = male, F = female, Ca = Caucasian, As = Asian, ACZ885 = canakinumab, NA=Not Applicable

† Investigator's assessment

* Adjudication category "possible B": Weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship.

There were no infectious SAEs in the triamcinolone acetonide and colchicine groups.

9.1.2 Placebo-controlled RA safety set

For placebo-controlled RA AEs refer to Table 7-13.

The numbers of subjects from the placebo-controlled RA safety set with at least one infection AE and SAEs are displayed in Table 9-3.

Table 9-3 Frequency of infection AEs, and SAEs (placebo-controlled RA)

	<150 mg ACZ885 N=12	150 mg ACZ885 N=69	>150 mg ACZ885 N=263	All ACZ885 N=344	Placebo N=121
with at least 1 AE of infection, n (%)	6 (50.0)	11 (15.9)	82 (31.2)	99 (28.8)	43 (35.5)
with at least 1 SAE of infection, n (%)	2 (16.7)	0	7 (2.7)	9 (2.6)	0
infection AEs (n per 100 pt-yrs)	10 (22.072)	15 (1.373)	132 (0.520)	157 (0.393)	60 (1.221)

ACZ885 = canakinumab

Across all 3 assessments of frequency of infection, there was no clear dose response relationship seen between canakinumab and occurrence of infection.

A summary of the individual infections SAEs together with the investigator's assessment of relationship to study drug and the adjudication category (if applicable) is provided in Table 9-4. There was no consistent pattern or cluster of infectious SAEs. There were no infectious SAEs with the placebo-controlled group.

Table 9-4 Infection and infestations SAEs (placebo-controlled RA)

Patient number (Age/sex/race)	Treatment	Description / Action taken	Study drug relationship	Adjudication category
[A2101-0002-00008] (63/F/Ca)	<150 mg ACZ885	Erysipelas of left lower leg; outcome: hospitalized, recovered and completed the study	Suspected	Possible B**
[A2101-0021-00001] (57/F/Ca)	<150 mg ACZ885	Pyrexia due to an infection in the lungs; outcome: hospitalized, recovered and completed the study	Not suspected	NA
[A2101-0001-00007] (47/F/Ca)	<150 mg ACZ885	Lung infection; outcome: hospitalized, recovered and completed the study	Suspected	Possible B**
[A2101-0001-00007] (47/F/Ca)	>150 mg ACZ885	Tracheobronchitis; outcome: hospitalized, recovered and completed the study	Not suspected	NA
[A2201-0053-00018] (38/F/Ca)	>150 mg ACZ885	Cellulitis with abscess formation on right hand; outcome: hospitalized and study drug permanently discontinued	Suspected	Possible A*
[A2201-0054-00004] (59/F/Ca)	>150 mg ACZ885	Urosepsis; outcome: hospitalized and study drug permanently discontinued	Suspected	Possible A*
[A2201-0054-00006] (42/F/Other)	>150 mg ACZ885	Appendicitis; outcome: hospitalized, recovered and completed the study	Suspected	Not related
[A2201-0056-00010] (74/F/Ca)	>150 mg ACZ885	Ovarian cyst; outcome: hospitalized	Not suspected	NA
[A2201-0056-00010] (74/F/Ca)	>150 mg ACZ885	Soft tissue infection; outcome: hospitalized, study drug permanently discontinued	Not suspected	NA
[A2201-0056-00048] (72/F/Ca)	>150 mg ACZ885	Diverticulitis; outcome: hospitalized, recovered, completed the study and entered the extension	Not suspected	NA

Patient number (Age/sex/race)	Treatment	Description / Action taken	Study drug relationship	Adjudication category
[A2207-0012-05231] (55/F/Ca)	>150 mg ACZ885	Ear infection, Sinusitis with neurosensory deafness; outcome: hospitalized	Not suspected	NA

M = male, F = female, Ca = Caucasian, ACZ885 = canakinumab

* Adjudication category: "possible A": No other compelling explanation, time frame is compatible but other circumstances may have induced the event: e.g. concomitant medication, food and exposure to external factors

** Adjudication category: "possible B": Weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship

9.1.3 All RA dataset

The numbers of subjects from the All RA safety set with at least one infection AE and SAEs are displayed in Table 9-5.

Table 9-5 Frequency of infection AEs, and SAE (all RA)

	ACZ885 overall N=441
with at least 1 AE of infection, n (%)	219 (49.7)
with at least 1 SAE of infection	21 (4.8)

ACZ885 = canakinumab

For a study population that was treated for up to 144 weeks with canakinumab, the percentage of subjects with at least 1 AE of infection was 49.7%.

Over time, the proportions of canakinumab-treated patients with any SAE varied from 2.5% in the first 24 week period to 1.5% in the last period, >96 to 144 weeks. Infections tended to occur more often in the first 24 weeks of treatment compared to the following periods: 2.5% of patients compared to 0.8-1.5% for subsequent periods except the >72-96 week period with 2.3%. Otherwise, the frequencies of infection SAEs over time were unremarkable given the low incidence and decreasing numbers of patients contributing to the longer time periods.

SAEs of infection suspected to be related to study drug by the investigator, including the adjudication category of causality, that were received in addition to the cases for the placebo controlled RA in Table 9-4 are provided in Table 9-6.

Table 9-6 Infections and infestations SAEs suspected by the investigator to be study drug related (all RA [additional cases to placebo-controlled RA])

Patient number (Age/sex/race)	Description / Outcome	Adjudication category
[A2201E1-0062-00003] (68/F/Ca)	Respiratory tract infection causing worsening of COPD from day 240-290, severe; outcome: hospitalized and study drug dosage adjusted/temporarily interrupted.	Possible B*
[A2201E1-0002-00018] (55/F/Ca)	Erysipelas of right upper extremity on day 554-606, mild in severity; outcome: hospitalized, study drug permanently discontinued	Possible B*
[A2201E1-0077-00002] (43/F/Ca)	Arthritis bacterial (reported as right tarsus septic arthritis) on day 177-239, severe; outcome: hospitalized and study drug dosage adjusted/temporarily interrupted. Urinary tract infection on day 355-365, severe; outcome: no action taken	Possible B*
[A2201E1-0507-00002] (51/M/Ca)	Dyspnea on day 243-253, moderate in severity; outcome: hospitalized and study drug dosage adjusted/temporarily interrupted.	Not related

M = male, F = female, Ca = Caucasian

* Adjudication category: "possible B": Weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship

Cases for placebo-controlled RA are presented in Table 9-4

9.2 Potential opportunistic infections

Opportunistic or unusual infections have been defined as systemic herpes or fungal infections, infections with toxoplasma, mycobacterial, aspergillus, pneumocystis, cryptococcus pathogens, polyoma and cytomegalovirus infections, and Kaposi syndrome.

A search has been conducted to identify opportunistic infections using MedDRA HLGs: fungal, viral and mycobacterial infectious disorders, and immunodeficiency syndromes, as well as several specific preferred terms associated with testing for tuberculosis. All retrieved cases were medically reviewed whether they could be confirmed as being opportunistic infections.

9.2.1 Gouty arthritis dataset

The events identified by the above defined MedDRA search were mostly viral infections (predominantly influenza and viral respiratory tract infections) and none were serious or led to discontinuation of study drug. None of these individual cases of potential opportunistic infections were identified as confirmed opportunistic infections on clinical evaluation of the data.

For patient (H2255-0123-00901, 54 year old male, Caucasian) in the canakinumab ≤100 mg group, latent tuberculosis was reported on day 4. He had a positive tuberculosis skin test, his chest X-ray was normal, and he was conservatively treated with isoniazid for tuberculosis prophylaxis. For two other patients a positive mycobacterium tuberculosis complex test was reported on day 1 and day 7, respectively, 1 (H2356-0139-00002, 60 year old male, Caucasian) in the canakinumab 150 mg group and 1 (H2357-0571-00010, 70 year old male,

Black) in the triamcinolone acetonide group. Both of these patients had normal chest X-rays and received no tuberculosis treatment.

Thus, no increased risk for tuberculosis or opportunistic infections was identified.

9.2.2 Placebo-controlled RA dataset

None of the identified individual cases were confirmed opportunistic infections on clinical evaluation.

9.2.3 All RA dataset

Two patients had a positive tuberculin test with sequential PPD skin testing in the longer time periods, one in the >48-72 week period (suspected to be related to study drug) and one in the >72-96 week period (not suspected). Both patients had no clinical signs or symptoms for active or latent tuberculosis i.e. no persistent cough, no weight loss and no sub-febrile temperature. Further diagnostic procedures including chest X ray did not confirm active or latent infection of *Mycobacterium tuberculosis* in both patients.

A review of data from patients with sequential PPD skin testing in clinical trials was performed following observations of asymptomatic patients with false-positive post-baseline PPD skin tests. The observed conversion of PPD skin reactions upon re-testing is most likely due to an immunologic booster reaction. The label for CAPS therefore recommends that in the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered. An alternative test could be an interferon- γ release assay. QuantiFERON-TB Gold[®] has specificity of 99% in a low-risk population (Mazurek et al 2007).

In summary, none of the identified individual cases were confirmed opportunistic infections on clinical evaluation.

9.3 Neutropenia and White Blood Cell Count decrease

9.3.1 Gouty arthritis dataset

Neutropenia was assessed through AE reports and the evaluation of laboratory values. Within the gouty arthritis dataset, one (0.4%) patient in the canakinumab ≤ 100 mg group, 3 (1.2%) patients in the canakinumab 150 mg group, 1 (0.9%) patient in the canakinumab ≥ 200 mg group, 1 (0.3%) patient in the triamcinolone acetonide group and 3 (2.8%) patients in the colchicine group experienced at least one of the following AEs: leukopenia, neutropenia, neutrophil count decreased or white blood cell (WBC) count abnormal.

Reports of leukopenia as an adverse events were infrequent with 150 mg canakinumab (3, 1.2%). There was a one potential relationship between lowered white cell counts and an infection in 1 patient who had an SAE of jaw abscess during a concurrent, transient decrease below 90% of the lower limit of normal in absolute neutrophils. This 52 year old male Caucasian patient [H2356-0121-00001] who had received canakinumab 150 mg, had jaw abscess reported as an SAE from day 29-58. Absolute neutrophils on day 28 were normal

($3.13 \times 10^9/L$) but were low on day 58 ($1.5 \times 10^9/L$) within normal limits by day 86 ($2.57 \times 10^9/L$).

White blood cell count, neutrophil count, and grading according to CTC criteria, are displayed in Table 9-7.

Table 9-7 Hematology values by parameter and CTC grading (gouty arthritis)

Laboratory test		ACZ885 ≤ 100 mg N=278 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥ 200 mg N=107 n (%)	colch N= 108 n (%)	TA N= 286 n (%)
WBCs	Grade 1 (<LLN – 3.0 10E9/L)	24 (8.8)	58 (23.0)	19 (17.9)	7 (6.5)	19 (6.7)
	Grade 2 (< 3.0 – 2.0 10E9/L)	7 (2.6)	9 (3.6)	2 (1.9)	2 (1.9)	1 (0.4)
	Grade 3 (<2.0 – 1.0 10E9/L)	1 (0.4)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)
	Grade 4 (<1.0 10E9/L)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophils	Grade 1 (<LLN – 1.5 10E9/L)	26 (9.5)	52 (20.6)	17 (16.0)	7 (6.5)	15 (5.3)
	Grade 2 (<1.5 – 1.0 10E9/L)	7 (2.6)	20 (7.9)	3 (2.8)	3 (2.8)	2 (0.7)
	Grade 3 (<1.0 – 0.5 10E9/L)	1 (0.4)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4 (<0.5 10E9/L)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine

The incidence of patients with decreased white blood cells and neutrophils was higher with canakinumab than with the respective comparators. For white blood cells, most of the decreases were in CTC Grade 1. The incidence of subjects with CTC grade 2 decreases ranged from 1.9-3.6% in canakinumab treated groups compared with 0.4-1.9% with the comparators. Similarly for neutrophils, most of the decreases were CTC Grade 1. For CTC Grade 2, the incidence was highest in the canakinumab 150 mg group (7.9%) compared with the other canakinumab groups or the comparators (0.7-2.8%).

Six patients receiving canakinumab were identified as having CTC Grade 3 and 2 patients in the ≥200 mg group had isolated occurrences of CTC Grade 4 neutrophil counts. Each patient with the isolated Grade 4 value had repeat labs within one week of these abnormal results, which were nonconfirmatory in both cases, leading to the plausible conclusion that these two values were spurious. There were no infections associated with neutrophil counts observed at CTC Grade 2 or higher.

9.3.2 Placebo-controlled RA dataset

Four canakinumab patients (1 (1.4%) in the 150 mg group and 3 (1.1%) in the >150 mg group) versus none in the placebo group had leukopenia or decreased WBC reported as AEs. All of these non serious events were suspected to be related to study drug by the investigators. Two of the patients discontinued study drug due to these AEs: patient [A2201-0023-00006]

and patient [A2201-0023-00009]. One patient, A2201-0026-00008, had a non-serious, bacterial skin infection.

