ARTHRITIS ADVISORY COMMITTEE MEETING
June 21, 2011

FDA Briefing Document
Supplemental BLA 125319: Ilaris (canakinumab) for the following proposed indication: "ILARIS is indicated for the treatment of gouty arthritis attacks. ILARIS has also been shown to extend the time to the next attack and reduce the frequency of subsequent attacks."

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Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the supplemental Biologics Licensing Application for canakinumab for the following proposed indication: "ILARIS is indicated for the treatment of gouty arthritis attacks. ILARIS has also been shown to extend the time to the next attack and reduce the frequency of subsequent attacks" to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

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Division Memorandum

Date: May 24, 2011

From: Sarah Yim, MD
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To: Members, Arthritis Advisory Committee

Subject: Overview of the FDA background materials for supplemental Biologic License Application (sBLA) 125319/66, Ilaris (canakinumab), at a dose of 150 mg subcutaneously for the indication of "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."

Introduction

Thank you for your participation in the Arthritis Advisory Committee (AAC) meeting to be held on June 21, 2011. The upcoming meeting is to discuss supplemental Biologic License Application (sBLA) 125319/66 from Novartis Pharmaceuticals, Inc. for Ilaris (canakinumab), a monoclonal antibody targeting interleukin-1β, for the indication of "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."

Canakinumab was approved in the United States on June 17, 2009 for the chronic treatment of the rare genetic disorders of Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome, also known as Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children 4 years of age and older. It is currently available in sterile, single-use, 6-mL glass vials containing 180 mg of canakinumab as a lyophilized powder for reconstitution. The approved dose in adult CAPS patients is 150 mg subcutaneously every 8 weeks.

Canakinumab is a long-half-life drug with extended pharmacodynamic effects, which include immunosuppression and laboratory abnormalities such as neutropenia, serum uric acid elevation, hypertriglyceridemia, and decreased creatinine clearance; and it is being proposed for the treatment of acute gout flares. Determining the benefit-risk profile of canakinumab for the treatment of acute gout flares in light of its extended pharmacodynamic effects, both desirable and undesirable, is complicated and will underlie the questions for discussion at the June 21, 2011 Arthritis Advisory Committee meeting. The Committee will be asked to discuss whether the totality of the data supports the efficacy and safety of canakinumab for the proposed indication.

The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Novartis. These materials reflect preliminary findings and do

not represent the final position of the Agency. The opinions and input provided by you at this AAC meeting will be an important factor in our decision on this application.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the Clinical Briefing Document and the product labels of other products approved the same indication.

Background

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. Gout is estimated to affect 5-6 million people in the US[1] and the prevalence of gout has been increasing over the past few decades[2]. The condition affects primarily middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical course of gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. If left untreated, the acute inflammatory episode is self-limited, typically peaking within 24-48 hours and eventually subsiding within 7-10 days. Treatment of acute attacks utilizes anti-inflammatory treatment of various mechanisms, such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS), or corticosteroids.

The chronic management of gout is founded upon control of hyperuricemia, as only this approach treats the underlying pathology of the disorder. However, it is common practice to use an agent to help reduce the frequency and severity of acute gout attacks, for which a patient is at increased risk during initiation of uric-acid lowering therapies. To this end, maintenance doses of either colchicine or an NSAID are continued as prophylaxis against gout flares; typically until the serum uric acid level has been maintained well within the normal range and there have been no acute attacks for 3 to 6 months.

Relevant Regulatory History for Canakinumab in Gout

The applicant's phase 3 study proposals were discussed at a November 2009 end-of-phase 2 meeting. The applicant proposed two co-primary endpoints: (1) pain assessments on the Visual Analogue Scale (VAS) at 72 hours post-dose and (2) assessment of time to

[1] Kramer HM, Curhan G, "The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988-1994." Am J Kidney Dis 2002 Jul; 40(1):37-42.
National Arthritis Data Workgroup, "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." Arthritis Rheum 2008 Jan; 58(1):26-35.

[2] Wallace KL et al., "Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population." J Rheumatol 2004 Aug; 31(8):1582-7.

a new gouty arthritis flare. The FDA accepted the two proposed co-primary endpoints but also recommended including efficacy measurements at earlier time points (24 hours and 48 hours) and analysis of proportions of patients with meaningful pain reductions (i.e. 50% pain reduction and an assessment of time to complete resolution of pain). Given the proposed number of secondary endpoints, the FDA recommended employing statistical correction methods for multiple comparisons.

The proposed indication for this supplemental Biologic License Application (sBLA) was the subject of discussion at both end-of-phase 2 and pre-sBLA meetings. The applicant has sought an indication that combines both acute and chronic treatment aspects, originally proposing "treatment and prevention of acute gout flares in patients for whom NSAIDs and/or colchicine are not tolerated or are ineffective." FDA expressed doubts that current data from the canakinumab development program in gout would be adequate to support a prevention claim, as data reflected only re-treatment on demand, and not chronic treatment intended to prevent flares. This lead to the proposed indication submitted with the original sBLA of: "*Treatment of gouty arthritis attacks. Ilaris has also been shown to extend the time to the first attack and reduce the frequency of subsequent attacks.*" The applicant later amended the proposed indication to: *"ILARIS (canakinumab) is an interleukin-1β 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."*

Product Information

Canakinumab is a humanized IgG1κ monoclonal antibody that binds with high affinity to human interleukin (IL)-1β, thereby preventing binding of endogenous IL-1β to its receptor, the Type I IL-1 receptor. It does not bind the other ligands of the Type I IL-1 receptor (IL-1α and IL-1Ra). Canakinumab is expressed in SP2/0-AG14 murine cells and has a molecular weight of approximately 145 kDa (after deglycosylation). Canakinumab drug product is supplied as a sterile, preservative free, lyophilized powder to be reconstituted with 1.0 mL preservative-free water for injection (WFI). When reconstituted, the final formulation contains 150 mg/mL canakinumab, (b) (4) histidine HCL, (b) (4) sucrose, and (b) (4)% (m/V) polysorbate 80, at a pH of 6.5. Each vial is for single-use and packaged in a single carton.

Nonclinical Pharmacology and Toxicology

No new nonclinical data were submitted in the sBLA. The original BLA included general toxicity, reproductive toxicity, and juvenile toxicity studies. Marmosets were used for general toxicity, reproductive and developmental toxicity studies because canakinumab bind to human and marmoset IL-1β with similar affinities. Additional reproductive and juvenile toxicity studies were conducted in mice using a murine surrogate of canakinumab. General toxicity studies identified no clear target organs of toxicity. Canakinumab is pregnancy category C, due to findings of delays in fetal skeletal development in marmosets and mice. Carcinogenicity studies were not conducted for canakinumab because it is not pharmacologically active in rodents and a carcinogenicity study in marmosets is considered infeasible.

Clinical Pharmacology
The absolute bioavailability of a subcutaneous injection of canakinumab is approximately 60%. A peak serum canakinumab concentration (Cmax) of 16 $\pm$ 3.5 µg/mL was observed approximately 7 days after subcutaneous administration of a single, 150 mg dose in adult CAPS patients. A negative correlation was observed between age and median time to reach Cmax (Tmax) in gout patients, with a range from 5 to 14 days. The elimination characteristics of canakinumab are similar between CAPS and gout patients. Clearance is positively correlated to body weight and negatively correlated to serum albumin. In gout patients, the clearance of canakinumab was 0.229 $\pm$ 0.0072 L/day for an average bodyweight of 93 kg and serum albumin of 43 g/L. The terminal half-life was 25.6 days.

Clinical Program

The clinical development program for canakinumab in gout investigated both acute and chronic treatment options, although the phase 3 program focused on acute treatment. As summarized in Table 1 below, the acute treatment gout program contained a proof of concept study (A2212) in 6 patients, a dose-ranging study in 200 patients (H2255), and the pivotal 12-week controlled studies H2356 (in 228 patients) and H2357 (in 226 patients) and their respective extensions. The chronic treatment gout program consisted of a large 24-week dose-ranging study in 431 patients (H2251) and its extension. No phase 3 studies have yet been conducted that would support a chronic treatment (i.e. prophylaxis of gout flares) indication.

The primary focus of this section will be the dose-ranging study (H2255) and the pivotal clinical studies. As study A2212 was a small proof of concept study, it will not be discussed in this memorandum.

Table 1: Summary of canakinumab clinical studies in gout

Study No.	Study Objectives	No. Treated	Study Duration	Treatment
Treatment of acute flares and reduction of frequency of subsequent flares (*claimed*)				
Early studies				
A2212	Tolerability / safety / efficacy of single doses in hospitalized acute flare patients	44 (plan) 6 (actual)	17 wks	10mg/kg i.v. (n=3) 12mg dexamethasone i.v. (n=3) *study completed early*
H2255	Dose-ranging / efficacy / safety for acute flares 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. triam. ac. (n=57)
Pivotal studies				
H2356	Efficacy / safety in frequently flaring , mostly comorbid patients unable to use NSAIDs / colchicine	228	12 wks	150mg s.c. (n=113) 40mg i.m. triamcinolone ac. (n=115)
H2357	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine	226	12 wks	150mg s.c. (n=112) 40mg i.m. triamcinolone ac. (n=114)
Extension study				
H2356E1	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine	175 (entered extension)	+12 wks (24 total)	150mg s.c. (n=90) 40mg i.m. triamcinolone ac. (n=85)
H2357E1	Efficacy / safety in frequently flaring, mostly comorbid patients unable to use NSAIDs / colchicine	160 (entered extension)	+12 wks (24 total)	150mg s.c. (n=84) 40mg i.m. triamcinolone ac. (n=76)
Prevention of flares when starting urate-lowering therapy (*unclaimed*)				
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 flare	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)]*

triamcinolone ac. = triamcinolone acetonide
Source: [SCS-Table 1-2]

Dose selection

Study H2255 was a randomized, double-blind, active-controlled 8-week clinical study in 200 patients with gout who had inadequate response to or inability to tolerate NSAIDS and/or colchicine. Patients received one dose of study medication (10, 25, 50, 90, 150 mg SC of canakinumab or 40 mg IM of triamcinolone). The primary objective of Study H2255 was to identify the target dose of subcutaneous (SC) canakinumab that would lead to similar efficacy to an intramuscular (IM) injection of 40 mg triamcinolone acetonide, which is approved for the treatment of acute attacks of gout. The primary efficacy variable used was change in pain intensity in the target joint from baseline to 72 hours

post-dose (Day 4) as measured on a 0-100 mm visual analog scale (VAS). All doses tested appeared to be more effective than triamcinolone 40 mg IM for the primary efficacy variable, as shown in Table 2 below, although only the 150 mg dose of canakinumab had a treatment effect large enough to reach statistical significance compared to triamcinolone. The 150 mg dose was also associated with the largest treatment effect on tenderness and swelling, but not erythema, in target joints. All doses were associated with a lower cumulative flare rate through 8 weeks, compared to triamcinolone. Therefore the applicant elected to study only the 150 mg dose regimen in Phase 3.

Table 2: Selected dose-ranging efficacy results from Study H2255

Selected Dose-Ranging Efficacy Results from Study H2255 in Acute Gout						
	Can. 10 mg N = 28	**Can. 25 mg N = 29**	**Can. 50 mg N = 28**	**Can. 90 mg N = 29**	**Can. 150 mg N = 27**	**Triam 40 mg N = 56**
Difference (c/w Triam.) in change from baseline in pain intensity (0-100 mm VAS) at Day 4 (72 hours post-dose)						
	-5.3	-3.2	-5.3	-9.4	-19.2	-
95% CI	(-15.9, 5.4)	(-13.9, 7.4)	(-16.3, 5.6)	(-20.0, 1.2)	(-30.2, -8.2)	
Odds Ratio (c/w Triam.) for physician's assessment of tenderness, swelling, and erythema of target joint at Day 4						
Tenderness	1.56	0.98	1.32	1.40	3.16	-
95% CI of OR	(0.63, 3.87)	(0.40, 2.35)	(0.53, 3.27)	(0.58, 3.37)	(1.27, 7.89)	
Swelling	2.61	1.30	1.75	1.09	2.66	-
95% CI of OR	(1.06, 6.44)	(0.55, 3.05)	(0.72, 4.26)	(0.48, 2.48)	(1.09, 6.50)	
Erythema	0.93	0.75	0.57	1.45	0.75	-
95% CI of OR	(0.33, 2.64)	(0.27, 2.08)	(0.17, 1.85)	(0.52, 4.07)	(0.26, 2.16)	
Cumulative flare rate through 8 weeks post-dose						
	3.6	10.3	3.6	13.8	3.7	45.4
95% CI	(0, 10.45)	(0, 21.43)	(0, 10.45)	(1.24, 26.34)	(0, 10.83)	(32.24, 58.55)

Source: Tables 11-5, 11-8, and 14.2.-8.1 from H2255 Clinical Study Report
Can = canakinumab; Triam = Triamcinolone

Although the applicant is not seeking a chronic treatment/prophylaxis claim, an initial 24-week dose-ranging study, H2251, was performed to evaluate canakinumab for prophylaxis of flares in gout patients initiating allopurinol therapy. Study H2251 was a randomized, double-blind, active-controlled 24-week dose-ranging study in 431 patients with gout who were starting allopurinol therapy. Patients received 25, 50, 100, 200, or 300 mg SC of canakinumab on Day 1 OR 50 mg SC canakinumab on Day 1 and 29 followed by 25 mg on Day 57 and 85 OR 0.5 mg colchicine daily. The primary objective was to determine the target dose of canakinumab that would provide comparable efficacy as colchicine at a dose of 0.5 mg daily, with respect to the mean number of gout flares occurring during the 16 weeks after randomization. Interestingly, this study only included one treatment arm where patients received chronic regular administration of canakinumab. In this group, patients received two doses of 50 mg SC, and then two doses of 25 mg SC at 4 week intervals. The primary efficacy analysis did not demonstrate a dose-response among the canakinumab treatment arms with respect to reduction in mean number of flares, and a target dose giving comparable efficacy to colchicine (0.5 mg daily) could not be identified. In other analyses, as shown in Table 3 below, canakinumab treatment appeared to reduce the proportion of patients having a flare within 16 weeks of randomization, although the regularly administered regimen did

not appear to provide an additional benefit over the single dose regimens during the 24-weeks of this study.

Table 3: Selected dose-ranging results from Study H2251

Selected Dose-Ranging Efficacy Results from Study H2251 in Prophylaxis of Gout							
	Can. 25 mg x 1 N = 55	Can. 50 mg x 1 N = 54	Can. 50 mg x 2 f/b 25 mg x 2 N = 54	Can. 100 mg x 1 N = 54	Can. 200 mg x 1 N = 54	Can. 300 mg x 1 N = 53	Colchicine 0.5 mg qd N = 108
Mean number of flares							
	0.5	0.4	0.7	0.2	0.4	0.2	0.7
Odds ratio (c/w colchicine) for number of patients with gout flares within 16 weeks of randomization							
Incidence, n (%)	15 (27.3)	9 (16.7)	9 (16.7)	8 (14.8)	10 (18.5)	8 (15.1)	48 (44.4)
Odds ratio	0.47	0.25	0.25	0.22	0.28	0.22	-
95% CI of OR	(0.23, 0.95)	(0.11, 0.56)	(0.11, 0.56)	(0.09, 0.51)	(0.13, 0.61)	(0.10, 0.52)	-

Sources: Table 11-4 and 11-5 from H2251 Clinical Study Report

Efficacy

Phase 3 studies H2356 (conducted entirely outside the US) and H2357 (conducted mostly within the US) were of identical design. In both studies, patients were given a single dose at Day 1 and followed for 12 weeks. Both studies utilized the co-primary endpoints of 1) mean difference in patient assessment of gout pain from baseline to 72 hours post-dose (on a 0 to 100 mm VAS) and 2) time to new gout flare. Although experience with clinical trials of products for the acute treatment of gout is limited, patient assessment of pain using either a VAS or Likert scale has precedent in the literature[3] and in other trials used to support approval for acute treatment of gout flares.[4] The endpoint of time to new gout flare has not previously been used to support approval of a product for either the acute treatment of gout indication or a chronic treatment (prophylaxis of gout) indication.

The applicant sought to enroll a more refractory patient population in the studies by specifying that patients be intolerant of or refractory to NSAIDS and colchicine. After difficulties with enrollment, the applicant amended these criteria to include patients who were intolerant of or refractory to NSAIDS and/or colchicine. However, as noted in Table 4 below, the majority of patients enrolled in studies H2356 and H2357 would likely not be considered refractory. Only half of the patients in H2356 and a third of the patients in H2357 were on urate-lowering therapy and less than half of the patients in each study were unable to receive treatment with either an NSAID or colchicine. A minority of patients had tophi, a potential indicator of difficult-to-treat disease. Nonetheless, the patient population generally appeared to include a representative sample of gout patients.

[3] Ahern MJ et al., "Does colchicine work? The results of the first controlled study in acute gout." Aust NZ J Med 1987; 17:301-304

[4] Colcrys prescribing information, Section 14: http://www.colcrys.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf

Table 4: Selected baseline gout characteristics in H2356 and H2357

Disease characteristics	H2356		H2357	
	Can-mab N=113	Triam. ac. N=115	Can-mab N=112	Triam. ac. N=114
Flares in the past year, mean (SD)	**6.5(5)**	7(5)	**6.5 (6)**	6(4)
Known presence of tophi, N (%)	**44(39)**	45(39)	**20(18)**	23 (20)
Current user of urate-lowering therapy, N(%)				
Yes	**57 (50)**	63(55)	**32(29)**	40(35)
Allopurinol	**57 (50)**	62(54)	**26(23)**	33(29)
Febuxostat	**0**	1 (1)	**2(2)**	2(2)
Probenecid	**0**	0	**1(1)**	0
Pegloticase	**0**	0	**0**	0
Other	**2(2)**	0	**7(6)**	7(6)
N (%) Subjects with contraindications to, or intolerance to, or lack of efficacy from				
NSAIDs	**107(95)**	113(98)	**97(87)**	96(84)
Colchicine	**27(24)**	39(34)	**67(60)**	59(52)
Both	**22(19)**	38(33)	**54(48)**	46(40)

Source: Table 11-3 of Study Reports H2356 and H2357

For the endpoint of change in pain from baseline to 72 hours post-dose, both treatments were associated with large decreases in pain VAS scores compared to baseline, however canakinumab treatment was associated with larger decreases compared to triamcinolone. The difference between treatments approaches the accepted minimum clinically important difference in the VAS (somewhere in the range of 10-20 mm)[5].