Clinically notable decreases in absolute neutrophils were defined as $\leq 0.9 \times$ LLN and notable decreases for WBCs were defined as $\leq 0.8 \times$ LLN. Seven (1+6) of the 332 (2.1%) canakinumab treated subjects met the criteria for notable WBC decrease and 20/332 (6.0%) met the criteria for notable neutrophil decrease. This compares with 1 subject (0.8%) each for notable WBC or notable neutrophil decreases in the placebo group. These frequencies of newly occurring, post-baseline notable hematology abnormalities in the placebo-controlled RA dataset are shown in Table 9-8. None of the patients with notable WBCs or neutrophil decreases experienced any serious infections.

Table 9-8 Hematology abnormalities (placebo-controlled RA)

Parameter Notable criterion	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	Placebo N=121 n (%)
Hemoglobin Total	68	261 or 263	120 or 121
≥ 20 g/L decrease from baseline	2 (2.9)	5/261 (1.9)	5/120 (4.2)
< 100 g/L	3 (4.4)	8/263 (3.0)	5/121 (4.1)
WBC Total	68	263	121
$\leq 0.8 \times$ LLN	1 (1.5)	6 (2.3)	1 (0.8)
$\geq 1.2 \times$ ULN	1 (1.5)	12 (4.6)	11 (9.1)
Absolute neutrophils Total	68	237	106
$\leq 0.9 \times$ LLN	4 (5.9)	16 (6.8)	1 (0.9)
$\geq 1.2 \times$ ULN	1 (1.5)	13 (5.5)	12 (11.3)
Absolute lymphocytes Total	68	237	106
$< LLN$	0	1 (0.4)	4 (3.8)
$\geq 1.1 \times ULN$	1 (1.5)	3 (1.3)	1 (0.9)
Absolute eosinophils Total	68	237	106
$\geq 1.1 \times ULN$	0	5 (2.1)	2 (1.9)
Platelets Total	68	263	119
$< LLN$	0	5 (1.9)	0

ACZ885 = canakinumab, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell counts, abs. = absolute, % = of evaluable data

9.3.3 All RA dataset

In addition to the 4 patients already described in the placebo-controlled RA dataset, there were 2 more patients with adverse event reports of neutropenia and decreased WBC in the All RA dataset that were suspected to be related to the study drug by the investigator.

Patient A2201E1-0021-00005 (30 year old, Black female, on canakinumab 300 mg s.c. q4wk in study A2201E1 and placebo in core study A2201) suffered severe influenza on day 420-430 at the same time as decreased WBC count was reported as an AE. Absolute neutrophils met the notably low ($\leq 0.9 \times$ LLN) criteria from day 71 to day 527 of the extension study.

One of the patients with a notable decrease in absolute neutrophils ($\leq 0.9 \times$ LLN) or WBCs ($\leq 0.8 \times$ LLN) had a serious infection. Patient [A2201E1-0073-00005] (68 year old, female,

Other race, on canakinumab 300 mg s.c. q4wk in study A2201E1 and 300 mg s.c. q2wk in core study A2201) experienced a device-related infection following elective surgery for left knee total replacement. Low neutrophil and WBC counts were recorded in the lab data (but were not reported as an AE) on day 169 (neutrophils $1.6 \times 10^9/L$, WBC $3.3 \times 10^9/L$) and day 529 (neutrophils $1.2 \times 10^9/L$, WBC $2.4 \times 10^9/L$, notably low) of the extension study. The left knee prosthetic infection occurred on day 473 of the extension study, 42 days after the surgery when WBC and absolute neutrophil counts had been normal. The last dose of study drug was received on day 449 of the extension study.

WBC and neutrophil counts were collected during the trials that contributed to the All RA safety set. Mean and median changes from baseline in these measures are displayed in Table 9-9.

Table 9-9 Mean WBC and neutrophil changes from baseline (all RA)

Parameter Period	n	Baseline	Post-baseline	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SD)	Median
WBC ($10^9/L$)					
week 24 (N=441)	434	8.547 (2.8907)	7.402 (2.6654)	-1.145 (2.0658)	-1.100
week 48 (N=332)	327	8.622 (2.8931)	7.491 (2.6620)	-1.131 (2.2136)	-1.200
week 72 (N=255)	253	8.645 (2.9289)	7.353 (2.7433)	-1.293 (2.2221)	-1.200
week 96 (N=149)	146	8.625 (2.9768)	7.600 (3.2081)	-1.025 (2.5430)	-0.950
week 144 (N=37)	37	9.257 (3.2108)	7.395 (2.1690)	-1.862 (2.1898)	-1.200
End of study (N=441)	438	8.539 (2.8821)	7.465 (2.8189)	-1.073 (2.3203)	-1.000
Neutrophils ($10^9/L$)					
week 24 (N=441)	395	6.263 (2.6845)	5.160 (2.5196)	-1.103 (2.0420)	-1.000
week 48 (N=332)	326	6.279 (2.6782)	5.123 (2.4686)	-1.156 (2.1567)	-1.250
week 72 (N=255)	252	6.382 (2.7713)	5.001 (2.4952)	-1.381 (2.1352)	-1.300
week 96 (N=149)	146	6.337 (2.7805)	5.197 (2.6378)	-1.140 (1.8259)	-0.950
week 144 (N=37)	37	6.957 (2.9089)	5.200 (2.0891)	-1.757 (2.2564)	-1.500
End of study (N=441)	400	6.254 (2.6725)	5.196 (2.5283)	-1.058 (2.1134)	-1.000

ACZ885 = canakinumab, WBC = white blood cells, SD = standard deviation

For both WBC count and neutrophil count, there were small decreases observed at Week 24 following initiation of canakinumab. These small decreases were maintained through Week 144 and end of study.

9.4 Thrombocytopenia

9.4.1 Gouty arthritis dataset

Thrombocytopenia was assessed through AE reports and the evaluation of laboratory values.

There were 3 patients with thrombocytopenia AEs, 1 in each of the canakinumab split 150 mg, 150 mg and colchicine groups, and 4 patients with platelet count decreased reported as an AE, 3 in the canakinumab 150 mg group and 1 in the canakinumab ≥ 200 mg group. These events in the canakinumab-treated patients were suspected to be related to study drug by the investigators. None of these AEs was reported as an SAE or led to discontinuation of study drug.

Although there was an increased incidence in observed decreased platelet counts, the magnitude of the decreases were mild (all CTC grade 1) (Table 9-10). Four patients had serious bleeding disorders, none of which were associated with decreased platelets. [Patients H2251-0100-00014 and H2251-0126-00001 reporting hematuria, patient H2251-0096-00001 with hemorrhoidal hemorrhage and patient H2257-0580-00004 with intracranial hemorrhage]

Table 9-10 Platelet count and grading according to CTC criteria (gouty arthritis)

Laboratory test		ACZ885 ≤ 100 mg N=278 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥ 200 mg N=107 n (%)	colch. N= 108 n (%)	TA N= 286 n (%)
Platelet count	Grade 1 (<LLN-75.0 10E9/L)	22 (8.1)	32 (12.7)	13 (12.3)	6 (5.6)	22 (7.7)
	Grade 2 (<75.0-50.0 10E9/L)	0	0	0	0	0
	Grade 3 (<50.0-25.0 10E9/L)	0	0	0	0	0
	Grade 4 (<25.0 10E9/L)	0	0	0	0	1 (0.4)

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine

9.4.2 Placebo-controlled RA and All RA datasets

There were no thrombocytopenia or decreased platelet count AEs in either the placebo-controlled RA or All RA datasets. Platelets <LLN were seen in 5 (1.9%) patients in the canakinumab >150 mg group versus none in the lower dose canakinumab and placebo groups. None reported any serious bleeding disorders.

Platelet counts were collected at the end of every 24 weeks in the trials that contribute to the All RA safety set. Mean and median changes from baseline in this measure are displayed in Table 9-11.

Table 9-11 Mean platelet count changes from baseline (all RA)

Parameter	n	Baseline	Post-baseline	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SD)	Median
Platelets (10⁹/L)					
week 24 (N=441)	426	321.7 (88.97)	291.6 (83.34)	-30.1 (59.48)	-28.5
week 48 (N=332)	320	325.4 (89.58)	290.9 (83.47)	-34.5 (67.39)	-30.5
week 72 (N=255)	248	322.1 (86.71)	279.3 (81.36)	-42.8 (64.95)	-38.5
week 96 (N=149)	143	318.4 (81.28)	265.5 (78.60)	-53.0 (75.33)	-50.0
week 144 (N=37)	35	311.5 (71.11)	240.4 (60.43)	-71.1 (49.01)	-61.0
End of study (N=441)	434	322.2 (88.70)	282.6 (88.82)	-39.6 (71.40)	-37.5

SD = standard deviation

9.5 Hepatic AEs and liver function tests

9.5.1 Gouty arthritis dataset

9.5.1.1 Hepatic AEs

The incidence of hepatic AEs was comparable in the canakinumab ≤ 100 mg (4.3%, 12 patients), 150 mg (6.3%, 16 patients) and ≥ 200 mg (4.7%, 5 patients) groups, and lower in the triamcinolone acetonide (3.1%, 9 patients), colchicine (2.8%, 3 patients) and canakinumab split 150 mg (1.9%, 1 patient) groups. The majority of these events were reported in the investigation SOC.

None of the events were reported as SAEs. For 1 patient with worsening liver function tests (LFTs) in the canakinumab ≤ 100 mg group [H2251-0502-00005] and 1 patient with hepatomegaly in the canakinumab ≥ 200 mg group [H2251-0520-00006], the hepatic events led to discontinuation of study drug. One triamcinolone acetonide patient [H2357-0571-00004] had elevations of ALT, aspartate aminotransferase (AST), GGT and alkaline phosphatase (ALP) reported as severe AEs starting on day 7. All the other hepatic AEs were asymptomatic, mild or moderate in severity.

9.5.1.2 Liver function test abnormalities

Liver function test abnormalities are presented in Tables 9-12 and Table 9-13.

Table 9-12 Liver function abnormalities (transaminases) (gouty arthritis)

ALT/AST notable value	AC885 ≤ 100 mg N=278 n (%)	AC885 150mg N=253 n (%)	AC885 ≥ 200 mg N=107 n (%)	TA N=286 n (%)	colch. N=108 n (%)
≥ 3 x ULN	7 (2.6)/ 5 (1.8)	4 (1.6)/ 2 (0.8)	5 (4.7)/ 2 (1.9)	7 (2.5)/ 7 (2.5)	2 (1.9)/ 1 (0.9)
≥ 5 x ULN	3 (1.1)/ 1 (0.4)	0 0	1 (0.9)/ 0	0 2 (0.7)	0 0
≥ 10 x ULN	1 (0.4)/ 1 (0.4)	0 0	0 0	0 1(0.4)	0 0
≥ 20 x ULN	0 0	0 0	0 / 0	0 0	0 0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, ULN = upper limit of normal

Table 9-13 Liver function abnormalities (bilirubin) (gouty arthritis)

Bilirubin notable value	AC885 ≤ 100mg N=278 n (%)	AC885 150mg N=253 n (%)	AC885 ≥ 200mg N=107 n (%)	TA N=286 n (%)	colch. N=108 n (%)
> ULN	22 (8.1)	20 (7.9)	3 (2.8)	26 (9.2)	6 (5.6)
≥ 1.5x ULN	4 (1.5)	3 (1.2)	0 (0.0)	3 (1.1)	0
≥ 2x ULN	1 (0.4)	2 (0.8)	1 (0.9)	0	0
≥ 1.5x ULN if ALT and/or AST ≥ 3x ULN	1 (0.4)	1 (0.4)	0	0	0
≥ 2x ULN if ALT and/or AST ≥ 3x ULN	1 (0.4)	0	0	0	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, ULN = upper limit of normal

A 55 year old male [H2251-0018-00003] had isolated LFT abnormalities on day 178 (25 weeks after canakinumab ≤100 mg): ALT 747 (ULN 48 U/L), AST 507 (ULN 45 U/L); GGT 229 (ULN 51 U/L) with, normal bilirubin and ALP. On day 204, follow-up LFTs were normal except for GGT of 91 U/L. No relevant medical history was reported for this patient.

In a 53 year old female [H2251-0018-00005] the abnormal LFTs formally met the laboratory criteria which define Hy's law (i.e. ALT or AST >3 x ULN and total bilirubin >2 x ULN and ALP <2 x ULN) (Food and Drug Administration 2009) on Day 176 (25 weeks after canakinumab ≤100 mg); bilirubin ≥2 x ULN (43, ULN 21 µmol/L) and AST ≥3 x ULN (124, ULN 36 U/L), ALT 40 (ULN 37 U/L) and ALP 128 (ULN 100 U/L), GGT 213 (ULN 49 U/L). The patient presented with LFT abnormalities at screening and they remained similarly elevated (within expected analytical variation) or improved at some visits during the study up to day 225. It can be concluded that these LFT abnormalities are unlikely to be related to study drug.

A 32 year old male in the canakinumab 150 mg group [H2357-0031-00002] had bilirubin ≥1.5 x ULN on day 29 of 41 µmol/L, from a baseline value of 7 µmol/L. Subsequently, bilirubin values were 38 µmol/L (≥1.5 x ULN) on day 57 and 17 µmol/L (normal) on day 85. This patient also had elevated ALT ≥3 x ULN on day 29 of 161 U/L, from a baseline value of 68 U/L. On day 57, ALT remained high at 142 U/L falling to 92 U/L on day 85.

Alkaline phosphatase >1.5 x ULN did not occur in the canakinumab groups compared to 1.4% (4 patients) and 0.9% (1 patient) of patients in the triamcinolone acetone and colchicine groups, respectively.

9.5.2 Placebo-controlled RA dataset

9.5.2.1 Hepatic AEs and Liver function test abnormalities

The incidence of hepatic AEs was comparable in the canakinumab >150 mg (4.2%, 11 patients) and placebo (4.1%, 5 patients) groups. No AEs have been reported in the lower dose canakinumab groups. None of the events were reported as severe or as SAEs.

There were two patients in the canakinumab >150mg group with ALT ≥ 5x upper limit of normal (ULN) who discontinued study drug :

- Patient [A2201-0002-00031] discontinued on Day 30. Baseline ALT - 17 U/L, bilirubin was normal. Day 30 ALT- 155 U/L (6.2 x ULN (25 U/L), AST-91 U/L
- Patient [A2201-0520-00001] discontinued on Day 31. Baseline ALT- 64 U/L, bilirubin was normal. Day 31 ALT- 140 U/L (5.6 x ULN (25 U/L), AST- 46 U/L

The frequencies of newly occurring, post-baseline liver function tests abnormalities in the placebo-controlled RA dataset are shown in Table 9-14.

Table 9-14 Liver function abnormalities (placebo-controlled RA)

Parameter Notable criterion	ACZ885 150 mg N=69 n (%)	ACZ885 >150 mg N=263 n (%)	Placebo N=121 n (%)
ALP Total	69	263	121
> 1.5 x ULN	2 (2.9)	5 (1.9)	2 (1.7)
ALT Total	69	263	121
≥ 3 x ULN	0	8 (3.0)	1 (0.8)
≥ 5 x ULN	0	2 (0.8)	0
≥ 10 x ULN	0	0	0
AST Total	69	263	121
≥ 3 x ULN	0	4 (1.5)	1 (0.8)
≥ 5 x ULN	0	0	0
Bilirubin (total) Total	69	263	121
> ULN	0	5 (1.9)	3 (2.5)
≥ 1.5 x ULN	0	0	1 (0.8)
≥ 2 x ULN	0	0	0
≥1.5 x ULN and ALT and/or AST ≥3 x ULN	0	0	0
GGT Total	0	102	36
> 3 x ULN	-	1 (1.0)	1 (2.8)

ACZ885 – canakinumab, ULN – upper limit of normal

For bilirubin, there were mean and median increases from baseline to end of study in the canakinumab 150 mg and >150 mg groups versus placebo (mean/median: 0.86/0.50 and 0.87/0.55 vs. 0.09/0.00 µmol/L, respectively). All absolute means and medians were within the normal reference range at both time points.

ALT or AST values ≥3 x ULN (ALT 3.0%, AST 1.5% of patients) or ≥5 x ULN (ALT 0.8%, AST 0%) post-baseline occurred only in the canakinumab >150 mg group except for a single placebo patient (0.8%) with values ≥3 x ULN. No patient had an increase to ≥10 x ULN.

ALP abnormalities >1.5 x ULN were seen in 2 (2.9%) patients in the canakinumab 150 mg group and 5 (1.9%) patients in the canakinumab >150 mg group. This was similar to the placebo group where ALP >1.5 x ULN occurred in 2 (1.7%) patients.

Bilirubin increases >ULN and ≥1.5xULN were infrequent and higher in the placebo group than in the canakinumab >150 mg group (bilirubin >ULN: 2.5% vs. 1.9%, bilirubin ≥1.5 x ULN: 0.8% vs. 0%, respectively) and did not occur in the canakinumab <150 mg and 150 mg groups

There were no cases of combined ALT and/or AST with bilirubin notable abnormalities in any treatment group, and no Hy's law cases (i.e. patients with ALT or AST >3 x ULN and total bilirubin >2 x ULN and ALP <2 x ULN) (FDA Guidance on Drug Induced Live Injury, 2009).

9.5.3 All RA dataset

9.5.3.1 Liver function test abnormalities

Table 9-15 summarizes the liver function test abnormalities over time in the All RA dataset.

Table 9-15 Liver function abnormalities (all RA)

Parameter Notable criterion	ACZ885 overall N=441 n (%)	ACZ885 0-24wks N=441 n (%)	ACZ885 >24-48wks N=332 n (%)	ACZ885 >48-72wks N=255 n (%)	ACZ885 >72-96wks N=149 n (%)	ACZ885 >96-144wks N=37 n (%)
AST						
≥ 3 x ULN	12 (2.7)	4 (0.9)	1 (0.3)	5 (2.0)	1 (0.7)	1 (2.7)
≥ 5 x ULN	2 (0.5)	0	0	2 (0.8)	0	0
≥ 10 x ULN	1 (0.2)	0	0	1 (0.4)	0	0
≥ 20 x ULN	0	0	0	0	0	0
ALT						
≥ 3 x ULN	16 (3.6)	11 (2.5)	2 (0.6)	5 (2.0)	0	0
≥ 5 x ULN	4 (0.9)	2 (0.5)	0	2 (0.8)	0	0
≥ 10 x ULN	2 (0.5)	0	0	2 (0.8)	0	0
≥ 20 x ULN	1 (0.2)	0	0	1 (0.4)	0	0
Bilirubin (total)						
$>$ ULN	17 (3.9)	8 (1.8)	8 (2.4)	5 (2.0)	4 (2.7)	0
≥ 1.5 x ULN	1 (0.2)	1 (0.2)	0	0	0	0
≥ 2 x ULN	0	0	0	0	0	0
≥ 1.5 x ULN and ALT and/or AST ≥ 3 x ULN	0	0	0	0	0	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, ULN = upper limit or normal

Four canakinumab-treated patients had ALT and/or AST ≥ 5 x ULN. These included patient [A2201-0520-00001] and patient [A2201-0002-00031] who are also in the placebo-controlled dataset and had ALT ≥ 5 x ULN but not AST. The other 2 cases were patient [A2201E1-0063-00002] and patient [A2211-0051-05169] who had both ALT and AST increases ≥ 5 x ULN in the extension studies between 48 and 72 weeks.

For patient [A2201E1-0063-00002], on day 337 of the extension study, ALT was 281 U/L (11.2 x ULN (25 U/L), extension day 1 value 11 U/L) and AST was 120 U/L (5.5 x ULN (22 U/L), extension day 1 value 14 U/L). Previous (day 253) and subsequent (day 351) ALT and AST values were normal and no total bilirubin elevations were observed. On day 330, the patient experienced a SAE of limb thrombosis (popliteal vein) and was treated with anticoagulants. The increases in ALT and AST were reported as AEs lasting for 15 days; the investigator did not suspect a relationship with study drug and no action was taken.

For patient [A2211-0051-05169], on day 85 of the extension study, ALT was 952 U/L (21.2 x ULN (45 U/L), core baseline value 15 U/L) and AST was 452 U/L (11.0 x ULN (41 U/L), core baseline value 18 U/L). At the end of study visit on day 99 ALT remained slightly raised at 66 U/L, AST was 36 U/L with no elevations in serum bilirubin. The elevated ALT and AST was reported as an AE; the investigator suspected it was related to study drug and the patient discontinued study drug.

There were no Hy's law cases in the All RA dataset (i.e. patients with ALT or AST >3 x ULN and total bilirubin >2 x ULN and ALP <2 x ULN).

9.6 Malignancies

The incidence of malignancies was assessed by:

1. Listing the patients and summarizing the rate across treatments in the 3 pooled datasets using SMQ narrow searches for Malignant or unspecified tumors [RMP-Annex 1].
2. Submitting all malignancies in the canakinumab program to the adjudication committee of independent medical experts who categorized the causality of each case according to the following definitions:
 - **Probable:** Proper time frame signature of drug (onset following drug administration)/ Event is related to the drug class, no other obvious cause identified.
 - **Possible A:** No other compelling explanation, time frame is compatible but other circumstances may have induced the event: e.g. concomitant medication, food and exposure to external factors.
 - **Possible B:** Weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship.
 - **Not related:** None of the above and/or another explanation has been identified for the event
 - **Not enough information:** Not enough information to assess the causality

9.6.1 Gouty arthritis dataset

Two patients had a malignancy, 1 (0.9%) in the canakinumab ≥ 200 mg group ([H2251-0010-00002], 68 year old male Caucasian with prostate cancer SAE starting on day 106) and 1 (0.9%) in the colchicine group ([H2251-0520-00001], 45 year old male Caucasian with renal cancer SAE starting on day 109). The causality was adjudicated as "Not related" for the prostate cancer case and "Possible B: Weight of the evidence suggests another cause, but the time frame is compatible with a drug relationship." for the renal cancer case.

9.6.2 Placebo-controlled RA dataset

The Standardized MedDRA Query (SMQ) narrow search identified one patient in the canakinumab >150 mg group who presented with a non-serious tumor of the left elbow of moderate severity that was not suspected to be related to study drug (A2101-0001-00007).

9.6.3 All RA dataset

The SMQ narrow search found a further 7 patients in addition to the one patient with a skin neoplasm in the placebo-controlled RA data set.

For 3 patients, the malignancy was reported as an SAE (Table 9-16). Patient A2201E1-0074-00008 died due to progression of metastatic lung adenocarcinoma (not suspected to be related to study drug, adjudicated causality: Possible A); patient A2201E1-0002-00029 had a non-Hodgkin's lymphoma/squamous cell carcinoma of the skin (suspected to be study drug-related, adjudicated causality: Possible B); and patient A2201E1-0526-00005 had lung adenocarcinoma (suspected to be study drug-related, adjudicated causality: Possible A).

The 2 patients who had basal cell carcinoma, [A2201E1-0051-00005] and [A2201E1-0053-00013], discontinued study drug due to these events which were reported as mild and not suspected to be related to study drug by the investigator; adjudicated causality for both cases was Possible B. These 2 cases were reported as non-serious AEs by and are recorded as non-serious in the clinical database, however they were upgraded to serious by Novartis DS&E.

The other 2 malignancy-related events were reported as worsening of thyroid nodules (patient A2201E1-0052-00001) and monoclonal gammopathy (patient A2201E1-0054-00017), mild to moderate in severity, not serious, not suspected to be study drug-related and not adjudicated.

Table 9-16 Malignant or unspecified tumors by onset period, SMQ (narrow search) and preferred term (all RA)

	ACZ885 Overall N=441 n (%)	ACZ885 0-24 wks N=441 n (%)	ACZ885 >24-48 wks N=357 n (%)	ACZ885 >48-72 wks N=276 n (%)	ACZ885 >72-96 wks N=173 n (%)	ACZ885 >96-144wks N=65 n (%)
Malignant or unspecified tumors (SMQ narrow)						
Total affected patients	8 (1.8)	2 (0.5)	4 (1.1)	2 (0.7)	0	0
Preferred terms:						
Basal cell carcinoma	2 (0.5)	0	2 (0.6)	0	0	0
Gammopathy	1 (0.2)	1 (0.2)	0	0	0	0
Neoplasm skin	1 (0.2)	1 (0.2)	0	0	0	0
Thyroid neoplasm	1 (0.2)	0	1 (0.3)	0	0	0
Lung adenocarcinoma	1 (0.2)	0	1 (0.3)	0	0	0
Lung adenocarcinoma metastatic	1 (0.2)	0	0	1 (0.4)	0	0
Non-Hodgkin's lymphoma †	1 (0.2)	0	0	1 (0.4)	0	0
Squamous cell carcinoma of skin †	1 (0.2)	0	0	1 (0.4)	0	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, † same patient, SMQ = Standardized MedDRA Query

The epidemiological analysis showed that the standardized morbidity rate (SMR), comparing the incidence rates of malignancy as monitored during the course of clinical trials to the morbidity experience of a general and RA population from the GPRD, did not suggest a signal for an increase in the incidence of malignancy in canakinumab-treated RA patients when compared to the RA population of the British General Practice Research Database (GPRD).

9.7 Immunogenicity

9.7.1 Gouty arthritis dataset

9.7.1.1 Anti-canakinumab antibodies

In all the blood samples tested for anti-canakinumab antibodies from patients in 5 gouty arthritis studies and 8 RA studies, with the analytical methods used, 8 of the patients treated with canakinumab (1 in core study H2251, 7 in extension study H2251E1) tested positive for anti-canakinumab antibodies at the end of the respective studies (Table 9-17).

Table 9-17 Anti-canakinumab antibodies by study

Indication Study number	Number of patients treated: canakinumab / comparator	Number of patients with treatment- related anti-canakinumab antibodies
Gouty arthritis		
H2255	143 / 57	0
H2356	113 / 115	0
H2357	112 / 114	0
H2251	323 / 108	1
H2251E1	100 / 0	7

The corresponding blood samples exhibited specific anti-canakinumab antibodies (inhibition signal >30% for a pre-determined positive/negative threshold of 30%), but titers were either below the limit of quantification (LoQ) or only slightly above the LoQ.