Table 5: Change in pain intensity VAS (0-100 mm scale) at 72 hours post-dose

	H2356		H2357	
	Can. 150 mg SC N=113	Triam. 40 mg IM N=115	Can. 150 mg SC N=112	Triam. 40 mg IM N=114
VAS pain baseline mean (SD)	**74(11)**	75(13)	**75(13)**	74(13)
Analysis by Least Squares Means with LOCF imputation (Primary Analysis)				
Est. LS Mean (SE)	28.1 (2.4)	39.5 (2.4)	22.1 (2.3)	31.9 (2.4)
*Est. diff to triam.	-11.4		-9.8	
One-sided p-value	p=0.0005		p=0.0018	

*Est diff = estimated difference; Can = canakinumab; Triam = triamcinolone acetonide
Source: Tables 11-3 and 11-4 of H2356 and H2357 Clinical Study Reports

With respect to the endpoint of time to first new gout flare, the median time to new flare could not be estimated because 50% of the patients in each group had not flared within the 12-week controlled period of the study. However, a cumulative event rate based on Kaplan-Meier estimates of flare probability and a hazard ratio could be calculated based on the available data; these results are summarized in Table 6 below. Canakinumab treatment was associated with a lower rate and risk of a new gout flare during the 12-week controlled period.

[5] Farrar JT et al., "Defining the clinically important difference in pain outcome measures." Pain 2000; 88:287-294.
Todd KH et al., "Clinical significance of reported changes in pain severity." Ann Emerg Med 1996; 27:485-489
Gallagher EJ et al., "Prospective validation of clinically important changes in pain severity measured on a visual analog scale." Ann Emerg Med 2001; 38(6):633-638

Table 6: Time to first new gout flare and estimates of flare probabilities in H2356 and H2357

New Gout Flare	H2356		H2357	
	Can 150 mg SC N=113	Triam. 40 mg IM N=115	Can 150 mg SC N=112	Triam. 40 mg IM N=114
Median time to new flare	Can not be est	Can not be est	Can not be est	Can not be est
Cumulative event rate* (95% CI)	19 (13-27)	36 (28-46)	14 (9-22)	38 (30-48)
Hazard Ratio**	0.45 (p=0.0014)		0.32 (p=0.0001)	

*Kaplan-Meier estimate of flare probability. Source Table 11-5 of H2356 and H2357 CSR.
**Using Cox's proportional hazard regression model, comparing canakinumab to triamcinolone, calculated with treatment group and BMI at baseline as covariates and nominal p-value <0.025

In order to allow for an extended period of evaluation, patients were offered continuation in their assigned treatment group for an additional 12-weeks, in a blinded fashion (extension E1). During this time period, patients would receive their originally assigned treatment again, if needed for occurrence of flare. Approximately 13 to 24% of patients elected not to continue in extension E1. As shown in Table 7 below, more flares occurred, allowing for a median time to flare calculation for the triamcinolone group, but not for the canakinumab group. Differences between treatment groups with respect to cumulative event rate and hazard ratio in the 2nd 12-weeks were consistent with the differences observed during the first 12-weeks.

Table 7: Time to first new gout flare and estimates of flare probabilities in H2356 and H2357 and their 12-week E1 extensions (24 weeks total)

New Gout Flare	H2356/H2356E1		H2357/H2357E1	
	Can 150 mg SC N=113	Triam. 40 mg IM N=115	Can 150 mg SC N=112	Triam. 40 mg IM N=114
Median time to new flare (days, 95% CI)	Can not be est	119 (94, not est.)	Can not be est	146 (94, not est)
Cumulative event rate* (95% CI)	35 (27-46)	57 (48-67)	29 (21-39)	54 (44-65)
Hazard Ratio**	0.48 (p=0.0003)		0.40 (p<0.0001)	

*Kaplan-Meier estimate of flare probability
**Using Cox's proportional hazard regression model, comparing canakinumab to triamcinolone, calculated with treatment group and BMI at baseline as covariates and nominal p-value <0.025
Source: Table 11-4 from H2356E1 CSR and Table 11-4 from H2357E1 CSR

Overall, both trials H2356 and H2357 demonstrated statistically significant decreases in pain intensity measured on VAS for canakinumab compared to triamcinolone, and statistically significant differences between treatment groups (favoring canakinumab) for the risk of a new gout flare. Subgroup analyses of the co-primary efficacy endpoints were generally consistent with the overall efficacy results, including results for the subgroup of patients intolerant to, with contraindications for, or lack of efficacy from NSAIDs and/or colchicine; however differences in the magnitude of the treatment effect in the subgroup of patients taking urate lower therapy versus those not taking urate therapy was observed.

Safety

In the safety dataset for the gout indications, a total of 691 patients have been exposed to canakinumab in the 6 controlled trials/extensions H2251, H2255, H2356, H2357, H2356E1, and H2357E1. Of the 691 patients, 253 were treated with the proposed dose of 150 mg administered subcutaneously, and 193/253 (76%) received canakinumab only once. In the original submission data on re-treatment included 60 gout patients re-treated with a second or third dose of canakinumab in H2356, H2357 or their extensions. With additional data from the 120-day safety update, the number of patients having been re-treated increased, as summarized in Table 8 below.

Table 8: Summary of canakinumab injections administered in the gout program

N of injections:	Can-mab 150mg treated in H2255 N=27	Can-mab 150mg treated in 2356/E1/E2 2357/E1/E2 N=225	Can-mab 150mg received triamcinolone in H2356/56E1, H2357/57E1 treated with can-mab in 56E2 and 57E2 N=67	Can-mab doses other than 150 mg, H2251 and H2255 N=438
1	27 (100%)	107(47%)	54 (81%)	385 (88%)
2	0	75(33%)	11(16%)	0
3	0	25(11%)	1(1.5%)	2 (0.5%)
4	0	15(7%)	1(1.5%)	51(11.5%)
≥5	0	3(2%)	0	0

Source: 120-day safety update submission

Table 9 below contains an overview of the adverse events and death in the gout clinical development program for canakinumab. The primary comparison between canakinumab and triamcinolone is highlighted in gray in the table. Compared with triamcinolone 40 mg IM, canakinumab 150 mg SC was associated with twice the proportion of serious adverse events (7% vs. 3%), a higher proportion of patients experiencing at least one adverse event (62% vs. 51%), a higher proportion of patients experiencing at least one serious adverse event (7% vs. 3%), and a higher proportion of patients experiencing infections (19% vs. 13%) and serious infections (2% vs. 0%). The types of adverse events and serious adverse events observed were generally consistent with the underlying patient population, with the exception of infections. However the increase in these AEs is particularly notable in light of the fact that they were observed after a single injection of canakinumab.

Table 9: Summary of adverse events and deaths in gout controlled studies (H2251, H2255, H2356, H2357, H2356E1, and H2357E1)

	Canakinumab ≤100mg N=278	Canakinumab split 150mg* N=53	Canakinumab 150mg N=253	Canakinumab ≥200 N=107	Triamcinolone N=286	Colchicine N=108
Number of Subjects with at Least 1 AE	137 (49%)	31 (58.5%)	**158 (62.5%)**	57 (53%)	**145 (51%)**	58 (54%)
Number of Subjects with at Least 1 Serious AE	11(4%)	1(1.9%)	**18(7.1%)**	6(5.6%)	**9(3.1%)**	6(5.6%)
Number of Subjects with at Least 1 Infection or Infestation	42(15.1)	10(18.9)	**49 (19.4)**	19(17.8)	**37 (12.9)**	13 (12)
Number of Subjects with at Least 1 Serious Infection	4(1.4%)	1(1.9%)	**5(2.0%)**	2(1.9%)	**0**	0
Number of Subjects with at Least 1 AE Leading to Discontinuation	4 (1.4%)	0	**2 (0.8%)**	7 (6.5%)	**1 (0.3%)**	3(2.8%)
Deaths	0	0	**1(0.4%)**	0	**1(0.3%)**	1(0.9%)

Source: Table 2.1-6A, Appendix 1 of Summary of Clinical Safety; Applicant's response to IR, Apr 14, 2011.
*From Trial 2251, consists of q4week dosing of 50, 50, 25, and 25 mg SC

Canakinumab treatment also appeared to be associated with an increase in a number of findings, which together, could ultimately result in a negative impact in gout patients—namely decline in renal function, hypertriglyceridemia, and serum uric acid elevation. As shown in Table 10 below, the degree of renal function decline observed is not large, but occurred in a greater proportion of canakinumab-treated patients. Approximately 5% of canakinumab treated patients experienced creatinine elevation greater than or equal to 1.5 times the upper limit of normal (ULN) compared to 3% of triamcinolone-treated patients. Similarly, approximately 11% of canakinumab treated patients experienced a ≥25% decline from baseline in estimated creatinine clearance compared to 9% of triamcinolone-treated patients.

Table 10: Renal function changes in the controlled trials in gout controlled studies (H2251, H2255, H2356, H2357, H2356E1, and H2357E1)

MedDRA Preferred Term	Can--mab ≤100mg N=278	Can--mab split 150mg N=53	Can--mab 150mg N=253	Can--mab ≥200 N=107	Can—mab all N=691	Triam N=286	Colch N=108
Subjects with measured laboratory parameters	N=273	N=53	**N=252**	N=106	N=684	**N=284**	N=108
Creatinine Elevation ≥ 1.5 ULN N(%)	3(1.1)	1(1.9)	**12(4.8)**	3(2.8)	19 (2.8)	**8(2.8)**	3(2.8)
Creatinine Elevation ≥ 3 ULN, N(%)	0	0	**1(0.4)**	0	1 (0.1)	**1(0.4)**	0
≥ 25 % decline from baseline in Creatinine Clearance by Cockroft Gault, N(%)	21 (7.7)	3(5.7)	**27 (10.7)**	9 (8.4)	60 (8.8)	**25 (8.7)**	4 (3.7)
Decline in GFR by MDRD*, 75-50 % LLN (90 ml/min), N(%)	47 (17.2)	14 (26.4)	**44(17.5)**	30 (28.3)	135 (19.5)	**67 (23.6)**	23(21.3)
Decline in GFR by MDRD*, <50 % LLN (90 ml/min) N(%)	8(2.9)	2(3.8)	**20 (7.9)**	1(0.9)	31 (4.5)	**19 (6.7)**	3(2.8)

Source: Table 3.4-2A, Appendix 1 of Clinical Summary of Safety; Tables 14.3-2.7 in trial reports H2356/E1, H2357/E1, H2251, and H2255.
*GFR was calculated by the Applicant based on the Modification of Diet in Renal Disease study (MDRD) formula, according to Levey, et al 2007, as follows:
GFR [mL/min/1.73m2] = 175*(C-1.154)*(A-0.203)*G*R; where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 if gender is female or G=1 if gender is male, and R=1.21 if race is black or R=1 otherwise.

With respect to lipid abnormalities, canakinumab was associated with a higher proportion of patients experiencing hypertriglyceridemia, as shown in Table 11 below. Again, the bulk of the increases appear to be of lower magnitude (i.e. 1.5 times the upper limit of normal or less), however a higher proportion of patients who received canakinumab treatment experienced triglyceride increases over a range of magnitudes from just greater than the upper limit of normal through 5 times the upper limit of normal.

Table 11: Shifts from normal to abnormal lipid parameters in the gout controlled trials

Lipid Parameters	Can-mab All N=691	Can-mab ≤ 100 mg N=278	Can-mab split 150 mg, N=53	Can-mab 150 mg N=253	Can-mab 200 mg N=107	Triam N=286	Colch N=108
N patients with measured lab parameters	0	0	0	N=211	0	N=218	N=108
HDL cholesterol, N(%)							
>ULN*	ND**	ND	ND	**6 (2.8)**	ND	**8 (3.7)**	ND
LDL cholesterol, N(%)							
>ULN	ND**	ND	ND	**17 (8.1)**	ND	**15 (6.9)**	ND
N patients with measured lab parameters	N=684	N= 273	N=53	N=252	N=106	N=218	N=108
Total Cholesterol, N(%)							
> ULN	158 (23)	63 (23)	13 (24)	**60 (24)**	22 (21)	**65 (23)**	27 (25)
> 1.5 X ULN	56 (8)	22 (8)	6 (11)	**23 (9)**	5 (5)	**15 (5)**	4 (4)
Triglycerides							
> ULN, N(%)	249 (36)	87 (32)	23 (43)	**101 (40)**	38 (36)	**75 (26)**	29 (27)
≥ 1.5 X ULN	166 (24)	61 (22)	14 (26)	**63 (25)**	28 (26)	**39 (14)**	17 (16)
≥ 2.5 X ULN	63 (9)	24 (9)	5 (9)	**26 (10)**	8 (7.5)	**9 (3)**	8 (7)
≥ 5 X ULN	18 (3)	9 (3)	2 (4)	**6 (2)**	1 (0.9)	**2 (0.7)**	6 (6)

Source: Table US6-1 Applicant's response to IR, May 9, 2011
*ULN- Upper Limit of Normal
**HDL cholesterol was measured only in pivotal trials H2356/56E1 and H2357/57E1; LDL cholesterol was calculated according to Cleeman et al, 2001: LDL=Total Cholesterol –HDL-[TG/5] with ULN=130mg/dL or 3.367mmol/L.

Interestingly, canakinumab treatment was also associated with increases in serum uric acid, as summarized in Table 12 and Table 13 below. On average, the magnitude of the elevation appears to be small (less than 1 mg/dL). However, up to 36% of patients experienced serum uric acid elevation of greater than 2 mg/dL in magnitude.

Table 12: Mean changes from baseline in serum uric acid in H2356 and H2357

	Day 2 post-dose	Day 4	Day 29	Day 57	Day 85 (12 weeks)
Trial H2356					
Canakinumab	+6 (40) µmol/L 0.1 (0.7) mg/dL	+18 (68) µmol/L 0.3(1.1) mg/dL	+ 17 (121) µmol/L 0.3 (2.0) mg/dL	+ 25 (120) µmol/L 0.4 (2.0) mg/dL	+ 35 (144) µmol/L 0.6 (2.4) mg/dL
Triamcinolone	-14 (42) µmol/L 0.2 (0.7) mg/dL	-19 (73) µmol/L 0.3 (1.2) mg/dL	-25 (104) µmol/L 0.4 (1.7) mg/dL	-29 (139) µmol/L 0.4 (2.3) mg/dL	-19 (128) µmol/L 0.3 (2.1) mg/dL
Trial H2357					
Canakinumab	+ 3(40) µmol/L 0.05 (0.7) mg/dL	+ 22 (57) µmol/L 0.4 (0.9) mg/dL	+38 (97) µmol/L 0.6 (1.6) mg/dL	+ 49 (110) µmol/L 0.8 (1.8) mg/dL	+ 41 (119) µmol/L 0.7 (2.0) mg/dL
Triamcinolone	- 27 (42) µmol/L 0.45(0.7) mg/dL	-15 (64) µmol/L 0.3 (1.1) mg/dL	+10 (71) µmol/L 0.17 (1.2) mg/dL	+ 20 (99) µmol/L 0.4 (1.7) mg/dL	+ 15 (92) µmol/L 0.3 (1.7) mg/dL

Source: Tables 14.3-2.2 in trials H2356, H2356E1 and H2357, H2357E1.

Table 13: Proportion of patients experiencing an increase in serum uric acid in H2356 and H2357

N(%) subjects experiencing increase in serum uric acid during the first 12 weeks of treatment	H2356		H2357	
	Can-mab 150 mg SC N=109	Triam. ac. 40 mg IM N=112	Can-mab 150 mg SC N=112	Triam. ac. 40 mg IM N=113
>0.5 mg/dL	83 (76)	63 (56)	93 (83)	65 (57.5)
>1 mg/dL	66 (60)	39 (35)	72 (64)	49 (43)
>2 mg/dL	39 (36)	15(13)	30 (27)	26 (23)

Source: Table US3. 2-3a_1b, US3. 2-3b_1b, US3. 2-3c_1b, US3. 2-4a_1b, US3. 2-4b_1b, US3. 2-4c_1b, US3. 2-5a_1b, US3. 2-5b_1b, US3. 2-5c_1b.

Although one would imagine that a serum uric acid increase of this magnitude would not be unmanageable with adequate doses of urate lowering therapy, one could also imagine that for certain patients whose serum uric acid is not adequately controlled that a further increase might enhance tophi formation. In any case, this finding, as with hypertriglyceridemia and creatinine elevation, raises questions regarding the net impact that canakinumab treatment could have on gout patients and their comorbidities.

Benefit-risk assessment

Based on the efficacy and safety data provided, the Advisory Committee will be asked to consider whether the benefit-risk profile of canakinumab is acceptable for the treatment of acute flares of gout. This question is complicated by a number of issues to include:

- Canakinumab has a long half life and extended pharmacodynamic effects. These are not characteristics typical of an acute treatment, and both efficacy and safety data suggest the effects of even a single subcutaneous 150 mg injection of canakinumab may be protracted.
- Canakinumab appears to be associated with an increased risk of infection and serious infection. Given that it is expected to provide primarily a symptomatic benefit, is the risk of infection still outweighed by the clinical benefits?
- Canakinumab appears to be associated with a number of laboratory abnormalities. The impact of decreased white blood cell counts may be considered with the risk of infection. However, canakinumab also appears to be associated with a decline in creatinine clearance, hypertriglyceridemia, and elevated serum uric acid, all of which could be deleterious in the gout patient population. However, because the magnitude of the effects is generally not large, it is difficult to surmise whether these changes are likely to result in negative outcomes long-term, particularly in light of the fact that it is not clear how often with "on-demand" re-treatment that a given patient would be exposed to canakinumab and its extended effects. Only limited data on re-treatment were provided in the sBLA.
- Finally, although a fairly wide range of doses were studied early on, only the 150 mg dose of canakinumab was studied further in the gout clinical development program. Given that some of the safety findings suggest a dose-response, it would have been useful to have additional data from a lower dose, to assess whether adequate efficacy could have been provided with less undesirable effects on susceptibility to infection and laboratory abnormalities. However these data are not available.

Summary

The purpose of the AAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Novartis to support the approval of canakinumab 150 mg subcutaneous injection 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." The major issues for discussion are whether the totality of the data support the efficacy and safety of canakinumab for the proposed indication and patient population.

At the AAC meeting, Novartis will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be posed to the committee following the presentations and discussion.

Draft Questions to the Committee

1. Discuss the efficacy data of canakinumab for gout considering the following:
    a. The dose ranging data and whether doses lower than 150mg should be explored further.
    b. Whether the proposed regimen (150 mg SC single-dose, with re-treatment on demand) represent acute treatment, or a more chronic treatment.
    c. The limited information regarding repeat dosing and whether additional data on repeat dosing over time should be obtained, particularly in light of the intended population of patients, who may be at risk for more frequent flares (patients in the studies had an average of 6-7 acute flares in the previous year).

2. Discuss the overall safety profile of canakinumab for gout considering the following:
    a. Safety signals of infections, increase in uric acid level, decline in renal function, and hypertriglyceridemia
    b. Potential risk of using canakinumab for gout on acute recurrent basis

3. Considering the totality of data, has canakinumab at a dose of 150 mg subcutaneously demonstrated substantial evidence of efficacy for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicine? **(voting question)**
    a. If not, what further efficacy data should be obtained?

4. Considering the totality of data, has canakinumab at a dose of 150 mg subcutaneously demonstrated substantial evidence of efficacy for the additional claim that canakinumab has shown to extend the time to next attack and reduce frequency of subsequent attacks? **(voting question)**
    a. If not, what further data should be obtained?

5. Is the safety profile of canakinumab sufficient for approval of canakinumab for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicine? **(voting question)**
    a. If not, what further safety data should be obtained?

6. Do the efficacy and safety data provide substantial evidence to support approval of canakinumab at a dose of 150 mg subcutaneously for treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicine? **(voting questions)**

7. Do the efficacy and safety data provide substantial evidence to support approval of canakinumab at a dose of 150 mg subcutaneously for the additional claim that canakinumab has shown to extend the time to next attack and reduce frequency of subsequent attacks? **(voting questions)**

Briefing Document for the Arthritis Advisory Committee Meeting

June 21, 2011

Ilaris®/Canakinumab
BLA 125319

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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Summary of FDA Review of Clinical Efficacy & Safety

Background

The focus of discussion for the June 21, 2011 Arthritis Advisory Committee meeting is canakinumab (also known as ACZ885, tradename Ilaris®), an interleukin-1β inhibitor, for the treatment of gouty arthritis attacks (flares). Canakinumab was approved in the United States on June 17, 2009 for chronic treatment of the rare genetic disorders of the Cryopyrin-Associated Periodic Syndromes (CAPS)—specifically, Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome—at a dose of 150 mg administered subcutaneously every 8 weeks. The product is currently approved for CAPS in over 40 countries worldwide including the US, EU, Canada, and Australia.

Background on Gout

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. Gout is estimated to affect 5-6 million people in the US[1], and the prevalence of gout has been increasing over the past few decades.[2] The condition affects primarily middle-aged and older men and may also occur in post-menopausal women. Gout in very young individuals is usually the result of genetic defects in the enzymes of uric acid metabolic pathway. Monosodium urate crystals start forming when the serum uric acid level consistently exceeds 6.8 mg/dL; MSU crystals surrounded by chronic mononuclear and giant cell reactions form tophi.[3] Not all patients with hyperuricemia develop gout: according to the Normative Aging Study[4], in a cohort of 2,046 initially healthy male subjects, only 22% of men who had uric acid level above 9 mg/dL developed gout within a period of 5 years.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. Monosodium urate crystals often remain at the sites of deposition during the intercritical gout; gradual resolution of tophi and crystal dissolution may be achieved with consistent control of the levels of serum uric acid below 6 mg/dL.[5] In untreated or poorly controlled gout, chronic intra-articular urate

[1] Kramer HM, Curhan G, "The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988-1994." Am J Kidney Dis 2002 Jul; 40(1):37-42.
National Arthritis Data Workgroup, "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." Arthritis Rheum 2008 Jan; 58(1):26-35.
[2] Wallace KL et al., "Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population." J Rheumatol 2004 Aug; 31(8):1582-7.
[3] Schumacher HR Jr, "The pathogenesis of gout." Cleve Clin J Med. 2008 Jul;75 Suppl 5:S2-4.
Richette P and Bardin T, "Gout" Lancet. 2010 Jan 23;375(9711):318-28. Epub 2009 Aug 17.
[4] Campion EW, et al., "Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study." Am J Med. 1987 Mar;82(3):421-6.
[5] Li-Yu J et al., "Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout?" J Rheumatol. 2001 Mar;28(3):577-80. Pascual E and Silvera F, "Time required

crystal deposition and tophi formation may lead to permanent joint destruction with formation of bone erosions leading to functional disability.

Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities observed in patients with gout.

A typical course of gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. If left untreated, the acute inflammatory episode is self-limiting: it would peak within 24-48 hours and eventually subside within 7-10 days. As untreated gout progresses, the attacks may become more frequent and involve multiple joints.

Diagnostic criteria for acute flare of gouty arthritis

Several sets of criteria for the diagnosis of acute flare of gouty arthritis exist (Table 1). The most frequently used in clinical trials are the American College of Rheumatology 1977 Preliminary Criteria for the classification of acute arthritis of primary gout proposed by Wallace et al in 1977.[6] As will be discussed later in this document, the applicant employed these criteria in their selection of patient population for the gouty arthritis development program.

Table 1: Criteria for the diagnosis of gout

ACR (ARA) Preliminary Criteria	New York Criteria	Rome Criteria
MSU crystals in joint fluid OR meets 6 of the following criteria: >1 acute arthritis attack Maximum inflammation within 1 d Monoarthritis attack Redness observed over joints First MTP painful or swollen Unilateral 1st MTP joint attack Unilateral tarsal joint attack Tophus (proven or suspected) Hyperuricemia Asymmetrical swelling within a joint on x-ray Subcortical cysts without erosions on x-ray Synovial fluid cultures negative for organisms	MSU crystals in joint fluid or tissue or tophus OR meets 2 of the following criteria: 2 attacks of painful limb joint swelling Abrupt onset and remission in 1–2 wk initially First MTP attack Presence of a tophus Response to colchicine-major reduction in inflammation within 48 h	Meets 2 of the following criteria: Painful joint swelling, abrupt onset, Clearing in 1–2 wk initially Serum uric acid: >7 in males, >6 in Females Presence of tophi Presence of urate crystals (MSU) in synovial fluid or tissues

Source: Clinical Diagnostic Criteria for Gout; J. Clin. Rheumatol., 2009; 15:22-24.

Available therapies for treatment of acute gouty arthritis and chronic gout

The available therapies for treatment of gout are generally distinguished according to their effects on both acute flares of gouty arthritis and chronic intercritical gout. The treatment options for management of chronic gout include urate-lowering agents that inhibit uric acid formation, uricosuric formulations (probenecid, sulfinpyrazone, and benzbromarone) that facilitate uric acid excretion, and agents intended for chronic

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for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout." Ann Rheum Dis. 2007 Aug;66(8):1056-8. Epub 2007 Jan 12.
Edwards NL, "Treatment-failure gout: a moving target." Arthritis Rheum. 2008 Sep;58(9):2587-90.

[6] Wallace SL, Robinson H, Masi AT, et al., "Preliminary criteria for the classification of the acute arthritis of primary gout." Arthritis Rheum 1977; 20:895-900.

prophylactic use to reduce the frequency and severity of gout flares, particularly upon initiation of urate-lowering therapy. Approved urate-lowering agents include: the xanthine-oxidase inhibitor allopurinol (Zyloprim ®, Lopurin®), the non-purine xanthine-oxidase inhibitor febuxostat (Uloric®), and the PEGylated uricase enzyme, pegloticase (Krystexxa®).

The treatment options for acute gout flares include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroid formulations, as well as ACTH (corticotropin). Symptomatic analgesic treatment with acetaminophen, opioids or other agents could be added for pain management during an acute flare.[7]

The pharmacological agents approved for treatment of acute gout flares include: Indomethacin (Indocin®), the injectable formulations of corticosteroids such as bethmethasone (Celestone-Soluspan®), methylprednisolone (Depo-Medrol®), and triamcinolone acetonide (Kenalog®) as well as Colchicine (Colcrys®). Of these, colchicine is the only product that is also approved for prophylaxis of gout flares.

As will be discussed later in this briefing document, the applicant chose to use a single 40 mg dose of triamcinolone acetonide (Kenalog®) administered intramuscularly as the active comparator in their Phase 3 clinical trials.

Role of IL-1 inhibitors in the therapeutic armamentarium for gout

As early as the 1980's, interleukin-1 was identified as a key mediator of inflammation in the crystal-induced arthritides.[8] However better characterization of the pathophysiology of MSU-related inflammation occurred much later, in 2006, when Martinon and colleagues demonstrated that MSU crystals engage the caspase-1-activating NALP3 inflammasome, resulting in the production of IL1β.[9] Although the first specific IL1 inhibitor, anakinra (Kineret®), was approved in 2001 for rheumatoid arthritis, the first clinical study of anakinra for the treatment of gout (specifically for treatment of acute gout flares) was not published until 2007.[10] Subsequently, a pilot study of rilonacept (Arcalyst®)[11] for the treatment of chronic active gouty arthritis and canakinumab

[7] EULAR Standing Committee for International Clinical Studies Including Therapeutics. "EULAR evidence based recommendations for gout. Part I: Diagnosis; Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)." Ann Rheum Dis. 2006 Oct;65(10):1301-24.
Chen LX and Schumacher HR, "Gout: can we create an evidence-based systematic approach to diagnosis and management?" Best Pract Res Clin Rheumatol. 2006 Aug;20(4):673-84.
[8] Malawista SE et al., "Crystal-induced endogenous pyrogen production. A further look at gouty inflammation." Arthritis Rheum. 1985 Sep;28(9):1039-46.
[9] Martinon F et al., "Gout-associated uric acid crystals activate the NALP3 inflammasome." Nature 2006 Mar 9;440(7081):237-41.
[10] So A, et al., "A pilot study of IL-1 inhibition by anakinra in acute gout," *Arthritis Research & Therapy* 2007, 9:R28.
[11] Terkeltaub R et al., "The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo controlled, monosequence crossover, nonrandomised, single-blind pilot study," Ann Rheum Dis 2009;68:1613–1617.

(Ilaris®)[12] for the treatment of acute gout flares have also been published. Thus to date, IL-1 inhibition has been explored for both acute and chronic treatment in gout.

The indication proposed in the canakinumab application is "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." The proposed indication requires evaluation of issues beyond the safety and effectiveness of canakinumab for the treatment of acute gout attacks to include:

- The intended patient population (i.e., are patients who have failed either NSAIDs or colchicine considered refractory?) and whether the risk-benefit profile of the product in this population is acceptable;
- The proposed indication's implication regarding prophylactic-use (i.e., chronic-use) benefits and whether the risk-benefit profile of the product in this usage scenario is acceptable.

We ask that the Committee assess the information that follows with these considerations in mind.

Summary of Product Information

The Molecule and Mechanism of Action

Canakinumab drug substance is a humanized IgG1κ monoclonal antibody that binds with high affinity to human interleukin (IL)-1β, thereby preventing binding of endogenous IL-1β to its cognate receptor, IL-1 receptor (R) Type I. IL-1β is a member of the IL-1 family and, together with IL-1α and IL-1receptor antagonist (Ra), is one of the ligands of IL-1R Type I.

Upon binding of IL-1β, IL-1R Type I associates with its co-receptor, IL-1 receptor accessory protein (RAcP) and initiates a transduction cascade resulting in the upregulation of inflammatory cytokines such as IL-6. IL-1β is a tightly controlled inflammatory cytokine present mostly in monocytes, macrophages, dendritic cells, B lymphocytes and NK cells. It requires cleavage by caspase-1 for activation and extracellular release. Caspase-1 is a component of the NALP3 (cryopyrin) inflammasome which when genetically mutated can render a constitutive activation of IL-1β.

Canakinumab is expressed in SP2/0-AG14 murine cells with a typical antibody structure consisting of two identical heavy chains, two identical light chains, and (b) (4) disulfide bridges. Canakinumab has a molecular weight of approximately 145 kDa (after deglycosylation), and a pI range of (b) (4). There is a typical heterogeneity at the heavy chain N-terminus due to (b) (4) to pyroglutamic acid and at the heavy chain C-terminus due to (b) (4) of the C-terminal lysine.

[12] So A et al., "Canakinumab for the Treatment of Acute Flares in Difficult-to-Treat Gouty Arthritis." Arthritis & Rheum 2010 Oct; 62(10):3064–3076.

Glycosylation is [redacted]. Heavy chain and glycosylation characteristics lead to [redacted] that are adequately controlled and do not impact the activity of canakinumab. Canakinumab showed no ability to generate antibody-dependent cell cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) responses despite its Fc heavy chain component. Canakinumab does not bind to IL-1α and IL-1Ra. Therefore, its mechanism of action is associated with IL-1β binding.

The potency assay is a proprietary reporter gene assay using [redacted] which are stably transfected with a reporter construct in which the [redacted] of the luciferase gene. It is a relative and indirect measure of the ability of canakinumab to inhibit IL-1β binding to IL-1R Type I.

Canakinumab drug product is supplied as a sterile, preservative free, lyophilized powder to be reconstituted with 1.0 mL preservative free water for injection (WFI). When reconstituted, the final formulation contains 150 mg/mL canakinumab, [redacted] histidine HCl, [redacted] sucrose, and [redacted]% (m/V) polysorbate 80, at a pH of 6.5. Each vial is for single use and packaged in a single carton.

The Pharmacology/Toxicology Program

The pharmacology and toxicology evaluation for canakinumab included general toxicity, reproductive toxicity, and juvenile toxicity studies.

The general toxicology studies were performed in marmosets because canakinumab was shown to bind to human and marmoset IL-1B with similar affinities (IC_{50} values were 35 and 95 pM in human and marmosets respectively). The 26-week IV bolus repeat dose toxicology study in marmosets that received doses up to 100 mg/kg administered twice per week and two 13-week subcutaneous toxicology studies in marmosets that received doses up to 150 mg/kg administered twice per week identified no conclusive target organs of toxicity. There was no evidence of immunosuppression (e.g. infections or malignancies) in these studies.

In reproductive and developmental toxicity studies in marmosets, there was no evidence of teratogenicity; however, there was some evidence of treatment-related developmental delays (i.e., bent/kinked tail at the high dose (150 mg/kg) in several fetuses and incomplete vertebral ossification at all doses). The results also suggested a treatment-related reduction in reproductive performance indicated by reduced numbers of fetuses per litter and placental weights at the HD.

Additional reproductive and juvenile toxicity studies were conducted in mice using a murine surrogate of canakinumab. No toxicity findings were noted in fertility studies in mice. In the teratology study in mice, there were increased incidences of incomplete ossification of the parietal bones and frontal bones. A pre- and post-natal development study was conducted in mice. Two HD (150 mg/kg) dams were found dead; histopathology examination showed splenic enlargement and lymphoid hyperplasia in both dams. The histopathology examination of the F_1 adults showed a treatment-related

increase in the incidence of histiocytosis in the mandibular and mesenteric lymph nodes. No toxicity findings were noted in the juvenile study in mice using this surrogate antibody. The test article was found to cross placental barrier, however, not known whether it is secreted in milk.

Carcinogenicity studies were not conducted for canakinumab because it is not pharmacologically active in rodents and a carcinogenicity study in marmosets is not feasible. There was one case of a uterine adenoma in the 6-month IV study in the marmosets. IL-1beta is known to modulate estrogen and uterine tumors are known to occur from endocrine disturbances. So, the finding might be test article related. The carcinogenic risk might be addressed through post-marketing surveillance. Further, the product label might be revised to include a balanced description of the literature information available to address the carcinogenic potential of canakinumab.

The Clinical Pharmacology of Canakinumab

The currently recommended subcutaneous dose of ILARIS is 150 mg for CAPS patients with body weight greater than 40 kg. For CAPS patients with body weight between 15 kg and 40 kg, the recommended dose is 2 mg/kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. ILARIS is administered every eight weeks as a single dose via subcutaneous injection for CAPS indication. It is proposed to be administered as single 150 mg dose subcutaneously in gouty arthritis patients.

Pharmacokinetics

Bioavailability

The absolute bioavailability of subcutaneous canakinumab in CAPS and Gouty arthritis patients was estimated to be approximately 60%. Exposure parameters (such as AUC and Cmax) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion or from 150 to 300 mg as subcutaneous injection.

Absorption

The peak serum canakinumab concentration (Cmax) of 16 ± 3.5 µg/mL occurred approximately 7 days after subcutaneous administration of a single, 150-mg dose subcutaneously in adult CAPS patients. Canakinumab absorption has been found to be negatively related to age and the median times to reach Cmax (Tmax) ranged from 5 to 14 days across all studies in gouty arthritis patients with Tmax measures.

Distribution

Canakinumab volume of distribution (Vss) is positively related to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg and 7.76 liters in a typical gouty arthritis patient of body weight 93 kg.

Elimination

The elimination characteristics are similar between CAPS and gouty arthritis patients. Clearance is positively related to body weight and negatively related to albumin. In CAPS patients, the clearance of canakinumab (CLD) was 0.17 ± 0.012 L/d for a bodyweight of 70 kg and an average serum albumin of 43 g/L. The terminal half-life was 26 days. In gouty arthritis patients, the clearance of canakinumab (CLD) was 0.229 ± 0.0072 L/d for a bodyweight of 93 kg and an average serum albumin of 43 g/L. The terminal half-life was 25.6 days.

Pharmacokinetics in specific populations

Pediatrics
Time to peak concentrations of canakinumab ranged between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric CAPS patients. The terminal half-life ranged from 22.9 to 25.7 days, comparable to the pharmacokinetic properties observed in adults.

Geriatric population
Based on the population PK analysis, age was identified as a covariate only for drug absorption rate from the subcutaneous injection site but not for other pharmacokinetic parameters such as clearance and volume of distribution. Therefore, no change in drug exposure was observed between patients ≥65 years of age and adult patients <65 years of age.