The patients showed no unexpected pharmacokinetics. None of the 8 patients had any evidence of immunogenicity-related AEs as determined from the search for events in the Immunology and allergy investigations HLG, as well as SMQ narrow searches for anaphylactic reaction, angioedema, and severe cutaneous adverse reactions and from the patient listings of all AEs.

9.7.1.2 Possible immunogenicity-related AEs

A thorough review of the clinical trial data for gouty arthritis to determine the presence of events reported that could be consistent with anaphylaxis resulted in finding of 4 patients, including 2 with reported elevated prostate specific antigen, not relevant for assessment of hypersensitivity. The remaining 2 potential events were identified by searching for Immunology and allergy investigations HLG, as well as using SMQ narrow searches for anaphylactic reaction, angioedema, and severe cutaneous adverse reactions. They both reported urticaria, one in the <=100 mg group and one in 150 mg group for gouty arthritis, 28 days and 84 days after drug administration, respectively. Both were mild, non-serious and not suspected to be related to study drug by the clinical investigator.

9.7.1.3 Local injection site reactions

Subcutaneous injections of canakinumab or placebo and intramuscular injections of triamcinolone acetonide or placebo were administered in the gouty arthritis studies H2255, H2356, H2357, H2356E1 and H2357E1, according to the study design. In gouty arthritis study

H2251, s.c. injections of canakinumab or placebo were administered and colchicine or placebo was taken orally.

Local tolerability of the s.c. and i.m. injections was evaluated by the investigator and reported on a specific CRF. Assessments were made in terms of signs/symptoms (pain, redness, induration, swelling, hemorrhage, itch, tenderness or other - unspecified) and the severity (none, mild, moderate, severe) of those signs/symptoms.

There were no severe injection site reactions. One patient (0.4%) in each of the canakinumab ≤ 100 mg and 150 mg groups reported a moderate s.c. injection site reaction. Mild s.c. injection site reactions occurred in 5.4% (15 patients), 3.8% (2 patients), 0.8% (2 patients) and 4.7% (5 patients) of patients in the canakinumab ≤ 100 mg, split 150 mg, 150 mg and ≥ 200 mg groups respectively, compared to 1.0% (3 patients) and 3.7% (4 patients) in the triamcinolone acetonide and colchicine (placebo) groups. The signs/symptoms at the s.c. injection site for the 3 affected patients in the canakinumab 150 mg group were swelling (0.8%, 2 patients), induration (0.4%, 1 patient) and other - unspecified (0.4%, 1 patient).

9.7.2 Placebo-controlled and All RA datasets

9.7.2.1 Possible immunogenicity-related AEs

Seven patients with 8 adverse events that could potentially signal immunological or allergic reactions were identified by using the above search strategy defined above in 9.7.1.2.

One patient in the >150 mg group experienced mild non-serious urticaria 13 days after receiving study drug, reported as not suspected to be related to study drug by the investigator. This patient subsequently developed a lip edema 9 days after receiving canakinumab and 4 hours after receiving methotrexate, reported as an SAE related to methotrexate. This event was adjudicated and considered probably related to methotrexate. All 6 additional cases were assessed as mild and non-serious: one patient with blepharodema 41 days after study drug administration, 1 with swollen upper lip 51 days after receiving study drug, 1 facial edema on the same day he received study drug, and concomitantly with a maxillae tooth inflammation, (which provides an alternative and more plausible explanation for the event), and 1 with edema of the eyelid 1 day after receiving study drug.

Two patients had AEs in the immunology and allergy investigations HLG: 1 with cold agglutinins (mild AE, suspected, causing study drug dosage adjustment/temporary interruption), and 1 with tumor marker increased (severe SAE, not suspected). For 6 of the 7 patients, these AEs started in the first 24 weeks of treatment. For the seventh patient [A2201E1-0062-00003], increased tumor marker occurred in the second 24 weeks of treatment.

9.8 AEs related to impaired renal function

9.8.1 Gouty arthritis dataset

Two patients (1.9%) in the canakinumab ≥ 200 mg group had renal failure, and 1 patient (0.4%) in the canakinumab 150 mg group had chronic renal failure.

Patient [H2356-0082-00011] (canakinumab 150 mg, 73 year old female) had worsening chronic renal failure reported as a severe SAE, not suspected to be related to study drug by the investigator. Her creatinine values were notably high at baseline (164, ULN 106 $\mu\text{mol/L}$) and increased to 202 $\mu\text{mol/L}$ on day 2, subsequently decreasing but remaining high until the last reported value of 145 $\mu\text{mol/L}$ on day 87. Blood urea nitrogen (BUN) values were also high at baseline (16.1, ULN 8.2 mmol/L) and throughout the study (15.4 mmol/L on day 87); estimated creatinine clearance (Cockcroft Gault) was 49 ml/min at baseline and 52 ml/min on day 87. The patient had multiple active medical conditions including coronary artery disease, coronary artery bypass, atrial fibrillation, hypertension, hypothyroidism, hypercholesterolemia, metabolic syndrome, obesity, back pain, insomnia and calcium deficiency, and was therefore receiving multiple co-medications. On day 46, she was hospitalized for gastritis (SAE), vomiting, worsening of chronic renal failure (SAE) and urinary tract infection. The events (gastritis, vomiting and renal failure) were considered resolved and she was discharged from the hospital on day 59. The patient's creatinine value on day 59 was reported to be 119 $\mu\text{mol/L}$.

Patient [H2251-0065-00003] (canakinumab ≥ 200 mg, 60 year old male) had renal insufficiency reported as moderate in severity, leading to discontinuation on day 92 and suspected to be related to study drug by the investigator. His creatinine value was high at screening on day -14 (156, ULN 115 $\mu\text{mol/L}$), remaining high during the study with a maximum value of 269 $\mu\text{mol/L}$ on day 84, subsequently decreasing to 182 $\mu\text{mol/L}$ on day 119, 118 $\mu\text{mol/L}$ on day 140 and 179 $\mu\text{mol/L}$ on day 169. High BUN and low estimated creatinine clearance (Cockcroft-Gault) values corresponded to the elevated creatinine levels with maximum BUN (28.6 mmol/L, ULN 8.6 mmol/L) and minimum creatinine clearance (41 ml/min) on day 84. The patient had active medical conditions of hypertension, hypercholesterolemia, angina pectoris and osteoarthritis.

Patient [H2251-0126-00001] (canakinumab ≥ 200 mg, 44 year old male) had worsening acute renal insufficiency reported as an SAE, moderate in severity, leading to discontinuation and not suspected to be related to study drug by the investigator. The patient had active nephrotic syndrome, acute renal failure and hematuria at study entry which worsened on day 17 leading to hospitalization and discontinuation from the study. His creatinine value was notably high at screening on day -7 at 178 $\mu\text{mol/L}$ (ULN 115 $\mu\text{mol/L}$) and 207 $\mu\text{mol/L}$ on day 85, no other values were reported. BUN was normal at screening (8.2, ULN 8.6 mmol/L) and high on day 85 (13.6 mmol/L). Estimated creatinine clearance (Cockcroft-Gault) was 65 ml/min at screening and 54 ml/min on day 85.

9.8.2 Placebo-controlled RA dataset

Two patients had renal insufficiency, 1 in each of the canakinumab >150 mg and placebo groups, and 1 placebo patient had oliguria. The 3 events were mild and not suspected to be related to study drug. For canakinumab-treated patient A2204-0505-05606 (63 years, female), who had a history of stress incontinence, the renal insufficiency AE started on day 189 of treatment and led to study drug dosage adjustment/temporary interruption. This patient's serum creatinine concentration was above the upper limit of normal throughout the study increasing from a baseline value of 97 $\mu\text{mol/L}$ to 129 $\mu\text{mol/L}$ (1.6 x ULN (80 $\mu\text{mol/L}$)) on day

155 and 174 $\mu\text{mol/L}$ (2.2 x ULN) on day 183, decreasing to 111 $\mu\text{mol/L}$ at the end of the study. Urea and uric acid values were also slightly high on days 155 and 183.

Three out of the 4 patients in the canakinumab >150 mg group had creatinine of ≥ 1.5 x ULN that were not reported as AEs. Patient A2201-0077-00003 (40 years, female) showed a creatinine of 389 $\mu\text{mol/L}$ (3.1 x ULN (124 $\mu\text{mol/L}$)) on day 10. Baseline (day 1) and subsequent (day 29) creatinine values were normal at 71 $\mu\text{mol/L}$. BUN and uric acid values were also high on day 10 (BUN 11.1 mmol/L, uric acid 369 $\mu\text{mol/L}$), but normal on day 1 (BUN 4.6 mmol/L, uric acid 232 $\mu\text{mol/L}$) and day 29 (BUN 3.9 mmol/L; uric acid 238 $\mu\text{mol/L}$).

Patient A2207-0002-05213 (52 years, female) with creatinine of 122 $\mu\text{mol/L}$ (1.5 x ULN (80 $\mu\text{mol/L}$)) at the end of study visit. Creatinine values were above the ULN at baseline (92 $\mu\text{mol/L}$) and throughout the study; urea was at the upper limit of normal and uric acid was raised at the same time as creatinine.

Patient A2207-0011-05251 (55 years, female) with creatinine of 127 $\mu\text{mol/L}$ (1.6 x ULN (80 $\mu\text{mol/L}$)) on day 43 and 126 $\mu\text{mol/L}$ (1.6 x ULN) at the end of study visit. Creatinine values were above the ULN at baseline (92 $\mu\text{mol/L}$) and throughout the study. Urea was at or slightly above the upper limit of normal (day 43: 8.9, end of study: 9.3, ULN 8.9 mmol/L) and uric acid was raised (day 43: 500, end of study: 480, ULN 450 $\mu\text{mol/L}$) at the same time as creatinine on day 43 and end of study.

9.8.3 All RA dataset

Three patients had AEs suggestive of renal impairment, the patient who is also in the placebo-controlled RA dataset (patient A2204-0505-05606 described above), and 2 other patients in the extension studies (patients A2201E1-0002-00018 and A2201E1-0077-00002). The events were reported as mild in severity and did not lead to discontinuation, one was suspected to be related to study drug (patient A2201E1-0002-00018).

The 5 patients with creatinine ≥ 1.5 x ULN in the All RA dataset (Table 3-12) includes the 4 previously described in the placebo-controlled RA dataset who had this abnormality firstly in the 0-24 week treatment period. Two of these patients also had a creatinine value ≥ 1.5 x ULN in the >24-48 week period. The fifth patient (A2201E1-0527-00004: 66 years, female) had creatinine of 186 $\mu\text{mol/L}$ (1.5 x ULN (124 $\mu\text{mol/L}$)) in the >48-72 week period only. This patient's creatinine values were above the ULN at baseline (150 $\mu\text{mol/L}$) and throughout the study, as were her BUN and uric acid values. No AEs associated with these laboratory abnormalities were reported.

9.9 Major Adverse Cardiac Events (MACE)

Potential extended MACE included the following:

- Cardiovascular (CV) Death (include presumed CV death)
- Myocardial infarction (MI)
- Hospitalization for unstable angina
- Stroke or Transient Ischemic Attack (TIA)

- Heart failure requiring hospitalization
- Coronary revascularization procedure: Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
- Peripheral revascularization procedure (vascular surgery or PCI)
- Stent thrombosis

The incidence of potential extended MACE was assessed by

1. Listing the patients and summarizing the rates across treatments in the 3 pooled datasets using relevant AEs to group affected patients in the above potential extended MACE
2. Submitting the cases of CCV events, which included some of the potential extended MACE in the gouty arthritis studies H2356 and H2357, to the CCV adjudication committee of independent medical experts who categorized the cases as follows:
 - Confirmed
 - No event (i.e. AE was not consistent with a CCV event)
 - Not enough information for adjudication

9.9.1 Gouty arthritis dataset

The incidence rates of MACE in the gouty arthritis dataset are summarized in Table 9-18.

Table 9-18 Potential extended MACE (gouty arthritis – safety set)

Potential extended MACE Preferred term	ACZ885 ≤100 mg N=278 n (%)	ACZ885 split 150 mg N=53 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	TA N=286 n (%)	colch N=108 n (%)
Total patients with any potential extended MACE	6 (2.2)	0	3 (1.2)	2 (1.9)	9 (3.1)	2 (1.9)
Potential extended MACE:						
CV Death	0	0	0	0	0	1 (0.9)
Myocardial infarction	0	0	0	0	0	1 (0.9)
Stroke or TIA	1 (0.4)	0	2 (0.8)	0	3 (1.0)	0
Carotid artery stenosis	1 (0.4)	0	0	0	0	0
Transient ischemic attack	0	0	1 (0.4)	0	0	0
Cerebrovascular accident	0	0	1 (0.4)	0	0	0
Hemorrhage intracranial	0	0	1 (0.4)	0	0	0
Cerebrovascular disorder	0	0	0	0	1 (0.3)	0
Vertebrobasilar insufficiency	0	0	0	0	1 (0.3)	0
Ischemic stroke	0	0	0	0	1 (0.3)	0
Myocardial infarction	5 (1.8)	0	1 (0.4)	2 (1.9)	6 (2.1)	2 (1.9)
Blood CPK increased	5 (1.8)	0	1 (0.4)	1 (0.9)	6 (2.1)	0
Acute myocardial infarction	0	0	0	1 (0.9)	0	0
Myocardial infarction	0	0	0	0	0	1 (0.9)
ECG ST segment elevation	0	0	0	0	0	1 (0.9)

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, MACE = major adverse cardiac event, CPK = creatine phosphokinase, CV= cardiovascular, TIA= transient ischemic attack, ECG=electrocardiogram

The incidence of potential extended MACE was low in all treatment groups. The 7 patients whose MACE(s) were reported as SAE(s) included 1 patient in each of the following treatment groups: canakinumab ≤100 mg (carotid artery stenosis), 150 mg (cerebrovascular accident and fatal intracranial hemorrhage), ≥200 mg (acute MI) and colchicine (MI and CV death), and 3 patients on triamcinolone acetonide (cerebrovascular disorder, vertebrobasilar insufficiency, ischemic stroke).