Hepatic Impairment
No formal studies were conducted to examine the effects of hepatic impairment on canakinumab PK.

Renal Impairment
No formal studies were conducted to examine the effects of either renal impairment on canakinumab PK.

Summary of the Clinical Development Program

Regulatory Background

In November 2009, the FDA and the applicant held an end-of-phase 2 meeting where the clinical development program for the indication for treatment of gout as well as pertinent efficacy endpoints for Phase 3 trials were discussed. The applicant proposed two co-primary endpoints: (1) pain assessments on the Visual Analogue Scale (VAS) at 72 hours

post-dose and (2) assessment of time to a new gouty arthritis flare. The FDA accepted the two proposed co-primary endpoints but also recommended including efficacy measurements at earlier time points (24 hours and 48 hours) and analysis of proportions of patients with meaningful pain reductions (i.e. 50% pain reduction and an assessment of time to complete resolution of pain). Given the proposed number of secondary endpoints, the FDA recommended employing statistical correction methods for multiple comparisons. Dose ranging and the choice of dose for the Phase 3 trials were not specifically discussed during the EOP2 meeting.

The proposed indication for this supplemental Biologic License Application (sBLA) was discussed at the end-of-phase 2 meeting in November 2009 and a pre-sBLA meeting in June 2010. The applicant's initial proposal for the indication was "for treatment and prevention of acute gout flares in patients for whom NSAIDs and/or colchicine are not tolerated or are ineffective." Given that the data available for treatment of acute gout flares included only treatment "on demand" and no relevant long term data for prevention of flares, FDA disagreed with the applicant's initial proposal for the indication. During the pre-sBLA meeting the applicant proposed including the indication of "delay in subsequent flares" instead of "prevention." The FDA conveyed that a more appropriate indication based on the available data would be "for treatment of acute gout flares in patients for whom NSAIDs and/or colchicine are not tolerated or are ineffective."

At the time of submission of this supplemental Biologic License Application, the applicant proposed the following indication:

"Treatment of gouty arthritis attacks. ILARIS has also been shown to extend the time to next attack and reduce the frequency of subsequent attacks".

On April 21, 2011, 2 months into the review cycle, the applicant modified their proposed indication to the following:

"ILARIS (canakinumab) is an interleukin-1β 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."

Summary of clinical studies in gout

The clinical development program for canakinumab was designed to investigate the product's properties in both treatment of acute gout flares and treatment of intercritical gout for amelioration of gout flares upon initiation of urate-lowering therapy. A summary of the design features of the trials that comprised the canakinumab development program is shown in Table 2.

After the first Phase 1 trial (A2212) demonstrated the favorable effect of intravenous treatment with 10 mg/kg canakinumab on pain assessments in patients with an acute flare

of gouty arthritis, two dose-ranging trials were conducted to investigate: (1) the effect of canakinumab on treatment of acute gout flares (H2255) and (2) the effect of canakinumab on amelioration (i.e., prophylaxis) of acute gout flares upon initiation of the urate-lowering agent allopurinol (H2251). While Phase 3 trials were conducted to further evaluate the effect of canakinumab in the acute treatment of gout flares, further studies investigating the effect of canakinumab on prophylaxis of gout flares have not yet been conducted. The data from the Phase 2 dose-ranging trial with allopurinol (H2251) and its extension (H2251E1) will be discussed in the review of safety, where pertinent.

The development program for treatment of acute gouty arthritis flare includes the aforementioned Phase 2 dose-ranging trial (H2255); two Phase 3 trials of identical design (H2356 and H2357) to compare canakinumab 150 mg administered subcutaneously (s.c.) and triamcinolone acetonide 40 mg administered intramuscularly (i.m.) as a single injection for acute treatment of gouty arthritis flare; and two extensions of the Phase 3 trials (H2356E1 and H2357E1).

Table 2: Clinical development program for canakinumab in gout

Study Objectives Design; Duration;	Dosage Regimen; Route of Administration	Number of Subjects No. of Study Sites	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1				
Protocol CACZ885A2212 Multicenter, randomized, double-blind, double-dummy, active-controlled, single dose trial to assess PK and preliminary efficacy. 1. Assess the effect of single intravenous (i.v.) 10 mg/kg dose of canakinumab compared to single dose of 12 mg i.v. dexamethasone on the Likert scale response in patients with acute gout.	Canakinumab 10 mg/kg as a single intravenous (IV) infusion administered over 2 hours and dexamethasone-matching placebo OR dexamethasone 12 mg as a single infusion administered over 30 minutes and canakinumab-matching placebo.	Planned N=44. 4 sites: U.S. (2), Switzerland (1), U.K. (1). Study was terminated for observed efficacy after 3 subjects in each group completed the treatment.	Adults ≥ 18 years with acute gouty arthritis, scoring over 40 on the 0-100 VAS pain scale.	Patient assessment of pain according to VAS 0-100 mm and Likert scale.
Phase 2 for treatment of acute gout flare				
Protocol ACZ885H2255 Adaptive, dose-ranging, multi-center, single-blind, double-dummy, active-controlled trial. 1. Determine the target dose of canakinumab for treatment of acute flares in gout patients who are refractory or contraindicated to NSAIDs and/or colchicine. The target dose was to be the dose that leads to the same efficacy as the comparator, triamcinolone acetonide 40 mg i.m. 2. Assess the efficacy, safety, and PK/PD of canakinumab administered at a range of doses. Duration of observation: 8 weeks.	Trial Arms: - canakinumab 10 mg subcutaneously (s.c.) once on Day 1; - canakinumab 25 mg s.c. once on Day 1; - canakinumab 50 mg s.c. once on Day 1; - canakinumab 90 mg s.c. once on Day 1; - canakinumab 150 mg s.c. once on Day 1; - triamcinolone acetonide 40 mg i m. once on Day 1.	N=200 10 mg-- N=28; 25 mg-- N=29; 50 mg-- N=29; 90 mg-- N=29; 150 mg-- N=28; triamcinolone -- N=57. 63 sites worldwide, including 27 sites in U.S.	Adults age ≥ 18 years who met the ACR 1977 preliminary criteria for the classification of acute arthritis of primary gout, with history of at least 1 gout flare prior to the Screening Visit, and presence of acute gout flare for no longer than 5 days.	1. Pain intensity measured using VAS 0-100 mm and 5-point Likert scale. 2. Recurrence of acute gout flare.
Phase 3 for treatment of acute gout flare				
Protocol ACZ885H2356 Multi-center randomized, double-blind, double dummy, active-controlled trial of treatment and prevention of gout flares in patients with frequent flares for whom NSAIDs and/ or colchicine are contraindicated, not tolerated, or ineffective. 1. Assess whether canakinumab 150 mg s.c. was superior to triamcinolone acetonide 40 mg i.m. with respect to patient's assessment of gout pain intensity and the time to the first new gout flare. 2. Assess safety and multiple secondary efficacy endpoints, PK and immunogenicity. Duration of observation: 12 weeks.	Canakinumab 150 mg s.c. on Day 1 or traimcinolone acetonide 40 mg i m. on Day 1. All subjects could receive re-treatment on demand no sooner than 14 days since the previous dose of the study medication.	N=230 115 subjects randomized to canakinumab group 115 subjects randomized to triamcinolone group 57 sites worldwide; all outside U.S.	Adults age ≥ 18 years who met the ACR 1977 preliminary criteria for the classification of acute arthritis of primary gout, with history of at least 1 gout flare prior to the Screening Visit, and duration of the acute gout flare for no longer than 5 days.	Two co-primary efficacy endpoints: 1. Improvement of pain measured on VAS 0-100mm analyzed by analysis of covariance AND 2. Time to the first new gout flare depicted with Kaplan-Meier curves and analyzed using a Cox proportional hazard regression model

Study Objectives Study Design; Duration	Dosage Regimen; Route of Administration	Number of Subjects; No. of Study Sites	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 3 for treatment of acute gout flare				
Protocol ACZ885H2357 Multi-center randomized, double-blind, active-controlled trial of treatment and prevention of gout flares in patients with frequent flares for whom NSAIDs and/ or colchicine are contraindicated, not tolerated, or ineffective. 1. Assess whether canakinumab 150 mg s.c. was superior to triamcinolone acetonide 40 mg i.m. with respect to patient's assessment of gout pain intensity and the time to the first new gout flare. 2. Assess safety, multiple secondary efficacy endpoints, PK, and immunogenicity. Duration of observation: 12 weeks.	Canakinumab 150 mg s.c. on Day 1 or traimcinolone acetonide 40 mg i m. on Day 1. All subjects could receive re-treatment on demand no sooner than 14 days since the previous dose of the study medication.	N=226 112 subjects randomized to the canakinumab group 114 subjects randomized to the triamcinolone group 75 sites including 64 US sites.	Adults age $\geq$ 18 years who met the ACR 1977 preliminary criteria for the classification of acute arthritis of primary gout, with history of at least 1 gout flare prior to the Screening Visit, and duration of the acute gout flare for no longer than 5 days.	Two co-primary efficacy endpoints: 1. Improvement of pain measured on VAS 0-100mm analyzed by analysis of covariance AND 2. Time to the first new gout flare depicted with Kaplan-Meier curves and analyzed using a Cox proportional hazard regression model
Extension studies of the Phase 3 trials for treatment of acute gout flare				
Protocol ACZ885H2356E1 Multicenter, double-blind, double-dummy, active -controlled clinical extension study. 1. Assess the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m. 2. Evaluate all efficacy endpoints and safety parameters, PK, and immunogenicity as in the core H2356 trial. Duration of observation: 12 weeks.	Patients from the core trial CACZ885H2356 were treated in this extension study for any new gouty arthritis flare with the same treatment as assigned in the core trial.	N=175 90 subjects continued in the canakinumab group 85 subjects continued in the triamcinolone group 48 sites worldwide, no US sites.	As per core trial	Assessment of long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i m. in patients randomized in the core study CACZ885H2356
Protocol ACZ885H2357E1 Multicenter, double-blind, double-dummy, active -controlled clinical extension study. 1. Assess the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m. 2. Evaluate all efficacy endpoints and safety parameters, PK, and immunogenicity as in the core H2356 trial. Duration of observation: 12 weeks.	Patients from the core trial CACZ885H2357 were treated in this extension study for any new gouty arthritis flare on demand with the same treatment as assigned in the core study.	N=160 84 subjects continued in the canakinumab group 76 subjects continued in the triamcinolone group 65 sites including 53 U.S. sites.	As per core trial	Assessment of long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i m. in patients randomized in the core study CACZ885H2357

Study Objectives Study Design; Duration;	Dosage Regimen; Route of Administration	No of Subjects; No. of Study Sites	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 2 for prevention of acute gouty attack upon initiation of allopurinol treatment				
Protocol CACZ885H2251 Dose-ranging, multi-center, double-blind, double-dummy, active-controlled trial to evaluate canakinumab for prophylaxis of signs and symptoms of acute flares in chronic gout patients initiating allopurinol therapy (≤ 1 month). 1. Determine the target dose of canakinumab that leads to at least comparable efficacy as colchicine (0.5 mg once daily) with respect to the mean number of gout flares occurring during 16 weeks after randomization. 2. Evaluate safety, tolerability, immunogenicity, and PK/PD of different doses and regimens of canakinumab in patients with chronic gout during 24 weeks after randomization. Duration of observation: 24 weeks.	Trial arms: -canakinumab 25 mg s.c. once on Day 1; -canakinumab 50 mg s.c. once on Day 1; -canakinumab 100mg s.c. once on Day 1; -canakinumab 200mg s.c. once at Day 1; -canakinumab 300mg s.c. once at Day 1; -canakinumab 50 mg s.c. on Days 1 and 29, then 25 mg s.c. on Days 57 and 85; or -colchicine 0.5 mg orally once daily for 16 weeks.	N=432 Canakinumab: 25 mg group- N=55, 50 mg group- N=54, 100 mg group- N=54, 200 mg group- N=54, 300 mg group- N=53, 150 mg split dose (4 injections Q4 weeks) group- N=54; Colchicine 0.5 mg group- N=108. 88 sites including 20 U.S. sites.	Adults of ≥ 18 years of age with history of at least 2 gout flares in the preceding year, eligible to initiate urate-lowering therapy, with confirmed diagnosis of gout according to the ACR 1977 preliminary criteria for the classification of arthritis of primary gout and no active gout flare at study entry.	Mean number of gout flares during the 16 week observation period.
Protocol CACZ885H2251E1-open-label extension of trial H2251E1 Multicenter, open-label extension study to CACZ885H2251. 1. Evaluate the safety and tolerability of "on demand" canakinumab treatment for acute flares of gouty arthritis in patients who were previously administered canakinumab or colchicine upon initiation of allopurinol treatment. Group A- received canakinumab both in the core trial and in the extension study; Group B- received canakinumab in the core trial only and no treatment in the extension study Group C- received colchicine in the core trial and received canakinumab in the extension study Group D- received colchicine in the core trial and no treatment in the extension study Duration of observation: 24 weeks.	All patients were eligible for treatment with canakinumab 150 mg s.c. on demand if they developed a gout flare.	N=341 Treatment groups were defined at the end of the study: Group A- N=75; Group B- N=181 Group C- N=25; Group D- N=60	As per core trial	Not applicable

Source: Reports for trials H 2212, H2255, H2356, H2356E, H2357, H2357E, H2251, H2251E.

The key inclusion criteria for enrollment were similar across trials H2255, H2356, and H2357. Enrolled in these trials were adults 18-85 years of age who met the ACR 1977 preliminary criteria for the classification of acute arthritis of primary gout with onset of current acute gout flare within 5 days prior to randomization and with baseline pain intensity in the target joint of ≥ 50 mm on the Visual Analogue Scale (VAS 0-100mm). In addition, patients enrolled in the Phase 3 trials had to have a history of ≥ 3 gout flares within the 12 months prior to randomization and evidence of contraindication (absolute or relative), or intolerance, or lack of efficacy for NSAIDs, or colchicine, or both. While

the applicant's initial intent was to enroll only patients who could not use both NSAIDs and colchicine, difficulty in recruitment prompted protocol amendments to allow enrollment of patients who could not use either NSAIDs or colchicine. If on urate-lowering therapy, stable dose and regimen with no changes in therapy for 2 weeks prior to randomization was required and subjects were expected to remain on a stable regimen for the duration of the trial.

The key exclusion criteria listed secondary gout (e.g. chemotherapy-, lead-, and transplant-related), evidence of any infections (including risk factors for tuberculosis and chronic viral infections), live vaccinations within 3 months prior to randomization, history of malignancies, significant medical conditions precluding from trial participation, and a number of restrictions to medication use before and during the acute flare of gouty arthritis as described below:

> i) corticosteroids:
> - a dose of $\geq$ 10 mg of prednisolone or equivalent within 24 hours before screening for any indication
> - chronic corticosteroid treatment (defined as a prednisolone dose of $\geq$ 5 mg/ day or equivalent taken for >28 days)
> - intra-articular corticosteroids into the most affected joint within 14 days before screening
> - intra-muscular corticosteroids for any indication within 14 days before screening;
>
> ii) narcotics (opiates and tramadol) within 24 hours before screening;
>
> iii) acetaminophen (paracetamol) within 4 hours before screening;
>
> iv) topical ice or cold packs within 6 hours before screening;
>
> v) chronic opiate treatment within 14 days before screening;
>
> vi) any IL-1 blocker, TNF-inhibitor, other biologic or investigational drug within 30 days or 5 half-lives before randomization, whichever is longer;
>
> vii) NSAIDs (including Cox-2 inhibitors), and other pain medications as defined below:
>
> - any ibuprofen within 4 hours before screening or > 400 mg within 8 hours before screening (i.e., 0-400 mg ibuprofen allowed between 4-8 hours before screening)
> -any acetaminophen within 4 hours before screening or > 1 g within 24 hours before screening
> -any aspirin within 4 hours before screening or > 600 mg within 24 hours before screening
> -over-the-counter analgesic aspirin-based or paracetamol-based combination medications: any number of tablets within 4 hours before screening or > 2 tablets within 24 hours before screening
> - any diclofenac formulation within 8 hours before screening or > 50 mg of diclofenac within 24 hours before screening
> - any naproxen formulation within 12 hours before screening or > 500 mg of naproxen within 24 hours before screening
> - cox-2 inhibitors within 48 hours before screening
> - other NSAIDs within 24 hours before screening;
>
> viii) colchicine >1.2 mg within 24 hours before screening.

The Phase 2 dose-ranging trial H2255 investigated the effect of single doses of canakinumab ranging from 10 mg to 150 mg administered subcutaneously (s.c.) in

comparison with a single dose of triamcinolone acetonide 40 mg administered intramuscularly (i.m.) on pain assessments in acute gouty arthritis flare over a period of 8 weeks. The objective of this trial was to identify a target dose for canakinumab s.c. that was comparable to 40 mg triamcinolone acetonide i.m. at 72 hour post-dose; however, such a dose could not be identified, as all doses tested appeared to be superior to triamcinolone for the endpoint of pain on VAS.

As shown in Table 3 below, a statistically significant difference in VAS (0-100mm) pain intensity scores between 150 mg canakinumab s.c. and 40 mg triamcinolone acetonide i.m. was observed at 72 hours post-dose (-19.2 mm). Over the observation period of 8 weeks, 3.6-13.8% subjects treated with different doses of canakinumab developed new flares compared to 45.4% subjects treated with triamcinolone acetonide. Based on the observed treatment effect, the Phase 3 trials (H2356 and H2357) were designed by the applicant to confirm superiority of 150 mg canakinumab s.c. over 40 mg triamcinolone acetonide i.m. for the change from baseline VAS pain score (0-100mm) in the most affected joint and occurrence of new flares. However, superiority to triamcinolone was not an expectation of the Agency with respect to the objectives of the Phase 3 program. Although dose selection was not specifically discussed in pre-submission meetings, the dose-ranging efficacy data in H2255 and the safety signals to be discussed later in this document give rise to questions regarding whether lower doses could have produced adequate efficacy with a better safety profile.