One patient in the canakinumab 150 mg group had a transient ischemic attack reported as non-serious and confirmed by the CCV adjudication committee.

All the potential extended MACE were not suspected to be related to study drug except for 2 patients with asymptomatic or mildly increased creatine phosphokinase (classified in “myocardial infarction”, Table 9-19), one in each of the canakinumab ≥200 mg and triamcinolone acetonide groups.

In the MedDRA search defining potential extended MACE described above, the AE preferred term “blood creatine phosphokinase increased” is classified as “myocardial infarction”. However, the cause of the increased total CPK (CKMB isoenzyme was not measured) may not necessarily have been MI. Medical review of the information available in the patient listings for the 13 patients with increased CPK reported as an AE (these cases were not adjudicated) revealed that 2 of the patients had a medical history of heart disease that could be related to the increased CPK (H2255-0111-00001 on canakinumab ≤100 mg, H2356-0024-00008 on triamcinolone acetonide), one patient (H2357-0591-00002 on triamcinolone acetonide) had evidence of a possible old MI on his baseline (day 1) ECG, and 2 patients (H2251-0111-00008 on canakinumab ≤100 mg, H2357-0032-00007 on triamcinolone acetonide) were taking rosuvastatin which could cause increased CPK (Table 9-19). None of these patients with CPK elevations showed any signs or symptoms of angina or myocardial ischemia.

Table 9-19 Cases of blood CPK increased (PT) coded to myocardial infarction by MedDRA search for potential extended MACE (gouty arthritis)

PID age/sex/race	Treatment	Reported increased CK AE (start day of CK AE)	Total CK value U/L (day) †	Statin Co-med Yes/No	Clin sig ECG Yes/No (day)	Relevant medical history
H2251-0033-00007 38/M/Other	≤100 mg ACZ885	elevated CPK (118), mild, NS	77 (-14) 91 (85) 1882 (114) 80 (134)	No	No	None
H2251-0111-00008 78/M/Asian	≤100 mg ACZ885	worsening of CPK value elevated (16), mild, NS	593 (-10) 1312 (16) 919 (29) high at all visits	Yes (rosuvastatin)	No	abnormal CPK, HT, spinal OA, cerebral thrombosis, metabolic syn.
H2255-0111-00001 41/M/Caucasian	≤100 mg ACZ885	High level CPK (57), mild, NS	211 (1) 218 (29) 469 (57)	No	Yes (1) (LVH)	HT, LVH, obesity
H2255-0128-00007 35/M/Caucasian	≤100 mg ACZ885	High blood level of CPK (29), mild, NS	318 (1) 272 (29) 272 (60)	No	No	hepatic steatosis, hyperglycemia

PID age/sex/race	Treatment	Reported increased CK AE (start day of CK AE)	Total CK value U/L (day) †	Statin Co-med Yes/No	Clin sig ECG Yes/No (day)	Relevant medical history
H2255-0529-00001 40/M/Caucasian	≤100 mg ACZ885	Elevated CPK (58), mod, NS	167 (1) 213 (29) 334 (58)	No	No	hyperglycemia, hyperlipidemia
H2357-0506-00006 48/M/Black	150 mg ACZ885	Elevated CPK (9), mild, NS	320 (1) 291 (9) 373 (85)	No	No	hepatitis C, elevated micro- albuminuria, amylase increased
H2251-0076-00006 49/M/Caucasian	≥200 mg ACZ885	Increasing CPK (15), asymptomatic, S	141 (-14) 366 (15) 907 (30) 106 (57)	No	No	dyslipidemia, HT, obesity
H2356-0024-00008 53/M/Caucasian	triam	Elevation of CPK (86), mod, NS	175 (1) 215 (57) 4105 (86)	No	No	CHF, CHD, dyslipidemia, obesity, HT
H2356E1-0140-00002 60/M/Caucasian	triam	Elevated CPK (141), mild, NS	72 (1) 69 (120) 1307 (141) 86 (165)	No	No	HT, anemia, obesity
H2357-0032-00007 60/M/Asian	triam	CPK elevation (85), mild, NS	268 (1) 252 (57) 572 (85)	Yes (rosuva statin)	No	HT, OA, hyperlipidemia,
H2357-0506-00007 57/M/Caucasian	triam	CPK increase (28), mild, S	63 (1) 327 (28) 37 (54)	No	No	elevated hsCRP & neutrophils
H2357-0540-00004 38/M/Caucasian	triam	elevated CPK (29), mild, NS	71 (1) 168 (8) 391 (29)	No	No	dyslipidemia, HT, obesity, back pain
H2357-0591-00002 56/M/Caucasian	triam	increased CPK (30), mild, NS	205 (1) 528 (30) 384 (32)	No	Yes (1) (?old MI)	HT, IDDM, obesity, heart valve incomp.

M = male, F = female, CPK = creatine phosphokinase, CK / CPK = creatine kinase / creatine phosphokinase, PT = preferred term, MACE = Major adverse cardiac event, NS = not suspected, S= suspected relationship to study medication (investigator's assessment), mod = moderate severity, M = male, F = female, HT = hypertension, LVH = left ventricular hypertrophy, CHF = congestive heart failure, CHD = coronary heart disease, IDDM = insulin dependent diabetes mellitus, hsCRP = high sensitivity C-reactive protein, OA=Osteoarthritis, MI=Myocardial Infarction, PID = patient identification, NA=Not Applicable, Clin sig ECG=clinically significant electrocardiogram result reported at a protocol-scheduled ECG visit, Co-med=concomitant medication, † CPK values are for total CPK, the isoenzyme CKMB were not measured

Two patients had MI reported as an SAE: [H2251-0080-00008] in the canakinumab ≥200 mg group, and [H2251-0508-00005] in the colchicine group who had a MI and died. One other patient on colchicine had asymptomatic ST elevation on ECG (classified as “myocardial infarction” by MedDRA search) for which no action was taken, according to the investigator’s report on the AE CRF.

9.9.2 Placebo-controlled RA dataset

None of the patients in the placebo-controlled RA dataset (including core studies A2101, A2201, A2204, A2207) reported an event in any of the potential extended MACE categories.

9.9.3 All RA dataset

The incidence rates of potential extended MACE in the all RA dataset are summarized in Table 9-20. For the 8 patients with a MACE, the event occurred during the extension studies and not during the core studies.

For 3 of the 6 patients with a potential extended MACE in the stroke or transient ischemic attack category, the event was reported as an SAE: [patient A2201E1-0002-00038] (transient ischemic attack on day 363), [patient A2201E1-0074-00008] (ischemic stroke on day 99), [patient A2211-0031-05205] (transient ischemic attack on day 266).

The 2 patients with potential extended MACE in the myocardial infarction category had moderate blood creatine phosphokinase increased in the one case, and asymptomatic electrocardiogram ST segment elevation in the other.

All of the potential extended MACE in the all RA dataset occurred during the extension studies and were not suspected to be related to study drug, according to the investigators. These events were not adjudicated by the CCV committee as the RA studies were completed before the committee was formed.

Table 9-20 Potential extended MACE by onset period (all RA)

Potential extended MACE Preferred term	ACZ885	ACZ885	ACZ885	ACZ885	ACZ885	ACZ885
	Overall N=441 n (%)	0-24 wks N=441 n (%)	>24-48 wks N=357 n (%)	>48-72 wks N=276 n (%)	>72-96 wks N=173 n (%)	>96- 144wks N=65 n (%)
Total patients with any potential extended MACE	8 (1.8)	1 (0.2)	2 (0.6)	3 (1.1)	2 (1.2)	0
Potential extended MACE:						
Stroke or TIA	6 (1.4)	1 (0.2)	2 (0.6)	2 (0.7)	1 (0.6)	0
Transient ischemic attack	3 (0.7)	0	1 (0.3)	1 (0.4)	1 (0.6)	0
Carotid artery stenosis	2 (0.5)	0	1 (0.3)	1 (0.4)	0	0
Ischemic stroke	0	1 (0.2)	0	0	0	0
Spinal hematoma	1 (0.2)	0	1 (0.3)	0	0	0
Myocardial infarction	2 (0.5)	0	0	1 (0.4)	1 (0.6)	0
Blood CPK increased	1 (0.2)	0	0	1 (0.4)	0	0
ECG ST segment elevation	1 (0.2)	0	0	0	1 (0.6)	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, MACE = major adverse cardiac event, CPK = creatine phosphokinase, CV= cardiovascular, TIA= transient ischemic attack, ECG=electrocardiogram

The epidemiological analysis showed that the Standardized Morbidity Rate (SMR), comparing the incidence rates of MACE, as monitored during the course of clinical trials, to the morbidity experience of a general and RA population from the General Practice Research Database (GPRD), did not suggest a signal for an increase in the incidence of MACE in canakinumab-treated RA patients when compared to the RA population of the GPRD.

9.10 Blood Pressure

9.10.1 Gouty arthritis dataset

Mean and median decreases in systolic blood pressure (SBP) were observed in the canakinumab 150 mg (mean/median: -2.8/-2.0 mmHg) and triamcinolone acetonide (mean/median: -2.9/-2.0 mmHg) groups, versus small mean and median increases in SBP in the colchicine group (mean/median: 3.2/2.0 mmHg). The other groups showed no relevant changes in SBP. There were no relevant changes from baseline to end of study in diastolic blood pressure (DBP) in any of the treatment groups.

Mean and median decreases in pulse were seen in the canakinumab 150 mg (mean/median: -2.7/-2.0 bpm) and triamcinolone acetonide (mean/median: -2.6/-2.0 bpm) groups. The other groups showed no relevant changes in pulse.

The frequencies of newly occurring, post-baseline, notable blood pressure and pulse abnormalities in the gouty arthritis dataset are shown in the Table 9-21.

Table 9-21 Vital sign abnormalities (gouty arthritis)

Parameter	ACZ885 ≤100 mg N=278 n (%)	ACZ885 split 150mg N=53 n (%)	ACZ885 150 mg N=253 n (%)	ACZ885 ≥200 mg N=107 n (%)	Triam N=286 n (%)	Colch N=108 n (%)
Sitting systolic BP						
Total	273	53	252	106	283	108
≥25% decrease from baseline	4 (1.5)	1 (1.9)	10 (4.0)	1 (0.9)	9 (3.2)	1 (0.9)
≥25% increase from baseline	10 (3.7)	1 (1.9)	19 (7.5)	4 (3.8)	14 (4.9)	11 (10.2)
≥140 mmHg	64 (23.4)	18 (34.0)	65 (25.8)	28 (26.4)	80 (28.3)	39 (36.1)
Sitting diastolic BP						
Total	273	53	252	106	283	108
≥25% decrease from baseline	18 (6.6)	2 (3.8)	19 (7.5)	5 (4.7)	15 (5.3)	3 (2.8)
≥25% increase from baseline	16 (5.9)	7 (13.2)	29 (11.5)	5 (4.7)	21 (7.4)	11 (10.2)
≥90 mmHg	54 (19.8)	14 (26.4)	76 (30.2)	34 (32.1)	75 (26.5)	38 (35.2)
Sitting Pulse						
Total	273	53	252	106	283	107
<50 bpm with ≥15% decrease from baseline	1 (0.4)	1 (1.9)	5 (2.0)	0	2 (0.7)	0
≥110 bpm with ≥15% increase from baseline	2 (0.7)	0	2 (0.8)	0	4 (1.4)	0

ACZ885 = canakinumab, TA = triamcinolone, colch. = colchicine, BP = blood pressure

Newly occurring, post-baseline SBP ≥140 mmHg and DBP ≥90 mmHg were common in all groups affecting about a quarter to a third of the patients in the canakinumab 150 mg and triamcinolone acetonide groups, and about a third of the patients on colchicine. The proportions of patients with increases in SBP or DBP of ≥25% from baseline were lower. Notable increases and decreases in pulse were infrequent in all treatment groups.

For patients with baseline co-morbidities, there were modest improvements with 150 mg canakinumab compared to triamcinolone acetonide in blood pressure (BP) in patients with hypertension, metabolic syndrome, and in those with chronic kidney disease.