Table 3: Selected results from Study H2255

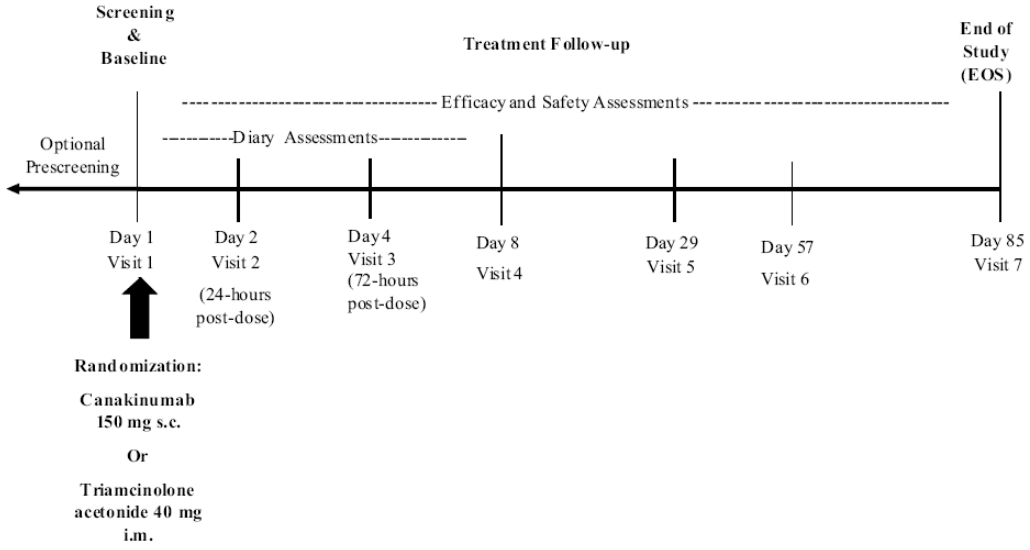
Selected Dose-Ranging Efficacy Results from Study H2255 in Acute Gout						
	Can. 10 mg N = 28	Can. 25 mg N = 29	Can. 50 mg N = 28	Can. 90 mg N = 29	Can. 150 mg N = 27	Triam 40 mg N = 56
Difference (c/w Triam.) in change from baseline in pain intensity (0-100 mm VAS) at Day 4 (72 hours post-dose)						
	-5.3	-3.2	-5.3	-9.4	-19.2	-
95% CI	(-15.9, 5.4)	(-13.9, 7.4)	(-16.3, 5.6)	(-20.0, 1.2)	(-30.2, -8.2)	
Odds Ratio (c/w Triam.) for physician's assessment of tenderness, swelling, and erythema of target joint at Day 4						
Tenderness	1.56	0.98	1.32	1.40	3.16	-
95% CI of OR	(0.63, 3.87)	(0.40, 2.35)	(0.53, 3.27)	(0.58, 3.37)	(1.27, 7.89)	
Swelling	2.61	1.30	1.75	1.09	2.66	-
95% CI of OR	(1.06, 6.44)	(0.55, 3.05)	(0.72, 4.26)	(0.48, 2.48)	(1.09, 6.50)	
Erythema	0.93	0.75	0.57	1.45	0.75	-
95% CI of OR	(0.33, 2.64)	(0.27, 2.08)	(0.17, 1.85)	(0.52, 4.07)	(0.26, 2.16)	
Cumulative flare rate through 8 weeks post-dose						
	3.6	10.3	3.6	13.8	3.7	45.4
95% CI	(0, 10.45)	(0, 21.43)	(0, 10.45)	(1.24, 26.34)	(0, 10.83)	(32.24, 58.55)

Source: Tables 11-5, 11-8, and 14.2.-8.1 from H2255 Clinical Study Report
Can = canakinumab; Triam = Triamcinolone

Trial H2356 was randomized, double-blind, double-dummy, active-controlled trial, where 230 patients with acute gout flares were randomized 1:1 and treated with a single injection of either 150 mg of canakinumab s.c. or 40 mg triamcinolone acetonide i.m., and then followed with efficacy and safety assessments at different time points for 12 weeks (Figure 1). Trials H2356 and H2357 were identical in their design, sample size, duration, and all planned analyses. Trial H2356 was conducted outside of United States, predominantly in Europe (41 sites), Central and South America (9 sites), Canada (5 sites),

Australia (1 site), and Asia (1 site). Trial H2357 was conducted primarily in the US (64 sites).

Figure 1: Trial schema (H2356 and H2357)



Source: Trial report H2356, H2357.

Subjects who developed new flares during the trial could be re-treated with another single dose of the trial medication according to their original treatment assignment. A "new flare" was defined in the protocol as:

> - a flare in a joint, which was not a previously affected joint (at baseline or during the study), OR
> - a flare in a joint previously affected (at baseline or during the study) after the previous flare in that joint has resolved completely.

Patients did not meet the criterion of having a new gout flare if they had increasing or renewed gout pain in an affected joint before the flare had resolved completely.

Complete resolution of a flare was originally defined in the protocols for both Phase 3 trials as improvement of pain in the affected joint to "none" on the 5-point Likert scale. When both trials H2356 and H2357 were ongoing, the applicant conducted a blinded analysis of the data which showed that many patients continued to have residual pain in the affected joints even when not experiencing flares. A subsequent amendment to both protocols changed the definition of the complete resolution to include any of the following:

- patient's assessment of pain graded as "none" on the Likert scale,
- patient's assessment of pain graded as "mild" on the Likert scale,
- patients's assessment of pain graded as <10mm on VAS scale.

Re-treatment for new flares could be administered no sooner than 14 days following the previous treatment. Use of rescue medication was not allowed before the first 6 hour post-dose efficacy assessment and within 4 hours prior to any efficacy assessment during

the first 7 days post-baseline treatment (12-, 24-, 48-, 72 hours and 4-, 5-, 6-, and 7-days). The following rescue medications were allowed within 7 days after randomization or after re-treatment:

- acetaminophen (paracetamol) 500 mg to a maximum of 1 g/dose or 3 g/day,
- codeine 30 mg p.r n. to a maximum of 30 mg/ dose or 180 mg/day,
- oral prednisone to a maximum of 30 mg p.r n. per day for 2 days followed by up to 20 mg p.r.n. per day for 3 subsequent days.

Efficacy endpoints in H2356 and H2357

The two co-primary efficacy analyses pre-specified in H2356 and H2357 were:

- mean difference between treatment groups in the patient's assessment of gout pain intensity in the joint most affected at baseline at 72 hours post-dose (on a 0-100 mm VAS), analyzed using an analysis of covariance with treatment group, baseline VAS score, and BMI at baseline as covariates, AND
- difference between treatment groups for time to a new gout flare analyzed using a Cox proportional hazard regression model with treatment and BMI at baseline as explanatory variables.

In this setting, "co-primary" is used to indicate that success with *both* analyses is required.

Although experience with clinical trials of products for the acute treatment of gout is limited, patient assessment of pain using either a VAS or Likert scale has precedent in the literature[13] and in other trials used to support approval for acute treatment of gout flares.[14] The endpoint of time to new gout flare has not previously been used to support approval of a product for either the acute treatment of gout indication or a chronic treatment (prophylaxis of gout) indication.

Both protocols pre-defined that the primary analysis would be done on the imputed data. Missing data were to be imputed using the Last Observation Carried Forward (LOCF) method for the VAS pain assessment primary endpoint at 72-hour post-dose if the 48 hour post-dose assessment was available. If the 48 hour assessment was not available, no missing value was imputed.

There were two sets of secondary endpoints (Table 4, below). The multiplicity corrections with Bonferroni-Holm were planned and conducted for the endpoints included in the first set. The Bonferroni-Holm method is a step-down procedure which starts with the smallest p-value and rejects it if the p-value is no greater than α/k where k is the number of variables yet to be tested and $\alpha=0.05$. If the first ordered hypothesis is rejected, the procedure examines the next hypothesis in the sequence, and so on. The trials' protocols did not provide for multiplicity corrections for other secondary endpoints.

[13] Ahern MJ et al., "Does colchicine work? The results of the first controlled study in acute gout." Aust NZ J Med 1987; 17:301-304

[14] Colcrys prescribing information, Section 14:
http://www.colcrys.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf

Table 4: Secondary efficacy endpoints for trials H2356 and H2357

The first set of the secondary endpoints:
- time to complete resolution of pain in the joint most affected at baseline (assessed as "none" on Likert scale), - time to 50% reduction of baseline pain intensity in the most affected joint, - proportion of patients taking rescue medication during the first week, and - SF-36v2 (acute version) physical function component score at Week 12
Other secondary endpoints:
- percentage of patients with at least 1 new gout flare during 12 weeks; - patient's assessment of gout pain intensity in the most affected joint (VAS on a 0-100 mm) over time; - patient's assessment of gout pain intensity in the most affected joint (Likert scale) - patient's global assessment of response to treatment (Likert scale); - physician's assessment of tenderness, swelling, erythema, and range of motion of the most affected joint (Likert scale); - physician's global assessment of response to treatment (Likert scale); - time to first rescue medication intake; - mean amount of rescue medication taken; - severity of each new gout flare; - change in inflammatory markers (high sensitivity C-reactive protein and serum amyloid A protein).

Source: Trial reports H2356 and H2357.

Trials H2356E1 and H2357E1 were 12 week double-blinded extensions of the controlled core trials H2356 and H2357, where patients who continued in the extension trials were treated upon development of new flares according to the same treatment assignments as in the core trials. The primary endpoint of these two identically designed extensions was assessment of long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m. in patients continuing from the respective core trials. All efficacy variables in the core trials were also evaluated and considered secondary endpoints in the E1 extension trials; no correction for multiple comparisons was planned or employed.

While not included in the original application, two interim analyses of safety data from the ongoing additional extensions of the extension trials H2356E1 and H2357E1 were submitted by the applicant on May 5, 2011 with the 120-day safety update (not included in Table 2). These second extension studies H2356E2 and H2357E2 are ongoing open-label studies where patients who completed core and E1 extensions (regardless of the randomization assignment in the core trials) were to be treated with canakinumab 150 mg subcutaneously upon demand if they developed a new flare of gouty arthritis.

Review of Efficacy

Patient Population Characteristics

Table 5 shows the baseline demographic characteristics of patients enrolled in trials H2356 and H2357. The treatment groups within each trial were generally well balanced for the baseline demographic characteristics, and the trial participants were predominantly overweight middle-aged males with the co-morbidities expected to occur in gout population. Trial H2357, conducted in the US, included more Asian and African-American patients. Of note, at baseline, the distribution of patients with concomitant stable hypertension and hypercholesterolemia was similar between the two treatment

groups in both trials. There were slightly more subjects with chronic kidney disease in the canakinumab groups in both trials.

Table 5: Baseline demographic characteristics and co-morbidities in trials H2356 and H2357

Demographics	H2356		H2357	
	Can-mab 150 mg N=113	Triam. ac. N=115	Can-mab 150 mg N=112	Triam. ac. N=114
Gender, N (%)				
Male	**101 (89)**	108 (94)	**100 (89)**	105 (92)
Female	**12 (11)**	7(6)	**12(11)**	9(8)
Race, N (%)				
Caucasian	**93 (82)**	96 (83.5)	**74 (66)**	80(70)
Black/African Am.	**0**	0	**26 (23)**	24(21)
Asian	**3(3)**	3 (3)	**10 (9)**	9(8)
Native American	**1(0.9)**	1(0.9)	**0**	0
Pacific Islander	**0**	0	**0**	0
Other	**16(14)**	15 (13)	**2(2)**	1(0.9)
Age (years), mean (SD)	**54 (11)**	55(11)	**51(12)**	53(12)
Weight (kg), mean (SD)	**96 (16)**	97 (18)	**101 (21)**	98 (20)
Co-morbid conditions, N(%)				
Hypercholesterolemia	**28 (25)**	35 (30)	**27 (24)**	29 (25)
On lipid-lowering treatments	**16 (14)**	15(13)	**23(21)**	24(21)
Obesity	**65(58)**	66(57)	**52(46)**	57 (50)
Chronic kidney disease	**20(18)**	13(11)	**13(12)**	9(8)
Current or prior symptoms of heart failure	**7(6)**	5(4)	**1(0.9)**	0
Diabetes	**15(13)**	11(10)	**19(17)**	21(18)
Stable hypertension	**78(69)**	82(71)	**53(47)**	57 (50)
Stable coronary artery disease	**12(11)**	13(11)	**11(10)**	8(7)

Source: applicant's Table 3-3 of Clinical Summary of Efficacy.

As shown in Table 6 below, the enrolled patients had an average of 6-7 recurrent attacks of gouty arthritis within the previous year. The disease characteristics were balanced between the treatment groups within each trial but somewhat differed between the two trials. Fewer patients with tophaceous gout were enrolled in trial H2357 (18% in the canakinumab group and 20% in the triamcinolone acetonide group), compared to trial H2356 (39% in both the canakinumab group and the triamcinolone acetonide group). Similarly, about half of the subjects enrolled in trial H2356 and one third of the subjects enrolled in H2357 were receiving urate-lowering therapy, which included mainly allopurinol treatment and a small subgroup of patients treated with febuxostat.

In trial H2357, the majority of patients found NSAIDs ineffective (78% in the canakinumab group and 73% in the triamcinolone group), whereas only about 15-17% patients in each treatment group had contraindications or could not tolerate NSAIDs. In trial H2356, conducted outside the US, in the canakinumab-treated group, 54% patients had contraindications and 39% patients were intolerant to NSAIDs, though again, the majority (66% patients) experienced lack of efficacy. With regard to colchicine therapy, more canakinumab-treated patients in trial H2357 experienced lack of efficacy from colchicine (39%) compared to canakinumab-treated patients in trial H2356 (12%).

Of note, only a minority of patients in both trials had contraindications to, was intolerant of, or did not benefit from both colchicine and NSAIDs: in trial H2356, 19% in the canakinumab group and 33% in the triamcinolone acetonide group; and in trial H2357,

48% in the canakinumab group and 40% in the triamcinolone acetonide group. Combined with the fact that only about one fifth of patients in trial H2357 and slightly over one third of the patients in trial H2356 had tophaceous gout, the study population does not appear to be representative of those with chronic tophaceous gout or intolerant to the majority of the available therapies, but rather a less refractory group who were intolerant to either NSAIDs or colchicine with the majority of patients experiencing lack of efficacy from NSAID treatment.

Overall, the characteristics of the acute gout flare at baseline were as expected from a typical gout attack; the majority of subjects had monoarticular involvement with an average VAS pain score above 70 mm, visible swelling and erythema, and elevated C-Reactive Protein (CRP) (see Table 6 below).

Table 6: Baseline disease characteristics in trials H2356 and H2357

Disease characteristics	H2356		H2357	
	Can-mab N=113	Triam. ac. N=115	Can-mab N=112	Triam. ac. N=114
Flares in the past year, mean (SD)	**6.5(5)**	7(5)	**6.5 (6)**	6(4)
Known presence of tophi, N (%)	**44(39)**	45(39)	**20(18)**	23 (20)
Current user of urate-lowering therapy, N(%)				
Yes	**57 (50)**	63(55)	**32(29)**	40(35)
Allopurinol	**57 (50)**	62(54)	**26(23)**	33(29)
Febuxostat	**0**	1 (1)	**2(2)**	2(2)
Probenecid	**0**	0	**1(1)**	0
Pegloticase	**0**	0	**0**	0
Other	**2(2)**	0	**7(6)**	7(6)
N (%) Subjects with contraindications to				
NSAIDs	**61 (54)**	50 (43)	**17 (15)**	19 (17)
Colchicine	**10 (9)**	12(10)	**12(11)**	2(2)
Both	**7(6)**	9(8)	**5(4)**	0
N (%) Subjects with intolerance to				
NSAIDs	**44(39)**	40 (35)	**17(15)**	17(15)
Colchicine	**16(14)**	20 (17)	**27(24)**	25(22)
Both	**9(8)**	10(9)	**6(5)**	6(5)
N (%) Subjects with lack of efficacy from				
NSAIDs	**75(66)**	86(75)	**87(78)**	83(73)
Colchicine	**14(12)**	21(18)	**44(39)**	41(36)
Both	**10(9)**	16(14)	**36(32)**	31(27)
N (%) Subjects with contraindications to, or intolerance to, or lack of efficacy from				
NSAIDs	**107(95)**	113(98)	**97(87)**	96(84)
Colchicine	**27(24)**	39(34)	**67(60)**	59(52)
Both	**22(19)**	38(33)	**54(48)**	46(40)
Characteristics of Acute Gout Flare at Baseline				
Number of joints affected at the baseline acute gouty attack, N (%)				
1	**57(50)**	59(51)	**71(63)**	73(64)
2	**23(20)**	26(23)	**19(17)**	23(20)
3	**7(6)**	13(11)	**8(7)**	5(4)
4	**6(5)**	5(4)	**5(4)**	4(3)
>4	**20(18)**	12(10)	**9(8)**	9(8)
VAS pain score at baseline acute gouty attack, mean (SD)	**74(11)**	75(13)	**75(13)**	74(13)
****Serum uric acid level, mean (SD), mg/dl**	**8.1 (2)**	8.4 (2.3)	**8.1 (2.2)**	8.2(1.8)
Pain in the most affected joint (5-point Likert Scale*), N (%)				
Moderate	**25(22)**	27(23)	**38(34)**	35(31)
Severe	**75(66)**	74(64)	**53(47)**	61(53)
Tenderness in the most affected joint, N (%)				
Pain and patient winces	**51(45)**	50(43)	**38(34)**	39(34)
Pain and patient winces and withdraws	**42(37)**	38(33)	**58(52)**	59(52)
Swelling in the most affected joint, N (%)				
Visible	**66(58)**	72(63)	**51(45)**	51(45)
Bulging beyond the joint margins	**37(32)**	33(29)	**44(39)**	47(41)
Erythema present, N (%)	**99(88)**	96(83)	**91(81)**	95(83)
hsCRP (mg/L), Median	**13.2**	9.4	**10.2**	8.9

Source: Tables 14.1-3.1, 14.1-3.2, 14.1-3.3, 14.1-3.4, 14.1-3.5 of Study Reports H2356 and H2357, Table 4-11, of Clinical Overview

*Likert Scale for pain (none, mild, moderate, severe, extreme).

**Average baseline/D4, Tables 14.3-2.2 in trials H2356 and H2357

Patient Disposition

Patient disposition for both core and extension E1 trials is shown in Table 7 below. Overall, the proportions of patients who discontinued from each trial appeared similar between treatment arms; the observed slight proportional differences were driven by the small numbers. Although not unexpected, there was substantial subject attrition in both trials between the core and extension parts (16.5% and 17% in trial H2356 and 13% and 24% in trial H2357).

Table 7: Subject disposition in trials H2356/H2356E1 and H2357/H2357E1

Study Disposition	H2356		H2357	
	Can-mab 150 mg N=115	Triam. ac. N=115	Can-mab 150 mg N=112	Triam. ac. N=114
Entered Core Study, N (%)	**115**	115	**112**	114
Discontinued, N (%)	**6 (5)**	10(9)	**13(12)**	11(10)
Withdrawn consent	**1 (<1)**	3(3)	**6(5)**	4(3)
Lost to follow up	**3(2)**	1(<1)	**5(4)**	3(3)
Admin. Problems	**2(2)**	1(<1)	**0**	1(<1)
Adverse events	**0**	0	**1(<1)**	1(<1)
Death	**0**	1(<1)	**1(<1)**	0
Protocol deviation	**0**	0	**0**	2(2)
Unsatisfactory treatment effect	**0**	4(3)	**0**	0
Completed Core Trial, N(%)	**109 (95)**	105 (91)	**99(84)**	103(90)
Subject attrition between core and extension trials	**19 (16.5)**	20 (17)	**15 (13)**	27(24)
Entered Extension Study (E1)	**90 (78)**	85(74)	**84(75)**	76(67)
Discontinued, N (%)	**3(2)**	5 (4)	**6(5)**	4 (4)
Withdrawn consent	**0**	1(<1)	**4 (4)**	3 (3)
Lost to follow up	**2(2)**	3(3)	**1(<1)**	0
Admin. Problems	**0**	0	**0**	0
Adverse events	**0**	0	**1(<1)**	0
Death	**0**	0	**0**	0
Protocol deviation	**1(<1)**	0	**0**	0
Unsatisfactory treatment effect	**0**	1(<1)	**0**	1(<1)
Completed Extension Study (E1)	**87 (76)**	80 (70)	**78 (70)**	72(63)

Source: Tables 10-1 in Study reports H2356 and H2357, Table 14.1-1.1 Appendix 1 of Summary of Clinical Efficacy.

Efficacy Results

Primary Endpoints

As mentioned earlier, each of the Phase 3 trials included two pre-specified co-primary efficacy analyses:

- mean difference between treatment groups in the patient's assessment of gout pain intensity in the joint most affected at baseline at 72 hours post-dose (on a 0-100 mm VAS), analyzed using an analysis of covariance (ANCOVA) with treatment group, baseline VAS score, and BMI at baseline as covariates, AND
- difference between treatment groups for time to the first new gout flare, analyzed using a Cox proportional hazard regression model with treatment and BMI at baseline as explanatory variables.

In this setting, "co-primary" is used to indicate success with *both* analyses is required.

Pain Intensity on 0-100mm Visual Analog Scale (VAS)

The results of the first co-primary endpoint, the pain intensity measured on VAS at 72 hour post-dose time point estimated from the ANCOVA Least Squared (LS) means is shown in Table 8 below. In trial H2356, canakinumab treatment was associated with a 46 mm mean decrease in VAS pain intensity at 72 hours post dose, compared to the 35 mm mean decrease observed with triamcinolone treatment. In trial H2357, canakinumab treatment was associated with a 53 mm mean decrease compared to a 42 mm mean decrease with triamcinolone treatment. The difference in VAS pain intensity between the the treatment and control groups in each study was statistically significant, as shown in Table 8. As a secondary analysis, the applicant has also conducted an analysis of VAS pain intensity using a repeated measures Generalized Estimated Equations (GEE) analysis, which incorporated the time-dependent relationships between the repeated measures of VAS and provides a sensitivity analysis for the LOCF imputation. Results of the GEE analysis are consistent with those of the primary analysis.

Table 8: Pain intensity changes assessed on VAS 0-100 mm scale at 72 hours post-dose

Pain intensity (mm)	**H2356**		**H2357**		**Pooled Data from Trials H2356 and H2357**	
	Can-mab 150 mg SC N=113	**Triam. ac. 40 mg IM N=115**	**Can-mab 150 mg SC N=112**	**Triam. ac. 40 mg IM N=114**	**Can-mab 150 mg SC N=225**	**Triam. ac. 40 mg IM N=229**
VAS pain baseline mean (SD)	74(11)	75(13)	75(13)	74(13)		
Analysis by Least Squares Means with LOCF method of imputation (Primary Analysis)						
Est. LS 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)
*Est. diff to triamcinolone	-11.4		-9.8		-10.7	
One-sided p-value	p=0.0005		p=0.0018		P<0.0001	

*Est. diff. – estimated difference
**ND-not determined
Source: Table 14.2-1.3, Table 14.2-1.4 Trial report H2356; Table 14.2-1.3, Table 14.2-1.4, Trial report H2357; Table 3.2-16, Appendix 1 of Summary of Clinical Efficacy.

Improvement in VAS pain intensity was observed at all time points in both the canakinumab and the triamcinolone acetonide groups, as shown in Table 9 below. In both trials, in a descriptive sense, a larger decrease in VAS pain intensity was observed with canakinumab treatment relative to triamcinolone starting at approximately 24 hours post-dose, although in trial H2356 canakinumab treatment was associated with a larger decrease than triamcinolone starting as early as 6 hours post-dose.

Table 9: Summary statistics (observed mean VAS scores) at different time points in trials H2356 and H2357

Pain intensity (mm), Mean (SD)	H2356		H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg s.c. N=113*	Triam. ac. 40 mg i.m. N=115*	Can-mab 150 mg s.c. N=112*	Triam. ac. 40 mg i m. N=114*	Can-mab 150 mg s.c. N=225*	Triam. ac. 40 mg i m. N=229*
Baseline	73.3 (11.4)	74.8 (12.7)	74.9 (13.3)	73.6 (12.6)	74.1 (12.4)	74.2 (12.6)
6 hours post-dose, mean (SD)	57 (19)	62.4 (21.8)	58 (22.8)	59.6 (22.7)	57.5 (21)	61 (22.3)
12 hours post-dose	49.6 (20)	58 (23.6)	50 (24.9)	50.8 (24.7)	49.8 (22.5)	54.5 (24.4)
24 hours post-dose	39.9 (22.6)	52.2 (25)	38.9 (24.5)	43.8 (28.1)	39.4 (23.5)	48.1 (27)
48 hours post-dose	31.8 (22.7)	44.6 (26.7)	28.5 (24.2)	37.6 (28)	30.2 (23.5)	41.2 (27.5)
72 hours post-dose	27.2 (21.6)	39.5 (29.4)	20.9 (21.7)	30.8 (26.5)	24.1 (21.8)	35.2 (28.3)
4 days post-dose	23.7 (21.3)	35 (27)	18.1 (20.9)	26.4 (25.7)	21 (21.3)	30.9 (27)
7 days post-dose	16 (19.8)	26 (27.6)	13.3 (19.5)	18.8 (25.2)	14.7 (19.6)	22.5 (26.6)

Source: Table 14.2-3.1, Study Report H2356, Table 14.2-3.1, Study Report H2357, Table 3.2-4 Appendix 1, Summary of Clinical Efficacy.
*numbers of patients with available VAS results varied with a few missing values in each group at different time points.

Time to the first new gout flare

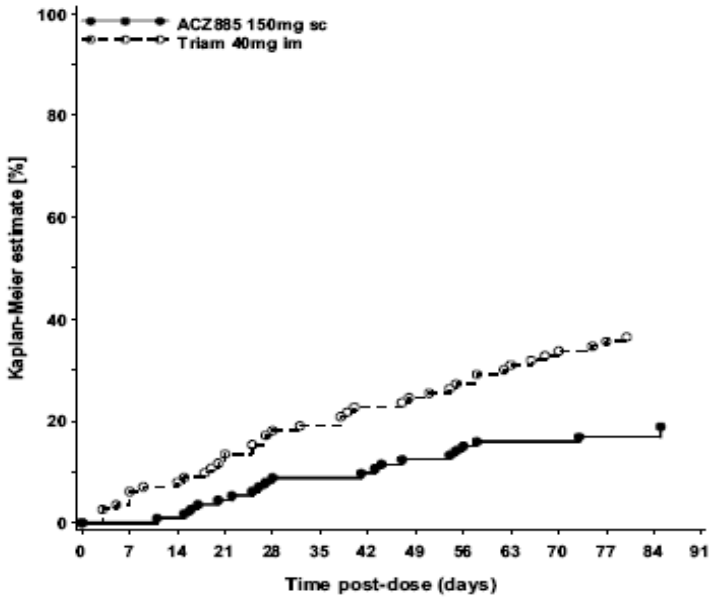
The second co-primary endpoint of the time to the first new flare was pre-specified to be analyzed using a Cox proportional hazard regression model with treatment and BMI at baseline as explanatory variables, and in each study resulted in a statistically significant difference between treatment groups for the risk of new gout flare (Table 10). Kaplan-Meier estimates at the end of the study of the proportions of patients with first new gout flare and the associated 95% confidence intervals were also provided (Table 10). Graphical representation of the Kaplan Meier curves for both trials is shown in Figure 2 and Figure 3.

Table 10: Time to first new gout flare and estimates of flare probabilities in trials H2356 and H2357

New Gout Flare	H2356		H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg SC N=113*	Triam. ac. 40 mg IM N=115*	Can-mab 150 mg SC N=112*	Triam. ac. 40 mg IM N=114*	Can-mab 150 mg SC N=225*	Triam. ac. 40 mg IM N=229*
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI)	19 (13-27)	36 (28-46)	14 (9-22)	38 (30-48)	16 (12-22)	38 (32-44)
Hazard Ratio by Cox's proportional Hazard Regression Model	0.45 (p=0.0014)		0.32 (p=0.0001)		0.38 (p<0.0001)	

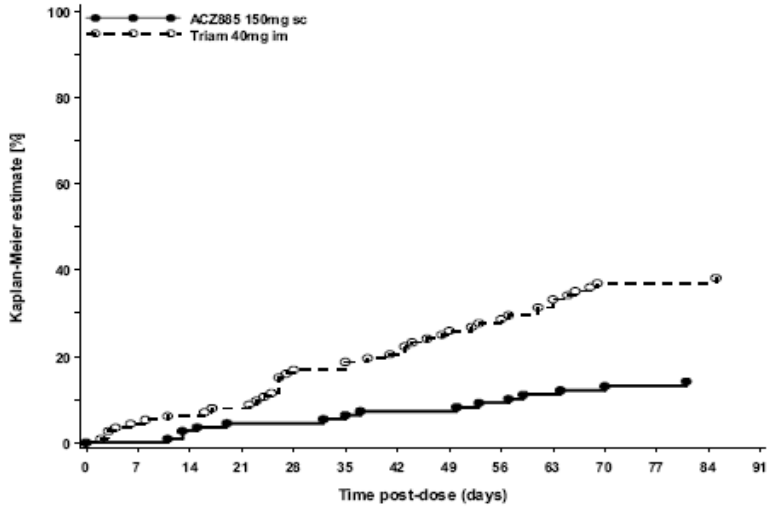
* Hazard ratio comparing canakinumab to triamcinolone was calculated using Cox's proportional hazard regression model with treatment group and BMI at baseline as covariates and nominal one-sided p-value < 0.025.
Source: Tables 14.2-1.1, 14.2-1.2, and 14.2-1.3 Trial reports H2356 & H2357; Table 4.2 of Clinical Summary of Efficacy.

Figure 2: Time to first new flare in trial H2356 at 12 weeks



Source: Figure 11.1, H2356 Clinical Study Report (CSR)

Figure 3: Time to first new flare in trial H2357 at 12 weeks



Source: Figure 11.1, H2357 CSR

Although efficacy was not the primary focus of the extension studies, a statistically significant difference between treatment groups for the risk of a new gout flare was also demonstrated in each study using the 24-week data (Table 11).

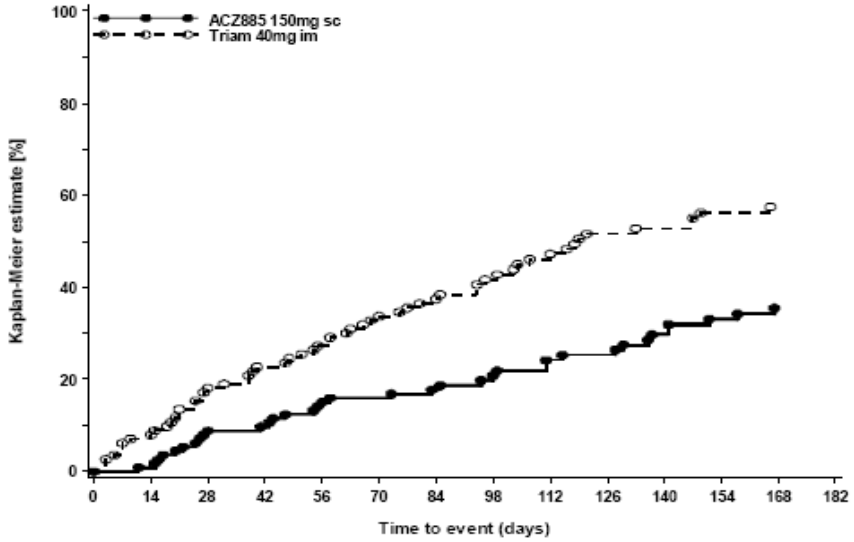
Table 11: Time to first new gout flare and estimates of flare probabilities in trials H2356/H2356E1 and H2357/H2357E1

New Gout Flare	Trial H2356		Trial H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg SC N=113*	Triam. ac. 40 mg IM N=115*	Can-mab 150 mg SC N=112*	Triam. ac. 40 mg IM N=114*	Can-mab 150 mg SC N=225*	Triam. ac. 40 mg IM N=229*
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI)	35 (27-46)	57 (48-67)	29 (21-39)	54 (44-65)	32(26-39)	56 (49-63)
Hazard Ratio by Cox's proportional Hazard Regression Model	0.48 (p=0.0003)		0.40 (p=0.0001)		0.44 (p<0.0001)	

Source: Tables 14.2-1.1 and 14.2-1.2 of Trial Reports H2356E1 and H2357E1; Tables 3.2-1 and 3.2-2 Appendix 1 of Summary of Clinical Safety.

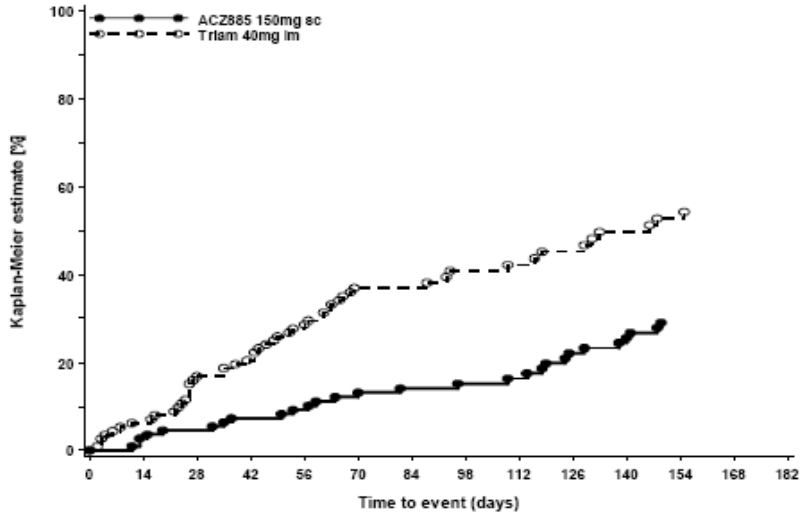
The respective graphical representations of the time to the first new flare at 24 weeks are shown in Figures 4 and 5.

Figure 4: Time to first new flare in trial H2356/H2356E1 at 24 weeks



Source: Figure 11-1, H2356E1 CSR

Figure 5: Time to first new flare in trial H2357/H2357E1 at 24 weeks



Source: Figure 11-1, H2357E1 CSR

Selected Subgroup Analyses

Patients who were intolerant, had contraindications, or experienced lack of efficacy from NSAIDs and Colchicine.

The applicant's proposed target populations for canakinumab treatment are patients who are intolerant to, or have contraindications for, or do not benefit from NSAIDs or colchicine. Table 12 shows results (for studies H2356 and H2357 pooled) of the primary efficacy endpoints for the subjects who could not use both NSAIDs and colchicine as well as for the subjects who could use either NSAIDs or colchicine. Overall, the treatment responses in the two subgroups were consistent with the results of the primary endpoints in trials H2356 and H2357. A Cox model with the terms prespecified for the

primary efficacy analysis as well as terms for study, subgroup, and the treatment-by-subgroup interaction suggested no differential effect by subgroup (as evidenced by a nonsignificant treatment-by-subgroup interaction (p=0.4 and p=0.3 for 12 weeks and 24 weeks respectively.))

Table 12: Efficacy results in patients who could not use NSAIDS and/or colchicine (H2356 and H2357 pooled)

Efficacy endpoint	**Subjects who were not able to use both NSAIDs and colchicine (intolerant to, or have contraindications for, or do not benefit from NSAIDs and colchicine)**		**Subjects who were able to use either colchicine or NSAIDs**	
	Can-mab 150 mg SC N=76	**Triam. ac. 40 mg IM N= 84**	**Can-mab 150 mg SC N=104**	**Triam. ac. 40 mg IM N=101**
LS Mean pain intensity at 72 hours post-dose, VAS 0-100 (mm) *	23	36	24	35
Between group difference at 72 h post-dose	-13 (95%CI: -21; -4.3) p=0.0015		-11 (95%CI: -18; -3) p=0.0022	
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI) at 12 weeks*	13 (8, 24)	45 (34, 56)	15 (9, 23)	34 (25, 44)
Hazard ratio by Cox's proportional hazard regression model at 12 weeks	0.24 (p<0.0001)		0.38 (p = 0.0012)	
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI) at 24 weeks*	29 (20, 42)	63 (52, 75)	30 (21, 45)	51 (40, 62)
Hazard ratio by Cox's proportional hazard regression model at 24 weeks	0.31 (p<0.0001)		0.46 (p = 0.001)	

* Statistically significant p <0.025
Source: Tables 3.3-2a2, Table 3.3-3a2, 3.3-1a1, Table 3.3-1a2, Table 3.3-2a1, Table 3.3-3a1, Table 3.3-4a1, Table 3.3-4a2, Table 3.3-5a1, Table 3.3-5a2, Table 3.3-6a1, Table 3.3-6a2 of the Appendix 1, Summary of Clinical Efficacy. Table US6.1-2a and US6.1-2b from response to information request dated 5-19-2011.