9.10.2 Placebo-controlled RA dataset

Newly occurring, notable values for blood pressure (SBP \geq 140 mmHg, DBP \geq 90 mmHg) and changes (>25% increases and decreases from baseline) in blood pressure were seen in lower proportions of patients in the canakinumab 150mg group than in the canakinumab > 150mg and placebo groups

9.11 Lipid profile

9.11.1 Gouty arthritis dataset

The incidence of dyslipidemia AEs identified by SMQ narrow searches for “Dyslipidaemia” was highest in the canakinumab 150 mg group (7.9%, 20 patients) compared with the other treatment groups: canakinumab \leq 100 mg (2.2%, 6 patients), split 150 mg (3.8%, 2 patients), \geq 200 mg (3.7%, 4 patients), triamcinolone acetonide (2.1%, 6 patients) and colchicine (1.9%, 2 patients).

None of the events were reported as SAEs nor led to discontinuation of study drug. For 4 patients, 2 in the canakinumab 150 mg group (H2356-0070-00003 and H2357-0551-00002) and 2 on triamcinolone acetonide (H2356-0070-00004 and [H2357-0571-00004]), the events were severe but not suspected to be related to study drug, according to the investigators. Those patients with suspected study drug-related dyslipidemia events included 1 in the canakinumab \leq 100 mg group (hypertriglyceridemia), 1 in the split 150 mg group (hyperlipidemia), 3 in the 150 mg group (hypertriglyceridemia) and 1 in the \geq 200 mg group (blood triglycerides increased).

Table 9-22 presents summary statistics and changes from baseline to end of study in cholesterol and triglycerides in gouty arthritis by parameter, treatment, and time point. There were only minor mean and median changes from baseline to end of study in any treatment group.

Table 9-22 Changes in lipid profile at week 24 (gouty arthritis)

	Baseline	24 weeks	change from baseline
Cholesterol			
ACZ885 150 mg (N=253)	5.302 \pm 1.2551 mmol/L (205.03 \pm 45.535 mg/dL)	5.330 \pm 1.3067 mmol/L (206.11 \pm 52.862 mg/dL)	0.028 \pm 0.9638 mmol/L (1.08 \pm 37.27 mg/dL)
TA (N=286)	5.300 \pm 1.1555 mmol/L (206.11 \pm 44.683 mg/dL)	5.342 \pm 1.2248 mmol/L (206.58 \pm 47.36 mg/dL)	0.042 \pm 0.9494 mmol/L (1.624 \pm 36.71 mg/dL)
HDL Cholesterol			
ACZ885 150 mg (N=253)	1.167 \pm 0.3377 mmol/L (45.13 \pm 13.059 mg/dL)	1.200 \pm 0.3356 mmol/L (46.40 \pm 12.98 mg/dL)	0.033 \pm 0.2521 mmol/L (1.28 \pm 9.71 mg/dL)
TA (N=286)	1.169 \pm 0.4235 mmol/L (45.21 \pm 16.38 mg/dL)	1.270 \pm 0.4805 mmol/L (49.11 \pm 18.58 mg/dL)	0.101 \pm 0.2794 mmol/L (3.91 \pm 10.80 mg/dL)
Triglycerides			

	Baseline	24 weeks	change from baseline
ACZ885 150 mg (N=253)	2.516 ± 1.9699 mmol/L (222.84 ± 177.47 mg/dL)	2.899 ± 2.1585 mmol/L (256.76 ± 191.18 mg/dL)	0.382 ± 1.8671 mmol/L (33.83 ± 165.37 mg/dL)
TA (N=286)	2.515 ± 2.3732 mmol/L (222.75 ± 210.19 mg/dL)	2.481 ± 2.4399 mmol/L (219.74 ± 216.10 mg/dL)	-0.035 ± 0.2606 mmol/L (3.10 ± 23.55 mg/dL)

ACZ885 = canakinumab, TA = triamcinolone acetonide
1 mmol/L cholesterol = 38.67 mg/dL, 1 mmol triglycerides = 88.57 mg/dL

Summary statistics and change from baseline to end of study in cholesterol and triglycerides in patients with hypercholesterolemia at baseline are summarized in Table 9-23 by parameter, treatment, and time point. The mean and median changes from baseline to end of study indicated some improvement in both treatment groups in terms of increases in HDL cholesterol and a slight increase in triglycerides in the canakinumab group.

Table 9-23 Cholesterol and triglycerides in patients with hypercholesterolemia at baseline (gouty arthritis)

Parameter Treatment	Baseline (BL)		End of study (EOS)		Change from BL to EOS	
	n	Mean / Median	n †	Mean / Median	Mean (SD)	Median
HDL cholesterol (mmol/L)						
ACZ885 150 mg (N=55)	55	1.166 / 1.040	52	1.185 / 1.170	0.015 (0.2261)	0.025
Triamcinolone (N=64)	64	1.210 / 1.090	58	1.264 / 1.190	0.051 (0.2697)	0.030
Total cholesterol (mmol/L)						
ACZ885 150 mg (N=55)	55	5.672 / 5.980	55	5.416 / 5.180	-0.256 (1.0697)	-0.280
Triamcinolone (N=64)	64	5.832 / 5.750	64	5.645 / 5.425	-0.187 (1.2555)	-0.220
Triglycerides (mmol/L)						
ACZ885 150 mg (N=55)	55	2.985 / 2.340	55	3.146 / 2.540	0.161 (1.5885)	0.020
Triamcinolone (N=64)	64	2.692 / 1.990	64	2.510 / 1.840	-0.183 (1.4976)	-0.235

ACZ885 = canakinumab, TA = triamcinolone acetonide, HDL = high density lipoprotein
1 mmol/L cholesterol = 38.67 mg/dL, 1 mmol triglycerides = 88.57 mg/dL

† n at EOS includes only patients with a value at both baseline and end of study.

9.11.2 Placebo-controlled RA dataset

Five canakinumab patients (1 of the 12 patients in the <150 mg group, 4 (1.5%) in the >150 mg group) and 2 (1.7%) placebo patients had dyslipidemia AEs. None of these events was reported as severe nor as an SAE, and none led to discontinuation of study drug. The 2 instances of mild hypercholesterolemia in a single patient (A2207-0002-05207) in the canakinumab >150 mg group were suspected to be related to study drug.

9.11.3 All RA dataset

Overall, 15 patients (3.4%) in the All RA dataset had an AE in the dyslipidemia SMQ (narrow) search including preferred terms of either blood cholesterol increased (2 patients, 0.5%), hypercholesterolemia (8 patients, 1.8%), hyperlipidemia (4 patients, 0.9%), or hypertriglyceridemia (1 patient, 0.2%). The incidence of dyslipidemia was slightly higher in the first 24 weeks of treatment (1.8%, 8 patients), compared to 0.8% (3 patients) in the >24-48 week period, 0.7% (2 patients) in the >48-72 week period, and 1.2% (2 patients) in the >72-96 week period.

None of the dyslipidemia AEs were reported as serious nor led to discontinuation of study drug. For 2 patients, the dyslipidemia AEs were suspected to be related to study drug by the investigator, patient A2207-0002-05207 (as mentioned above in the placebo-controlled RA dataset) and patient A2211-0514-05167.

9.12 Uric acid levels

9.12.1 Gouty arthritis dataset

Patients treated with canakinumab had a transient increase in uric acid levels from baseline. This effect is best studied in patients treated with a single dose of canakinumab. After a single dose, uric acid increased modestly and rapidly, by approximately 10 $\mu\text{mol/L}$ (<0.2 mg/dL) within a week, from baseline values of approximately 470 $\mu\text{mol/L}$ (7.9 mg/dL). Uric acid returned to baseline after 56 to 84 days (Table 9-24).

Table 9-24 Changes in urate levels at Weeks 12 and 24 (pivotal gout trials)

	Baseline Mean \pm SD	Change at week 12 Mean \pm SD	Change at week 24 Mean \pm SD
Overall population			
ACZ885 150mg (N=253)	485 \pm 122 $\mu\text{mol/L}$ (8.1 \pm 2.0 mg/dL)	+42 \pm 123 $\mu\text{mol/L}$ (0.7 \pm 2.1 mg/dL)	+32 \pm 119 $\mu\text{mol/L}$ (0.5 \pm 2.0 mg/dL)
TA (N=286)	488 \pm 122 $\mu\text{mol/L}$ (8.2 \pm 2.0 mg/dL)	+ 7 \pm 110 $\mu\text{mol/L}$ (0.1 \pm 1.8 mg/dL)	9 \pm 105 $\mu\text{mol/L}$ (0.2 \pm 1.8 mg/dL)
Patients on UALT			
ACZ885 150mg (N=136)	455 \pm 137 $\mu\text{mol/L}$ (7.6 \pm 2.3 mg/dL)	+55 \pm 156 $\mu\text{mol/L}$ (0.9 \pm 2.6 mg/dL)	+17 \pm 133 $\mu\text{mol/L}$ (0.3 \pm 2.2 mg/dL)
TA (N=126)	446 \pm 119 $\mu\text{mol/L}$ (7.5 \pm 2.0 mg/dL)	+ 6 \pm 10 $\mu\text{mol/L}$ (0.1 \pm 1.8 mg/dL)	+4 \pm 115 $\mu\text{mol/L}$ (0.1 \pm 1.9 mg/dL)
Patients not on UALT			
ACZ885 150mg (N=89)	511 \pm 113 $\mu\text{mol/L}$ (8.6 \pm 1.9 mg/dL)	+ 27 \pm 113 $\mu\text{mol/L}$ (0.4 \pm 1.9 mg/dL)	+29 \pm 107 $\mu\text{mol/L}$ (0.5 \pm 1.8 mg/dL)
TA (N=103)	538 \pm 108 $\mu\text{mol/L}$ (9.0 \pm 1.8 mg/dL)	-12 \pm 117 $\mu\text{mol/L}$ (-0.2 \pm 2.0 mg/dL)	-4 \pm 96 $\mu\text{mol/L}$ (-0.1 \pm 1.6 mg/dL)

ACZ 885 = canakinumab, TA = triamcinolone acetonide, SD = standard deviation, UALT = urate lowering therapy
1mg/dL urate equals 59.48 $\mu\text{mol/L}$

In patients not on UALT an increase of approximately 30 $\mu\text{mol/L}$ (0.5 mg/dL) from a baseline value of approximately 510 $\mu\text{mol/L}$ (8.6 mg/dL) was observed at week 12. In patients on UALT, whose baseline was approximately 455 $\mu\text{mol/L}$ (7.6 mg/dL), uric acid levels did increase of approximately 55 $\mu\text{mol/L}$ (0.9 mg/dL) at week 12.

Patients treated with single dose triamcinolone acetonide did not show any increase in uric acid levels throughout the course of the study.

Accordingly, in those patients who switched from triamcinolone acetonide to canakinumab in extension 2 an increase in uric acid levels was also observed after treatment for a new flare with canakinumab, compared to the baseline flare. This increase trends towards baseline at 84 days post-switch to canakinumab flares.

Similarly, there was an increase of uric acid in patients with multiple canakinumab treatments. The increase of uric acid was rapid (7 days after baseline treatment), achieved the maximum effect at approximately 57 days (approximately 60 $\mu\text{mol/L}$, 1.0 mg/dL) and decreased over time.

There was no cumulative effect, since the increase observed during the baseline flare was comparable to the effect observed during the subsequent flares.

Although canakinumab patients re-treated with canakinumab tended to have higher uric acid levels than those that were not re-treated, there was no clear association between the number of re-doses and increasing uric acid levels, though the number of re-treatments (particularly >1 re-dose) in each group was small.

Overall, there was a modest increase of uric acid following treatment with canakinumab that returned to baseline over time.

9.12.2 Placebo-controlled RA dataset

An increase in uric acid level was not observed in rheumatoid arthritis patients.

9.13 Vertigo

9.13.1 Gouty arthritis dataset

The frequency of patients with either vertigo or dizziness AEs was similar in the canakinumab ≤ 100 mg (1.8%, 5 patients), split 150 mg (1.9%, 1 patient) and 150 mg (2.4%, 6 patients) groups and slightly higher in the canakinumab ≥ 200 mg (3.7%, 4 patients) group versus 0.7% (2 patients) for triamcinolone acetonide and 0% for colchicine.

Vertigo AEs were experienced by only 2 (0.7%) patients in the ≤ 100 mg group, 1 (0.9%) patient in the ≥ 200 mg group and 1 (0.3%) patient on triamcinolone acetonide versus none in the other treatment groups.

Five patients had dizziness AEs that were suspected by the investigators to be related to study drug, 1 in the canakinumab ≤ 100 mg group, 2 in the 150 mg group, 1 in the ≥ 200 mg group, and 1 in the triamcinolone acetonide group.

None of the vertigo or dizziness AEs were reported as severe or serious, or led to discontinuation of study drug.

9.13.2 Placebo-controlled RA dataset

The frequency of patients with either vertigo or dizziness AEs was highest in the placebo group (10.7%, 13 patients) compared to 2.9% (2 patients) for canakinumab 150 mg and 7.2% (19 patients) for canakinumab >150 mg, and 1 of the 12 patients in the canakinumab <150 mg group had dizziness. Dizziness was more frequent than vertigo in the placebo group (8.3% vs. 2.5%, 10 vs. 3 patients), whereas the frequencies of dizziness and vertigo were similar in the canakinumab 150 mg (1.4%, 1 patient each) and >150 mg (4.2%, 11 patients and 3.0%, 8 patients, respectively) groups.

None of the vertigo or dizziness AEs were reported as severe or serious. One patient in the canakinumab >150 mg group [A2204-0501-05629] discontinued study drug due to dizziness after suffering 3 episodes between days 1 and 21, each lasting for 2-3 days.

One patient (1.4%) in the canakinumab 150 mg group, 14 patients (5.3%) in the >150 mg group and 2 placebo patients (1.7%) had dizziness or vertigo AEs that were suspected to be related to study drug by the investigators.

9.13.3 All RA dataset

Overall, 30 patients (6.8%) treated with canakinumab in the all RA dataset experienced either dizziness or vertigo with similar frequencies, 3.2% (14 patients) with dizziness and 3.6% (16 patients) with vertigo, mostly in the first 24 weeks of treatment (dizziness: 3.2%, vertigo 2.9%). In subsequent periods of >24-48 weeks and >48-72 weeks of treatment, frequencies of patients with these AEs were low (0 - 0.7%, 0 - 2 patients).

None of the vertigo or dizziness AEs were reported as severe or serious, and, as described above in the placebo-controlled RA dataset, only patient [A2204-0501-05629] discontinued study drug due to dizziness on day 21.

For 18 of the patients with these AEs, 9 (2.0%) for dizziness and 9 (2.0%) for vertigo, the event was suspected to be related to study drug by the investigators.

9.14 Postmarketing Experience in CAPS

The third 6 monthly Periodic Safety Update Report (PSUR) was finalized in February 2011 to provide a cumulative experience with canakinumab after first registration for CAPS in 2009. Ilaris® is indicated for the treatment of Cryopyrin-Associated Periodic Syndrome (CAPS), in adults and children aged 4 years and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS) /Familial Cold Urticaria (FCU),
- Muckle-Wells Syndrome (MWS).

In the European Union and in other countries canakinumab is also approved for

- Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).

At the cut-off date of the most recent PSUR 03, 31-Dec-2010, the product was approved in 45 countries.

During the overall 18.5 month period since first launch, there were no marketing authorization withdrawals, revocations or suspensions, failures to obtain a marketing authorization renewal, restrictions on distribution, clinical trial suspensions, dosage modifications, changes to target population or indications or formulation changes made for safety reasons.

The cumulative post-marketing exposure in CAPS since the first launch of the product is estimated to be 314 patient-treatment years. This estimate is calculated based on worldwide sales volume in mg of active substance sold and the recommended dose of Ilaris® for CAPS i.e. 150 mg for patients with body weight >40 kg, and 2 mg/kg for patients with body weight ≥15 kg and ≤40 kg every eight weeks as a single dose via s.c. injection.

Presentation of individual case histories

An overview of the total numbers of adverse reaction reports received between 17-Jun-2009 and 31-Dec-2010 is given in Table 9-25. Detailed presentations of the individual case safety reports and cumulative analyses are provided in the respective PSURs.

Table 9-25 Adverse reactions per PSUR

PSUR	Serious spontaneous reports				Serious solicited reports				Non-serious spontaneous reports				Total
	Unlisted		Listed		Unlisted		Listed		Unlisted		Listed		
	HCP	Non-HCP	HC P	Non-HCP	H CP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	
01	0	0	0	0	3	0	0	0	4	0	3	0	10
02	19	0	5	0	18	0	38	0	22	1	8	9	120
03	26	0	6	0	76	0	67	0	14	0	10	0	199
Total	45	0	11	0	97	0	105	0	40	1	21	9	329

PSUR = Periodic Safety Update Report, HCP = Health Care Provider

Identified and potential safety findings

Each 6 monthly safety update provides a detailed analysis of identified and potential safety findings. This especially concerns the following topics:

- **Infections:** The PSUR 03 includes detailed analyses of identified and potential safety findings for canakinumab based on its mode of action and information from the drug class as well as experienced gained with CAPS. Infections are considered as an identified finding and are a well known class effect. Opportunistic or unusual infections are viewed as a potential risks. IL-1 is a pro-inflammatory cytokine secreted by macrophages and dendritic cells. It enhances the immune response (activation and proliferation of T and B cells upon antigen stimulation) and, the inflammatory process. Inhibiting IL-1 could therefore have an effect on the immune response against bacteria and other infectious agents (Juffermans et al 2000). There is no evidence from postmarketing data that canakinumab treatment is linked to opportunistic infections. The label for CAPS provides detailed information and guidance concerning infections and the need for tuberculosis testing.
- **Neutropenia** has been reported with other anti-IL1 therapies. Patients that are immunosuppressed or have low baseline neutrophil levels could potentially be at higher risk for developing infections. The cumulative review showed that the majority of events were confounded by underlying conditions or comorbidities. The label for CAPS provides detailed information and guidance concerning neutropenia.
- **Immunogenicity and allergenicity** may be caused by injecting proteins including canakinumab. The cumulative review did not identify any report of antibodies against canakinumab or any signs of hypersensitivity. No case has been identified for whom loss of efficacy may have been caused by an antibody development.

- Lymphoid hyperplasia in spleen size in male marmosets was observed in pre-clinical trials. The postmarketing experience did not show any reports suggestive for lymphoid organ toxicity.
- The biological activity of any anti-cytokine therapeutics may theoretically be linked to autoimmunity reactions. The postmarketing experience is not indicative of an increased risk for the development of autoimmune reactions.
- Injection site reactions are a known tolerability issue in association with other biologics use. The postmarketing experience confirmed the findings from clinical trials that injection site reactions were mild in nature and resolved quickly. This information is also included in the label for CAPS.
- Malignancies: Immunomodulation through blockade of inflammatory cytokines is implicated to potentially lead to an increase in the risk for tumors. Based on the biological activity of IL-1, no increased risk for malignancies linked to canakinumab administration can be anticipated; the effect of potential immunosuppression due to IL-1 β suppression on tumor development has not yet been established. The postmarketing experience did not support a causal relationship of malignancy and canakinumab administration. All received cases of malignancy were confounded e.g. the underlying conditions, comorbidities and concomitant medications.
- In humans and primates, several cytokines are known to reduce both HDL cholesterol and LDL-cholesterol levels; activation of the reticuloendothelial system is likely associated with such changes, but other mechanisms may be involved (Choy 2009). Consequently, treatment of RA and dampening of inflammation, may be expected to increase lipid levels; this not only occurs in HDL cholesterol, but also other lipid moieties, including total and LDL-cholesterol and, perhaps, triglyceride levels. This has been observed with a range of biologic and non-biologic disease-modifying antirheumatic drugs. The postmarketing experience does not point to any clinically relevant findings.
- DILI is defined as hepatic transaminases increase and bilirubin elevations for canakinumab. Underlying conditions and concomitant diseases provided a plausible explanation for the majority of postmarketing cases.
- Vertigo is known to occur in CAPS patients and may be associated with disease-related CNS inflammation (including cochlear inflammation). The underlying pathophysiology of vertigo remains to be determined. As CAPS often leads to aseptic meningitis, sensorineural deafness, and a variety of other CNS symptoms, it is possible that there is a drug-disease interaction. The reported events related to vertigo have generally been mild and transient. The label includes accurate information on vertigo.
- Concomitant use of canakinumab and immunosuppressant agents: The combination of canakinumab and methotrexate does not appear to result in incremental toxicity as does concomitant steroid administration.
- The frequency and outcome of reported Macrophage activation syndrome (MAS) cases in Systemic Juvenile Idiopathic Arthritis (SJIA) patients is consistent with the expected presentation in the studied population. MAS is an acquired form of secondary

haemophagocytic lymphohistiocytosis (HLH) and observed exclusively in the context of rheumatic diseases.

The postmarketing experience for 18.5 months covered by three safety update report confirms that canakinumab is well tolerated and safe, with a favorable benefit-risk profile when it is used correctly in the CAPS indication. The presently valid label correctly reflects the current safety knowledge.

10 Overall safety conclusions

The AEs and affected SOC with 150 mg canakinumab in patients with gouty arthritis were more frequent than with triamcinolone acetonide and occurred at rates similar to those observed with colchicine. This finding was mainly due to the higher incidence of infections reported for canakinumab. In comparison to RA trials, AEs and affected SOC with 150 mg canakinumab were less. Rates of deaths, SAEs or discontinuations were low. Compared to the experience gained in CAPS no new relevant safety finding has been identified.

Rates of deaths, SAEs or discontinuations were low and there were no new relevant safety findings.

AEs of infections and infestations were higher than the controls for 150 mg canakinumab, as expected and mostly resolved with standard therapy. A limited number of infections were serious but none were opportunistic. Immunogenicity, potential hypersensitivity AEs, and injection site reactions were absent or scarce.

Overall, the imbalance in total AEs between canakinumab and triamcinolone acetonide in gouty arthritis is attenuated because:

- AEs were mostly mild and uncomplicated (not severe, serious or causing discontinuation)
- AE rates did not rise, but fell with repeated doses and increasing duration of exposure
- AE imbalances mostly reflected known drug class effects (infections, low blood counts)
- AE imbalances were not seen in all gout studies, nor in RA, which also show high levels of comorbidities in this population of mainly female but older patients
- the new ADRs identified for gouty arthritis (beyond the already known drug class effects), consisted of AEs of lesser clinical concern (e.g. back pain, fatigue/asthenia).
- The postmarketing experience for 18.5 months in CAPS confirms that canakinumab is well tolerated and safe, with a favorable benefit-risk profile. The presently valid label correctly reflects the current safety knowledge.

Hematology changes, mainly of low white blood cell and platelet counts, already known for canakinumab and other IL-1 blockers, were mostly asymptomatic with the 150 mg dose. Low white cell counts of CTC grade ≤ 2 were not associated with infections, and low platelet counts did not lead to bleeding, or reach levels of increased bleeding risk ($<50 \times 10^9/L$).

Patients with common co-morbidities of hypertension, hyperlipidemia, metabolic syndrome, renal insufficiency or high cardiovascular risk, did not show signs that canakinumab worsened

their existing conditions, even after prolonged use, and there were trends for some improvements in BP and lipid parameters during canakinumab treatment.

A small, self limiting rise in urate levels after canakinumab and a smaller rise after triamcinolone acetonide, are not felt to be direct drug effects, but the effect of treatment on inflammation, as urate levels during flares are known to fall parallel with the fall in inflammatory markers, and such rises were absent during prophylactic use without flares.

Long-term data on regular dosing in RA patients at exposures many times higher than expected for the treatment of flares in gouty arthritis showed no long-term safety concerns. Data from gouty arthritis patients re-treated for new flares did not show any increases in clinically relevant events or in AEs attributable to the re-treatment.

11 Benefit / risk analysis and conclusions

11.1 Efficacy benefits

11.1.1 Summary of efficacy benefits

As a targeted therapy against IL-1 β , canakinumab directly neutralizes one of the key inflammatory pathways involved in the pathogenesis of gouty arthritis. Canakinumab at 150 mg s.c., administered upon an acute flare or attack, showed clinically relevant efficacy benefits in the treatment of gouty arthritis, in both the 12 week and 24 week periods.

Canakinumab was significantly better than triamcinolone acetonide at treating the signs and symptoms of the baseline flare, producing greater and faster pain relief, improving the physician's assessments of global response, tenderness, swelling and erythema, inflammatory markers and in reducing the use of corticosteroid rescue medication, as seen in Table 11-1.

Table 11-1 Summary of efficacy in treating the baseline flare

	Study H2356		Study H2357		pooled data	
	ACZ885	TA	ACZ885	TA	ACZ885	TA
Early pain relief (6, 12 and 24 hours)						
VAS pain change at 6 hrs (mm)	-16.1	-13.1	-16.6	-13.8	-16.3	-13.4
VAS pain change at 12 hrs (mm)	-23.4	-17.5	-23.9	-22.1	-23.6	-19.8
VAS pain change at 24 hrs (mm)	-33.3	-23.2	-36.1	-29.0	-34.7	-26.1
Later pain relief (72 hours and 7 days)						
VAS pain at 72 hrs (mm)	28	40	22	32	25	36
mean difference (p value) vs. triam.	-11.4 (p=0.0005)		-9.8 (p=0.0018)		-10.7 (p=0.0001)	
≥50% reduced VAS pain at 72 hrs (%)	64	47	79	62	72	54
≥75% reduced VAS pain at 7 days (%)	69	50	76	68	73	59
≤10 mm VAS pain within 7days (%)	60	45	65	55	n.d.	n.d
patient global resp. of excell./good at 7 days (%)	65	52	81	69	73.	61
Physician's assessments (72 hours)						
global response of good/very good (%)	65	46	86	62	75	53
any tenderness (%)	66	74	52	70	60	72
any swelling (%)	62	70	52	64	57	67
any erythema (%)	21	35	25	33	23	34
Corticosteroid use						
prednisone/prednisolone usage (%)	10	27	13	20	11	24
prednisolone/prednisone use (first flare) (mg)	7	24	9	19	8	22

ACZ885 = canakinumab, TA = triamcinolone acetonide, VAS = visual analogue scale for pain
n.d. = not determined

Canakinumab also reduced the frequency of subsequent attacks, as shown by reducing the probability of a new flare, increasing the number of patients free of new attacks and reducing the average number of attacks per patient, as seen in Table 11-2. The median time to a new attack is approximately 4.4 months (131 days) with triamcinolone acetonide and the median time for canakinumab is >6 months based on core and extension 1 data (Table 4-20).