Patients treated with urate-lowering therapy vs. those who were not treated with urate-lowering therapy (ULT)

The results (for studies H2356 and H2357 pooled) of the two co-primary endpoints were examined in the subgroup of subjects who were taking the ULT (primarily allopurinol, Table 6) and in those who were not taking the ULT. The overall results of the VAS pain assessments and the estimates of time to the first new flare and flare occurrence appeared consistent with the primary analysis, however, the magnitude of the difference in flare occurrence between the canakinumab and triamcinolone treatment groups was smaller among subjects who were treated with the ULT compared to subjects who were not treated with the ULT at both 12 and 24 week time points (Table 13). The occurrence of this quantitative treatment-by-subgroup interaction is also supported by the results of a Cox model with the terms prespecified for the primary efficacy analysis as well as terms for study, subgroup, and the treatment-by-subgroup interaction. This analysis suggested a differential effect by subgroup (as evidenced by significant treatment-by-subgroup interactions (p = 0.005 and p = 0.03 for 12 weeks and 24 weeks respectively)). This

difference in the magnitude of effect could be consistent with an expectation of decreased number of flares with maintenance ULT.

Table 13: Efficacy results in the subgroups of patients treated or not treated with urate-lowering therapy (H23256 and H2357 pooled)

Efficacy endpoint	**Patients taking urate-lowering therapy**		**Patients not taking urate-lowering therapy**	
	Can-mab 150 mg SC N=89	**Triam. ac. 40 mg IM N=103**	**Can-mab 150 mg SC N=136**	**Triam. ac. 40 mg IM N=126**
LS Mean pain intensity at 72 hours post-dose, VAS 0-100 (mm) *	26	35	24	37
Between group difference at 72 h post-dose	-9 (95%CI: 15.8;1.3, p=0.01)		-13 (95%CI: 18.8; 6.5. p<0.0001	
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI) at 12 weeks	20 (13; 31)[1]	26 (19; 36) [1]	14 (9; 21)	47 (39; 57)
Hazard ratio by Cox's proportional hazard regression model at 12 weeks	0.73 (p = 0.1492)		0.23 (p<0.0001)	
Kaplan Meier estimate of flare probability—cumulative event rate (95% CI) at 24 weeks	33(24; 45) [2]	48 (38; 59) [2]	32 (24; 41)	63(53; 73)
Hazard ratio by Cox's proportional hazard regression model at 24 weeks	0.64 (p = 0.0337)		0.32 (p<0.0001)	

Source: Tables 3.3-2g1, 3.3-2g2, 3.3-1g2, Appendix 1 Summary of Clinical Efficacy
[1] p-value for the between treatments difference p=0.15; [2] p-value for the between treatments difference p=0.03

Secondary Endpoints

A number of secondary efficacy endpoints were evaluated in trials H2356 and H2357; the results of the pertinent secondary endpoints are shown in Table 14 and Table 15. As discussed earlier, Bonferroni-Holm method of correction for multiple comparisons was planned in the protocols and employed for the first set of the secondary endpoints in both trials (Table 14). Only two of the four pre-specified endpoints from the first set have achieved statistical significance in favor of canakinumab treatment in trial H2356: the proportion of subjects taking rescue medication during the first week and the median time to at least 50 % reduction in pain intensity measured by VAS 0-100 mm. None of the 4 endpoints from the first set achieved statistical significance in trial H2357.

Table 14: Summary of the results of the first set of secondary efficacy endpoints in H2356 and H2357

Secondary Efficacy Endpoints	H2356		H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg s.c. N=113*	Triam. ac. 40 mg i.m. N=115*	Can-mab 150 mg s.c. N=112*	Triam. ac. 40 mg i.m. N=114*	Can-mab 150 mg s.c. N=225*	Triam. ac. 40 mg i m. N=229*
Proportions of patients taking rescue medication during the first week						
N (%)	35 (31)	60 (52)	49 (44)	65 (57)	84 (37)	125 (55)
p-value	0.002		0.02		0.0001	
Median time to at least 50% reduction of baseline pain intensity						
Kaplan-Meier estimate (hours)	48	72	25	48	47	48
p-value	0.01		0.08		0.003	
Time to complete resolution of pain						
Kaplan-Meier estimate of rates of complete resolution (%)	34	31	57	43	46	37
SF-36 (Physical Component) at end of study, 12 weeks						
LS Mean (SE), mm	72(3)	71(3)	81(3)	79(3)	77 (2)	75(2)

Source: Adopted from applicant's Table 3-15 and the respective source tables of the trial reports H2356 and H2357.
*the denominators slightly varied for different endpoints.

No correction for Type I error was planned or conducted for other secondary endpoints (Table 15). Therefore it is difficult to have confidence regarding conclusions pertaining to the statistical significance of the results for these endpoints. Overall, the trends observed with the changes in the secondary endpoints were supportive of the primary analysis.

Table 15: Summary of the results for other secondary efficacy endpoints in H2356 and H2357

Secondary Efficacy Endpoints	H2356		H2357		Pooled Data Trials H2356 and H2357	
	Can-mab 150 mg s.c. N=113*	Triam. ac. 40 mg i.m. N=115*	Can-mab 150 mg s.c. N=112*	Triam. ac. 40 mg i.m. N=114*	Can-mab 150 mg s.c. N=225*	Triam. ac. 40 mg i m. N=229*
VAS, 0-100 mm (patient's assessment of pain intensity in the most affected joint)						
Range of LS mean differences in VAS between the treatment groups at time points from 6 hours to 7 days post-dose	-6 to -11.4 mm		-8 to -9.8 mm		-7.3 to -10.7 mm	
Proportion of patients achieving various levels of pain relief						
Proportion of patients achieving 50% reduction in pain intensity at						
72 hours post-dose	64%	47%	79%	62%	72%	54%
Proportion of patients achieving 75% reduction in pain intensity at						
72 hours post-dose	38%	36%	57%	42%	48%	39%
Physician's Assessment of Global response to treatment at 72 hours post-dose						
N (%) patients with good and very good response	73(65)	50 (45)	92 (86)	67 (62)	165 (75)	117 (53)
Physician's assessment of the clinical signs at 72 hours post-dose						
*N (%) patients with no tenderness	38 (34)	29 (26)	51 (48)	33 (30)	89 (40)	62 (28)
*N (%) patients with no swelling	43 (38)	33 (30)	51 (48)	39 (36)	94 (43)	72 (33)
*N (%) patients with no erythema	88 (79)	71 (65)	80 (75)	72 (67)	168 (77)	143 (66)
Patient's Global Assessment of response to treatment at 72 hours post-dose						
N(%) patients with good or excellent response on Likert's scale)	58 (51)	46(41)	79 (73)	56 (52)	137 (62)	102 (47)

Rescue medication intake						
Median time to intake of first rescue medication (hours, 95%CI)	NE	124 (30; NE)	NE	37.5 (14; NE)	NE	72 (28; NE)
Mean dose of Acetaminophen intake (mg)	1555	2397	1375	2527	1465	2462
Mean dose of Codeine intake (mg)	7.7	47.2	27.2	60.6	17.4	53.9
Mean dose of Prednisone/Prednisolone intake (mg)	6.5	24.3	9.2	19.3	7.8	21.8
Proportion of patients with complete resolution of pain 7 days post-dose, N(%)						
Likert scale "none"	39 (34)	36(31)	64 (57)	49 (43)	103 (46)	85 (37)
Likert scale "mild"	60 (53)	54 (47)	38 (34)	46 (40)	ND	ND
VAS pain <10 mm	68 (60)	52 (45)	73(65)	63 (55)	ND	ND
Inflammatory Markers						
hsCRP (mg/L)						
Median at baseline	13.2	9.4	10.2	8.9	ND	ND
Median at 72 hours	4.4	5.2	4.3	7.0	ND	ND
Median at 7 days	2.1	3.6	4.8	7.2	ND	ND
SAA (mg/L)						
Median at baseline	18.0	9.9	11.2	9.8	ND	ND
Median at 72 hours	5.2	10.1	5.1	11.1	ND	ND
Median at 7 days	3.3	7.9	2.9	7.3	ND	ND

Table 3.2-9 Appendix 1, Tables 3-18, 3-19, 3-22 of the Summary of Clinical Efficacy, Tables 14.2-3.4, 14.2-3.7, 14.2-7.1, and 14.2-8.1 in Trials H2356 and H2357
*the denominators slightly varied for different endpoints; ND--not determined;

Efficacy Conclusions

Overall, both trials H2356 and H2357 demonstrated statistically significant decreases in pain intensity measured on VAS for canakinumab compared to triamcinolone, and statistically significant differences between treatment groups (favoring canakinumab) for the risk of a new gout flare. Subgroup analyses of the co-primary efficacy endpoints were generally consistent with the overall efficacy results, including results for the subgroup of patients intolerant to, with contraindications for, or lack of efficacy from NSAIDs and/or colchicine; however differences in the magnitude of the treatment effect in the subgroup of patients taking urate-lowering therapy versus those not taking urate-lowering therapy was observed.

Review of Safety

Discussion of Clinical Studies Used to Evaluate Safety

This application's pooled safety database contained safety data from six double-blind, active comparator-controlled clinical trials in gouty arthritis comparing canakinumab and triamcinolone acetonide or colchicine (H2251, H2255, H2356, H2357, H2356E1, and H2357E1). In addition, this sBLA contained the safety data from an open-label extension study H2251E1 in gouty arthritis where patients completing the dose-finding study in prophylactic treatment of gout (H2251) could receive canakinumab re-treatment on

demand upon development of gout flares (Table 2). The six trials were of sufficiently similar design to allow for pooled analyses of the controlled safety data by dose and treatment group and provided safety data for up to 24 weeks of observation. Because the 150 mg dose of canakinumab was tested in the two pivotal trials and their double-blinded extensions (H2356, H2357, H2356E1 and H2357E1), and a range of other doses were tested in the dose-ranging studies (H2251 and H2255), the dosing and treatment groups were pooled as follows:

(1) ≤100 mg (includes 10, 25, 50, 90 and 100 mg canakinumab s.c. single doses),
(2) split 150 mg (includes q4week dosing regimen of 50 mg, 50 mg, 25 mg and 25 mg canakinumab s.c.),
(3) 150 mg s.c. (includes pooled data from trials H2356, H2356E1, H2357, H2357E1 and the 150 mg arm from trial H 2355),
(4) ≥200 mg (includes data with 200 mg and 300 mg canakinumab s.c. single doses),
(5) 40 mg triamcinolone acetonide i.m. (includes pooled data from trials H2356, H2356E1, H2357, H2357E1, and triamcinolone acetonide arm from trial H2355),
(6) 0.5 mg colchicine p.o. once daily.

The applicant also provided additional safety data from their program in rheumatoid arthritis (RA) which included data on 441 RA patients exposed to canakinumab in four double-blind placebo-controlled clinical trials of 12-26 week duration (A2101, A2201, A2204, and A2207) and four uncontrolled open-label trials (A2206, A2201E1, A2201E2, A2211). Given the differences in dose and regimen of administration as well as in the clinical characteristics of the patient populations of RA and gout, these data will be considered supportive and discussed only where pertinent in the broader review of safety of canakinumab.

In addition to the safety data from the gout and RA programs, the applicant has also included safety data from the ongoing trials in other patient populations, canakinumab's named patient program (intended to provide access to canakinumab for patients with serious conditions whose physicians deemed canakinumab treatment as the only therapeutic option based in medical need in countries and regions where canakinumab is not available through other means), and three post-marketing safety update reports.

The focus of this safety discussion will be on the analyses of the pooled data from the six double-blind active comparator-controlled trials in gouty arthritis. Due to design differences, data from the open-label extension of the gout prophylaxis dose-ranging study (H2251E) were not pooled in these safety analyses, but were evaluated separately. Where pertinent, available data from the RA program were used supportively. Overall, the safety results from the combined data from the two pivotal Phase 3 trials were consistent with the safety results of the gouty arthritis safety database. For a more focused view on certain safety signals, data combined from the controlled Phase 3 trials H2356 and H2357 will be discussed separately.

Extent of exposure

At the data cut-off for the original submission (Dec 6, 2010) the extent of exposure to canakinumab for all completed trials in gouty arthritis was as shown in Table 16. In the gouty arthritis dataset, a total of 691 patients have been exposed to canakinumab in the six controlled trials. Of the 691 patients, 253 patients were treated with the proposed dose of 150 mg administered subcutaneously; 193/253 (76%) patients received canakinumab one time. In addition to 691 patients exposed to canakinumab in the controlled trials and their extensions, 25 patients were exposed to canakinumab in the open-label extension H2251E after being treated with colchicine in H2251 core trial (group C, Table 17).

With regard to re-treatment, the data provided in the original submission included 60 patients re-treated with a second or third dose of canakinumab in the pivotal trials or their double-blinded extensions (H2356, H2356E1, H2357, and H2357E1) as shown in Table 16 and 75 patients re-treated with canakinumab (group A) in the open-label trial H2251E (Table 17).

Table 16: Exposure to canakinumab in the gout controlled trials (H2251, H2255, H2356, H2357, H2356E1 and H2357E1)

Exposure to canakinumab	Canakinumab ≤100mg N=278	Canakinumab split 150mg N=53[1]	Canakinumab 150mg N=253	Canakinumab ≥200 N=107	Canakinumab all N=691
Duration of Observation (days): Mean (SD)	87 (30)	113 (8)	139 (46)	110 (19)	n/a
N of injections:					
1	278 (100%)	0	193(76%)	107(100%)	578(84%)
2	0	0	47 (19%)	0	47(6.8%)
3	0	2(4%)	11(4%)	0	13 (1.6%)
4	0	51(96%)	2 (1%)	0	53 (7.6%)

[1]Design of trial H2251 allowed split dosing of 150 mg administered on days 1, 29, 57, and 85 in 4 injections.
Adapted from Sponosor's Table 1-8 of the Summary of Clinical Safety.

Table 17: Exposure to canakinumab in the open-label extension trial H2251E1

Exposure to canakinumab	Group A N=75	Group B N=248	Group C N=25	Group D N=83
Duration of Observation (days): Mean (SD)	343 (10)	286 (97)	348(15)	275 (108)
N of injections:				
1	75*	0	21	0
2	65	0	3	0
3	10	0	1	0
4	0	0	0	0

Source: Table 14.3-1.3 Clinical Study Report H 2251E1
*** all received first injection in the core portion H2251**

Overall, according to the original submission (data cut off Dec 6, 2010), 135 patients were re-treated with canakinumab upon developing a new flare after previous treatment with canakinumab.

On May 5, 2011, the applicant submitted 120-day safety update with additional data on re-treatment. The data on the number of injections administered in gouty arthritis program submitted to the FDA to date are summarized in Table 18. In addition to the

update on the subjects randomized to canakinumab in trials H2356 and H2357, the applicant has also submitted safety data on 67 subjects who were treated with canakinumab 150 mg s.c. on demand in E2 after receiving triamcinolone acetonide in the core trials and the E1 extensions. The majority of these subjects received one injection of canakinumab 150 mg s.c. (54/67 -81%).

Table 18: Updated summary of canakinumab injections in the gout clinical development program

N of injections:	Can-mab 150mg treated in H2255 N=27	Can-mab 150mg treated in 2356/E1/E2 2357/E1/E2 N=225	Can-mab 150mg received triamcinolone in H2356/56E1, H2357/57E1 treated with can-mab in 56E2 and 57E2 N=67	Can-mab doses other than 150 mg, single treatments in H2251 and H2255 N=438
1	27 (100%)	107(47%)	54 (81%)	385 (88%)
2	0	75(33%)	11(16%)	0
3	0	25(11%)	1(1.5%)	2 (0.5%)
4	0	15(7%)	1(1.5%)	51(11.5%)
≥5	0	3(2%)	0	0

Data from re-treatment in H2251E1 (Table 18 above) are not included
Source: applicant's 120-day safety update

Safety overview

All safety analyses were performed on the population who received at least 1 injection of study medication. Table 19 summarizes adverse events (AEs) that were reported in the canakinumab pooled safety database by dose and treatment group. The majority of patients in these trials experienced at least one AE during the course of the trial. The data from the two pivotal trials and their extensions (E1) are included in the columns referring to 150 mg s.c. canakinumab and 40 mg i.m.triamcinolone acetonide groups.

The proportions of subjects experiencing an AE or an SAE were highest in the 150 mg canakinumab group (62.5 % and 7.1%) and exceeded those in the triamcinolone acetonide-treated (51% and 3.1%) and colchicine-treated (54 % and 5.6%) groups. The proportion of patients with any SAE in 150 mg canakinumab group was twice that of the triamcinolone acetonide group: the difference was likely due to the occurrence of serious infections observed exclusively in the canakinumab treatment groups. Relatively few patients discontinued due to adverse events in the pivotal trials; the proportion of patients who discontinued for adverse events was the highest among patients who received ≥ 200 mg of canakinumab. Six deaths occurred in the gouty arthritis dataset: three in the controlled Phase 3 trials, one in the open-label extension study H2356E2, and two in the open-label study H2255E1; the reports of fatal cases will be discussed further below.