Table 11-2 Summary of efficacy in reducing the frequency of new flares

	Study H2356		Study H2357		pooled data	
	ACZ885	TA	ACZ885	TA	ACZ885	TA
within 12 weeks						
new flare probability (12 wks) (%)	19	36	14	38	16	38
<i>hazard ratio (95% CI) vs. triam.</i>	<i>0.45 (p=0.0014)</i>		<i>0.32 (p=0.0001)</i>		<i>0.38 (p=0.0001)</i>	
absence of new flares (%)	81	65	87	63	84	64
mean no. of flares per patient	0.21	0.53	0.17	0.49	0.19	0.51
within 24 weeks						
new flare probability (24 wks) (%)	35	57	29	54	32	56
<i>hazard ratio (95% CI) vs. triam.</i>	<i>0.48 (p=0.0003)</i>		<i>0.40 (p<0.0001)</i>		<i>0.44 (p<0.0001)</i>	
absence of new flares (%)	68	49	75	54	72	51
mean no. of flares per patient	0.40	0.87	0.35	0.80	0.37	0.83

ACZ885 = canakinumab, TA = triamcinolone acetonide

11.1.2 Overall efficacy benefit

The treatment benefits with canakinumab relating to efficacy come from both an acute benefit by treating the signs and symptoms of the flare, from the longer term benefit of the reduced frequency of new flares and also from the high predictability of the response to re-treatment.

The percentages of patient showing each type of benefit are shown in Table 11-3, which categorizes the presence or absence of a new attack and a strong or weak ($\geq 50\%$ or $< 50\%$) reduction in VAS pain as criteria for major benefit. Over 80% of patients receiving canakinumab had a major benefit (strong pain reduction and no repeat attacks), or strong benefit (strong pain reduction with the first and subsequent attack). These high rates of major and strong benefit at 12 weeks (84%) and 24 weeks (82%), were much greater than with the triamcinolone active comparator (66% at 12 weeks and 64% at 24 weeks, data not shown).

Table 11-3 Evaluation of integrated efficacy benefits (12 and 24 weeks)

	12 weeks ACZ885 N = 225; % (n)	24 weeks ACZ885 N = 225; % (n)
Patients with major benefit (dual benefit) <i>strong pain relief, no new flare</i>	77% (174)	65% (147)
Patients with strong benefit (repeated pain benefit) <i>strong pain relief for baseline flare & new flare</i>	6% (14)	17% (38)
% of patients with a Major or Strong Benefit	84% (188)	82% (185)
Patients with uncertain benefits (weak/varying benefit) <i>weak pain relief, no new flare</i>	5% (11)	5% (11)
<i>inconsistent pain relief for baseline & new flare</i>	3% (7)	4% (10)
<i>new flare within 2 weeks / no re-treatment</i>	2% (4)	2% (4)

	12 weeks ACZ885 N = 225; % (n)	24 weeks ACZ885 N = 225; % (n)
Patients with major benefit (dual benefit)		
Patients with no benefit <i>weak pain relief for baseline flare & new flare</i>	4% (10)	4% (10)

patients without baseline values are not counted (12 on triamcinolone acetonide and 2 on ACZ)
strong pain relief = $\geq 50\%$ reduction in pain by 72 hours
ACZ885 = canakinumab, TA = triamcinolone acetonide

11.1.2.1 Implications of no benefit (lack of efficacy)

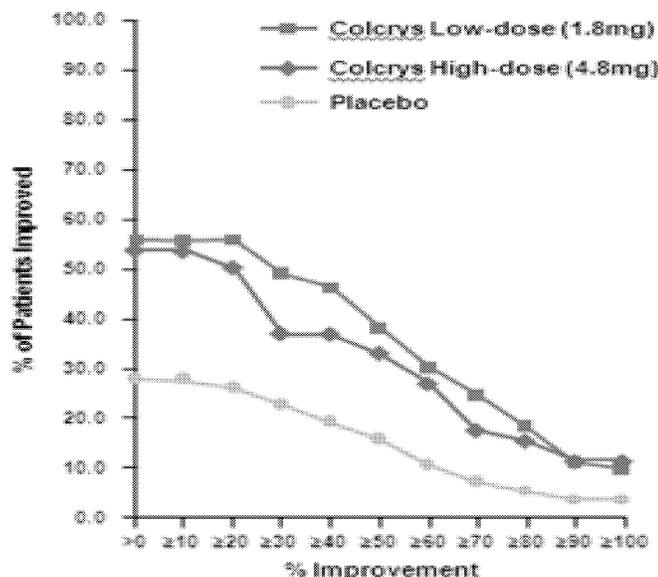
For some patients, a less than optimal clinical response may still represent a benefit compared to their prior condition. However, in others, it may indicate that their arthritis had an alternative pathology, not primarily mediated by IL-1 β , such as can occur when gouty arthritis is exacerbated by other factors (e.g. trauma, infection). Patients with no benefit (4%) were evident in the first 12 weeks, suggesting that in these few patients who received no initial and no later benefit, other pathologies, which are not IL-1 β driven, may explain their condition. Thus, for the few patients without strong pain relief for their initial flare, re-treatment for a new attack is not recommended.

11.1.2.2 Efficacy benefits relative to published trials

Clinical trial data with NSAIDs (more often studied in gouty arthritis) and corticosteroids (only studied in a few small trials), is very limited (often no placebo control, various efficacy criteria, unverified active controls, inadequate randomization or blinding). Thus, there is little data with which to assess the degree and speed of pain relief with canakinumab compared to other agents.

Recent data used to register colchicine in the US (Colcrys[®] PI), allow an indirect comparison with canakinumab by using the same efficacy variable (response to treatment defined as $\geq 50\%$ pain reduction in 24 hours without use of rescue medication). The colchicine data are shown in Figure 11-1. At 24 hours approximately 55% of patients with colchicine and almost 30% of patients with placebo have responded to treatment according to the definition provided.

Figure 11-1 Response rates to various levels of pain relief at 24 hours in published trials with colchicine



Published data with Colcrys (redrawn from Colcrys[®] PI).

Data from the pivotal canakinumab studies compare favorably with these data: a higher number of patients (approx 55% in H2356 and 70% in H2357) have pain relief without use of rescue medication at the same timepoint.

In gouty arthritis, there have been no controlled studies on reducing the frequency of new attacks, other than when initiating urate-lowering therapy. There are also few studies of efficacy in initial and subsequent new flares, where a first treatment is followed by subsequent re-treatment, and where efficacy and safety have been followed over a longer period.

Thus, one major benefit of the presented clinical development program with canakinumab in patients with severe, therapy-resistant acute gouty arthritis is that it provides the first extensive, longer-term, controlled data on reducing flare frequency and delaying flares compared to a fixed corticosteroid regimen, and thus supplies a solid foundation for evidence-based treatment decisions.

11.2 Risk Assessment

11.2.1 Important safety concerns

As with all biologics the potential exists for the development of antibodies to the biologic and injection site reactions. In the canakinumab clinical development program, immunogenicity was assessed to determine the potential to develop anti-canakinumab antibodies. Based on data to date, canakinumab demonstrates low immunogenicity and few injection site reactions. (Table 11-4). Some IL-1 blockers used off-label in individual cases of therapy-resistant gouty

arthritis or in clinical trials, have much greater immunogenicity and higher rates of injection site reaction, as seen in Table 11-4.

Table 11-4 Injection site reactions and immunogenicity of canakinumab, rilonacept and anakinra treatment

	Canakinumab		rilonacept		anakinra
	gouty arthritis	CAPS	gouty arthritis	CAPS	RA
Injection site reactions	1.2%*	9%	14%	48%	71%
Antibody development	<5%**	0	3/10	35%	49%

CAPS – cryopyrin-associated periodic syndrome, RA = rheumatoid arthritis

* for 150 mg canakinumab, ** positive anti-canakinumab antibody in 8 of 691 canakinumab-treated patients

Data from: Ilaris® (canakinumab) US Prescribing Information, Arcalyst® (rilonacept) US Prescribing Information, Kineret® (anakinra) US Prescribing Information, Terkeltaub et al 2010 (injection site reaction), Terkeltaub et al, 2009

11.3 Safety risks

No new safety risks were identified in the gouty arthritis program beyond those identified for the CAPS indication. The identified risks linked to the use of canakinumab relate primarily to infections. Important potential risks based on canakinumab being a monoclonal antibody and the potent anti-inflammatory mechanism of action and molecular properties are outlined in the safety section. These include, but are not limited to, opportunistic infections, neutropenia, and increased risk of malignancy, immunogenicity / allergenicity and injection site reactions.

The overall safety experience includes over 2,500 patients from the use of canakinumab in CAPS, RA, gout and clinical trials in other indications. Thus, the overall safety is examined across a variety of patient populations, doses, durations and routes of administration.

In the pivotal gouty arthritis trials (core and extension 1), there was a higher rate of AEs with canakinumab (62.8 and 69.6 %) compared with TA (48.7 and 57.0 %), driven primarily by an imbalance in infections (22.1 and 18.8% with canakinumab and 15.7 and 8.8% with triamcinolone acetonide, respectively). This imbalance is consistent with increased risk of infections previously identified in the approved CAPS indication. Although most infections were mild or moderate upper respiratory infections, there were 4 SAEs of infections in the phase 3 pivotal gouty arthritis studies (1.6%) that required hospitalization (2 abscesses, pneumonia and gastroenteritis). An imbalance in the incidence of infections was not seen at the 150 mg dose in RA. No infections in any patient in the entire safety database were identified as opportunistic. An increased risk of infections, including serious infections, is included as a Warning in the currently approved label for CAPS.

There was also a higher incidence of SAEs reported for patients on canakinumab than on triamcinolone acetonide in each of the pivotal gouty arthritis studies. In general, these SAEs were single occurrences and were not suspected by the investigator to be related to study drug.

Mild hematologic effects with decreases in white blood cells, neutrophils and platelets associated with canakinumab were also observed. All resolved without intervention and there were no events of bleeding associated with the transient thrombocytopenia. There was one

patient treated with canakinumab who had a serious infection (jaw abscess) and, in addition, had a low isolated neutrophil count, highlighting the need for the labeling on infections.

There were no new safety signals and no negative impacts on hepatic, renal or cardiac systems that emerged. The safety data supports the use of canakinumab for the selected population in the proposed indication: for patients with severe gouty arthritis who may not be candidates for NSAIDs or colchicine and for whom a prolonged interval between attacks is important.

11.4 Overall benefit/risk conclusion

As a targeted therapy against IL-1 β , canakinumab directly neutralizes one of the key inflammatory pathways involved in the pathogenesis of gouty arthritis. Canakinumab at 150 mg s.c. administered upon flares, showed substantial efficacy benefits in the treatment of gouty arthritis, in both the 12 week and 24 week periods and superiority to a relevant comparator in two well controlled, well conducted, placebo-controlled randomized clinical trials. Canakinumab also reduced the frequency of subsequent attacks, as shown by reducing the probability of a new flare, thereby increasing the number of patients free of new flares and reducing the average number of flares per patient with an acceptable safety profile.

The overall benefit/risk for the proposed indication: *ILARIS (canakinumab) is an interleukin-1 β blocker indicated for the treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDs or colchicine. ILARIS has also been shown to extend the time to next attack and reduce the frequency of subsequent attacks* is positive.

This intended gouty arthritis population for this indication includes patients who are intolerant of or contraindicated to NSAIDs and/or colchicine or for those who have inadequate response to these conventional anti-inflammatory agents. It is estimated that this novel, potent, targeted anti-inflammatory monoclonal therapy would be considered a treatment option for only a small proportion (<10%) of the overall treated gouty arthritis patients in the US (approximately 300,000 patients).

In patients who have failed or cannot take first-line therapies, there is a need for effective management of signs and symptoms of an acute flare. In these patients comorbidities can make corticosteroid less preferred. If not successfully treated, gouty arthritis worsens over time. With increased frequency and severity of attacks, more joints become involved and structural joint damage (bone erosions) develops, resulting in chronic pain and disability.

In summary, canakinumab has a positive overall benefit/risk ratio for the intended population of gouty arthritis patients who cannot obtain adequate response with NSAIDs and/or colchicine. It is generally well tolerated with an acceptable safety profile. In patients who have failed or cannot take first-line therapies, there is a need for effective management of an attack of gouty arthritis. By lowering the frequency of attacks and thereby reducing the need for use of additional medications, canakinumab can provide significant clinical benefit for the relatively small (estimated approximately 300,000 patients) who need new treatment options. By neutralizing a key cytokine that causes the inflammatory pain, canakinumab can alleviate the suffering associated with an attack of gouty arthritis among patients who cannot achieve an adequate response with NSAIDs or colchicine.

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