Table 19: Overview of adverse events and deaths in the gout controlled studies (H2251, H2255, H2356, H2357, H2356E1, and H2357E1)

	Canakinumab ≤100mg N=278	Canakinumab split 150mg N=53	Canakinumab 150mg N=253	Canakinumab ≥200 N=107	Triamcinolone N=286	Colchicine N=108
Number of Subjects with at Least 1 AE	137 (49%)	31 (58.5%)	**158 (62.5%)**	57 (53%)	**145 (51%)**	58 (54%)
Number of Subjects with at Least 1 Serious AE	11(4%)	1(1.9%)	**18(7.1%)**	6(5.6%)	**9(3.1%)**	6(5.6%)
Number of Subjects with at Least 1 Infection or Infestation	42(15.1)	10(18.9)	**49 (19.4)**	19(17.8)	**37 (12.9)**	13 (12)
Number of Subjects with at Least 1 Serious Infection	4(1.4%)	1(1.9%)	**5(2.0%)**	2(1.9%)	**0**	0
Number of Subjects with at Least 1 AE Leading to Discontinuation	4 (1.4%)	0	**2 (0.8%)**	7 (6.5%)	**1 (0.3%)**	3(2.8%)
Deaths	0	0	**1(0.4%)**	0	**1(0.3%)**	1(0.9%)

Source: Table 2.1-6A, Appendix 1 of Summary of Clinical Safety; applicant's response to IR, Apr 14, 2011.

Deaths

There were a total of 6 deaths reported in the gouty arthritis development program and 3 deaths reported in the canakinumab groups in the RA program. Brief case descriptions are provided in Table 20.

Of the six deaths that occurred in both treatment arms in the gouty arthritis development program, four were of cardiovascular and cerebrovascular etiology; the causes of deaths in these four patients appear to be consistent with expected etiologies of death related to the patients' underlying medical conditions. For Subject H2251E1-0074-0004, given the lack of laboratory results immediately prior to death or any reported biopsy findings other than those listed in Table 20, it remains undetermined whether gradual worsening of thrombocytopenia in this patient contributed to the fatal outcome.

Occurrence of pneumonia in Subject H2356E2-0013-00001 treated with canakinumab in trial H2356 and its extensions, as well as occurrences of the wound infection complicating intestinal rupture in Subject A2201E2-0002-00015 and the gluteal abscess in Subject 2201E1-0074-00008 would be consistent with the anticipated immunosuppressive effects of canakinumab related to its mechanism of action through blocking IL-1β and inhibiting the innate responses to infectious pathogens resulting in an increased risk of infections. Whether 13 months of chronic treatment with canakinumab could have influenced development of lung adenocarcinoma in Subject 2201E1-0074-00008 (who had comorbidities of RA and chronic obstructive pulmonary disease) remains uncertain but would not be inconsistent with possible impaired malignancy immunosurveillance due to chronic immunosuppression.

Table 20: Deaths in the gout and RA development programs

Patient/ Study	Study Drug/Dose	Reported Cause of Death (PT)	Days Since Study Enrolment	Days Since Last Dose	Pertinent History
Gouty Arthritis Program					
67 yo/M H2251E1-0074-0004	canakinumab, split 150 mg repeat dosing (4 doses in Jul-Oct 2009)	Myocardial ischemia	27 (ext), 195 (from core baseline)	114 (core)	Previous h/o CHF, HTN, CAD, acute MI (1997), post-infarction cardiosclerosis, and ventricular ectopies. Sudden death- not waking up in the morning after going to bed the previous night. The reported cause of death at autopsy was ischemic heart disease and severe myocardial fibrosis. During the study participation, the platelet count gradually decreased from 142 X 10E9/L at baseline to 105 X 10XE9/L (last available lab reading was at 1 mo before death).
35 yo /M H2251E1-0514-00005	canakinumab, 100 mg	Gun shot wound to head	223 (from core baseline)	118 (core)	Gun shot wound to the head in a local night club.
63yo/M H2357-0580-00004	canakinumab, 150 mg	Intracranial hemorrhage	67	66	Prior h/o HTN and previous thrombotic CVA, depression, obesity, bilateral deafness, epilepsy. On Day 55 developed unilateral arm and lip numbness, was hospitalized, head CT showed "small area of edema" in the left hemisphere and MRI showed 70% occlusion of the left middle cerebral artery. Clopidogrel sulfate was administered and patient was discharged home. On Day 65, the patient developed seizure-like activity and was found unresponsive, required intubation and life-support. Repeat head CT showed parenchymal hemorrhage to the left internal capsule with midline shift.
74 yo/M H2356E2-0013-00001	canakinumab, 150 mg	Pneumonia	262	49	H/o COPD, treated with fluticasone, salmeterol, hospitalized with pneumonia on (b) (6)--Day 49 following second injection of canakinumab. Death occurred during the same hospitalization on (b) (6).
54yo/M /H2251-0508-00005	colchicine	Myocardial infarction	42	31	Previous h/o HTN, CAD, s/p Acute MI in 2004 and 2007 previously treated with stent placement and aspirin.
59 yo/M / H2356-0101-00001	triamcinolone	Sudden cardiac death / Pulmonary embolism	10	1	Previous h/o HTN, obesity, "atrial dilatation", h/o immobility due to frequent gout flares.
RA program					
60yoF/ A2201E2-0002-00015	canakinumab last dose 150 mg s.c., cumulative dose 6450mg	Wound infection complicating intestinal rupture	630	44 (last dose on Day 586	Concomitant medications included meloxicam, folic acid, methotrexate and pantoprazol sodium. Past medical history included RA and hyperlipidemia.
56 yo/ M A2201E2-0051-05179	canakinumab last dose 600 mg i.v., cumulative dose 3600 mg	Right femoral neck fracture. Disseminated Intravascular Coagulation reported at autopsy	433	407	Right hip fracture following an episode of heavy alcohol use for 5 days, complicated by acute alcoholic psychosis, intestinal obstruction, acute liver failure, and acute renal failure. Past medical history included duodenal ulcer, chronic pancreatitis, aortic arteriosclerosis, and urolithiasis.
70yo /M/2201E1-0074-00008	canakinumab last dose 300 mg s.c., cumulative dose 5100mg	Multi-organ metastases from lung adenocarcinoma*	421	N/a	Previous h/o rheumatoid vasculitis, hyperlipidemia, carotid artery stenosis, and COPD. During the course of the study, the subject developed a small ischemic CVA after 3 months in the study and a gluteal abscess after 5 months in the study (both treated and resolved). After 13 months of chronic dosing with canakinumab at least every 6 weeks, the subject presented with symptoms of malaise and, upon a diagnostic work up in the hospital, was found to have bronchial mucinous adenocarcinoma with liver and brain metastases and subsequently died of multi-organ failure during the same hospitalization.

Source: Tables 2-18 and 2-21 of Summary of Clinical Safety, case summary reports of the respective cases, 120-day safety update report.

Ten additional fatal outcomes among canakinumab-treated patients were reported from the ongoing clinical trials in systemic Juvenile Idiopathic Arthritis (sJIA), Chronic Obstructive Pulmonary Disease (COPD), the applicant's "named patient program" and spontaneous post-marketing reports. The causes of death listed in these reports included two cases of sepsis (confirmed pneumococcal sepsis in one case), two cases of macrophage activating syndrome, a case of respiratory failure secondary to aspergillus pneumonia (COPD program), and a case of disseminated pulmonary and peritoneal tuberculosis in a 40 year old male patient with Tumor Necrosis Associated Periodic Syndrome (TRAPS) enrolled in the named patient program.

Overall, the reported causes of deaths in the gouty arthritis and RA development programs appear to be consistent with etiologies of death related to underlying medical conditions and medications used in these patient populations. However, the immunosuppressive effects of canakinumab were also observed in the occurrence of events related to serious infections or malignancy

Nonfatal Serious Adverse Events

Serious Adverse Events

A summary of the serious adverse events (SAE) observed in the gouty arthritis program is shown Table 21. Overall, the proportions of patients who had a SAE were higher for the 150 mg and ≥200 mg canakinumab groups (7.1% and 5.6%) compared with triamcinolone (3.1%) and colchicine (5.6%) groups. Numeric imbalances in the number of SAEs are most notable in the Infections and Infestations SOC with serious infections occurring exclusively in the canakinumab-treated groups. Numeric imbalances are also notable in the following system organ classes: Cardiac Disorders, Gastrointestinal Disorders, Eye Disorders and Renal and Urinary disorders, although, the observed numbers appear small and preclude definitive conclusions. Serious adverse events related to Infections and Infestations and Renal Disorders are discussed separately in other sections of this briefing document.

The vast majority of SAEs reported in the gout program, including SAEs reported in the Metabolism and Nutrition Disorders, Musculoskeletal and Connective Tissue Disorders, General Disorders and Administrative Site Conditions, and Injury, Poisoning and Procedural Complications, are known to occur in chronic gout population where concomitant conditions of diabetes, hypertension, metabolic syndrome, obesity, and osteoarthritis are common co-morbidities, therefore, occurrence of these SAEs is not unexpected. All SAEs reported in the Cardiac Disorders occurred in patients who had prior significant history of coronary problems and hypertension; these SAEs occurred in patients from both canakinumab groups and triamcinolone or colchicine groups who had major risk factors for development of cardiovascular events. Two occurrences of SAEs in Eye Disorders included acute retinal artery occlusion in a patient with poorly controlled diabetes and hypertension and a case of acute presentation of glaucoma in a patient previously treated with a corticosteroid medication.

Table 21: Serious Adverse Events (SAE) in the gout safety database

MedDRA Primary SOC[2]/ Preferred term[2]	ACZ885 All N=691	ACZ885 ≤ 100 mg N=278	ACZ885 split 150 mg, N=53	ACZ885 150 mg N=253	ACZ885 ≥ 200 mg N=107	Triam N=286	Colch N=108
Total number of patients with any SAEs[1]	**36 (5.2)**	**11(4)**	**1(1.9)**	**18(7.1)**	**6(5.6)**	**9(3.1)**	**6(5.6)**
Infections and infestations	**12 (1.7)**	**4(1.4)**	**1(1.9)**	**4(1.6)**	**2(1.9)**	**0**	**0**
Abscess jaw (mandible)		0	0	1	0	0	0
Abscess limb		0	0	1	0	0	0
Gastroenteritis		0	0	1	0	0	0
Pneumonia		0	1	1	0	0	0
Appendicitis		2	0	0	0	0	0
Bronchitis		1	0	0	0	0	0
Acute bilateral purulent otitis		0	1	0	0	0	0
Erysipelas		1	0	0	0	0	0
Gangrene		0	0	0	1	0	0
Sepsis		0	0	0	1	0	0
Tonsillitis		0	0	0	1	0	0
Cardiac disorders, N (%)	**5(0.7)**	**0**	**0**	**4 (1.6)**	**1(0.9)**	**1(0.3)**	**1(0.9)**
Angina pectoris		0	0	1	0	0	1
Arrhythmia		0	0	1	0	0	0
Atrial fibrillation		0	0	1	0	0	0
Myocardial ischemia		0	0	1	0	0	0
Myocardial infarction		0	0	0	1	0	0
Aortic valve incompetence		0	0	0	0	1	0
Cardiomyopathy		0	0	0	0	1	0
Eye disorders	**2(0.3)**	**0**	**0**	**2(0.8)**	**0**	**0**	**0**
Glaucoma		0	0	1	0	0	0
Retinal artery occlusion		0	0	1	0	0	0
Gastrointestinal disorders	**5(0.7)**	**1(0.4)**	**0**	**2(0.8)**	**2(1.9)**	**1(0.3)**	**1(0.9)**
Gastritis		0	0	1	1	0	0
[4]Pancreatitis		0	0	1	0	0	0
Abdominal pain		0	0	0	0	0	1
Colitis ulcerative (enteritis)		0	0	0	1	0	0
Diarrhea		0	0	0	0	1	0
Hemorrhoidal hemorrhage		1	0	0	0	0	0
Nausea		0	0	0	0	1	0
Umbilical hernia		0	0	0	0	0	1
Vomiting		0	0	0	0	1	0
General disorders and admin. site conditions	**1 (<0.2)**	**0**	**0**	**1(0.4)**	**0**	**0**	**0**
Device dislocation (hip endoprosthesis)		0	0	1	0	0	0
Hepatobiliary disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1(0.9)**
Cholelithiasis		0	0	0	0	0	1
Injury, poisoning and procedural complications	**2(0.3)**	**1(0.4)**	**0**	**0**	**1(0.9)**	**1(0.3)**	**1(0.9)**
Femur fracture		0	0	0	0	0	1
Hand fracture		0	0	0	0	0	1
Ligament rupture		0	0	0	1	0	0
Meniscus lesion		0	0	0	0	1	0
Radius fracture		0	0	0	0	0	1
Tibia fracture		1	0	0	0	0	0
Ulna fracture		0	0	0	0	0	1
Investigations	**1(<0.2)**	**0**	**0**	**1(0.4)**	**0**	**0**	**0**
Prostatic specific antigen increased		0	0	1	0	0	0
Metabolism & nutrition disorders	**1(<0.2)**	**0**	**0**	**1(0.4)**	**0**	**2(0.7)**	**0**

Hyperglycemia		0	0	1	0	0	0
Gout		0	0	0	0	2	0
Musculoskeletal and connective tissue disorders	**3(0.4)**	**1(0.4)**	**0**	**2(0.8)**	**0**	**0**	**1(0.9)**
Back pain		0	0	1	0	0	0
Intervertebral disc protrusion		0	0	1	0	0	0
Lumbar spinal stenosis		0	0	1	0	0	0
Spondylolisthesis		0	0	1	0	0	0
Osteoarthritis		1	0	0	0	0	0
Tendonitis		0	0	0	0	0	1
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	**1(<0.2)**	**0**	**0**	**0**	**1(0.9)**	**0**	**1(0.9)**
Prostate cancer		0	0	0	1	0	0
Renal cancer		0	0	0	0	0	1
Nervous system disorders	**5(0.7)**	**2(0.7)**	**0**	**3(1.2)**	**0**	**3(1.0)**	**0**
Cerebrovascular accident		0	0	1	0	0	0
Convulsion		0	0	1	0	0	0
Spinal cord ischemia		0	0	1	0	0	0
Carotid artery stenosis		1	0	0	0	0	0
Cerebrovascular disorder		0	0	0	0	1	0
Ischemic stroke		0	0	0	0	1	0
Stupor[3]		1	0	0	0	0	0
Vertebrobasilar insufficiency		0	0	0	0	1	0
Renal and urinary disorders	**4(0.6)**	**2(0.7)**	**0**	**1(0.4)**	**1(0.9)**	**0**	**0**
Renal failure		0	0	1	0	0	0
Hematuria		1	0	0	1	0	0
Nephrolithiasis		1	0	0	0	0	0
Nephrotic syndrome		0	0	0	1	0	0
Renal failure		0	0	0	1	0	0
Vascular disorders	**0**	**0**	**0**	**0**	**0**	**1(0.3)**	**0**
Aortic stenosis		0	0	0	0	1	0

[1] This table does not include SAEs leading to fatal outcomes (PE, intracranial hemorrhage and fatal MI)
[2] Number and percent are represented by n of patients in the SOC rows and n of events in the PT rows
[3] The event was judged by the investigator to be related to patient's psychiatric condition
[4] The event occurred 6 mo following a single injection of canakinumab while subject was followed in the extension phase H2356E1; the event was considered unrelated to study treatment by the investigator
Source: Table 2.1-3A, Appendix 1 of the Summary of Clinical Safety.

Review of SAEs from the open-label extension study H2351E1 and the RA program did not reveal any additional safety signals except for an event of lip edema which is discussed later in the Hypersensitivity Reactions Section.

Overall, more SAEs occurred in the canakinumab-treated groups compared with triamcinolone- or colchicine-treated groups; the incidence of SAEs with the 150 mg canakinumab dose intended for marketing was twice of that observed with the triamcinolone treatment. The difference appeared to be primarily driven by serious infections occurring in the canakinumab groups. For SAEs other than infections, given multiple co-morbidities of the treated population, alternative explanations for events occurrences, and the small numbers of the observed events, it is difficult to draw conclusions regarding the impact of canakinumab treatment on occurrence of these events.

Serious Infections

Because of its mechanism of action, canakinumab would be anticipated to increase the risk of infections, including serious infections. Infections and Infestations were the most common System Organ Class (SOC) reported with canakinumab treatment; the exposure-adjusted incidence rate of serious infections and all infections are shown in Table 22. As shown, in both RA and gout programs, serious infections occurred exclusively in the canakinumab groups; the incidence-adjusted rate of infectious SAEs was lower with the mostly one time intermittent use of canakinumab in the gout program compared to chronic use in the RA program. Although the occurrence of infections would not be unexpected with an IL-1 inhibitor, the increased rate of the serious infections in gout patients after just a single injection of canakinumab is a unique and concerning observation in this development program.

Table 22: Exposure-adjusted incidence rates of all infections and serious infections in the gout and RA safety databases

Adverse Events	Gout program							RA program	
	Can-mab All N=691	Can-mab ≤ 100 mg N=278	Can-mab split 150 mg, N=53	Can-mab 150 mg N=253	Can-mab ≥ 200 mg N=107	Triam N=286	Colch N=108	Can-mab N=344	Placebo N=121
All Adverse Events of Infections Number of events (per 100-pt years)	144 (68)	49 (74)	15 (91)	58(60)	22(68)	44 (45)	16 (51)	157 (135)	60 (148)
Adverse Events of Serious Infections Number of events (per 100-pt years)	13(6)	4(6)	2(12)	4(4)	3(9)	0	0	12 (10)	0

Source: Table 2.1-3A, Appendix 1 of the Summary of Clinical Safety.

With regard to the kinds of infections observed, in addition to the events listed above in Table 21, other infectious events observed in gout and RA programs included cases of meningitis and septic arthritis (both in RA program) and rectal abscess (gouty arthritis program after re-treatment). Apart from the serious mycobacterium tuberculosis infection leading to the fatal outcome Table 21, a few cases of asymptomatic PPD test seroconversion were reported in the RA program.

It is important to note that several serious infections observed in both gout and RA development programs were reported in patients who developed leucopenia and neutropenia after treatment with canakinumab. Two patients in the gout program developed acute respiratory infection and submandibular abscess (reported as an SAE, Table 21) and three patients in RA program developed severe influenza (1), severe bacterial skin infection (1), and a left knee prosthetic infection (1), while having low white blood cell counts observed with canakinumab treatment. Occurrence of leucopenia and neutropenia is further discussed in the Laboratory Findings Section.

Opportunistic and unusual infections reported with use of canakinumab in post-marketing included mainly fungal and herpetic infections; a few cases of Epstein-Bar viral infections and a case of infection with metapneumovirus were also reported.

Malignancy

Immunosuppression and impairment of immunosurveillance would be expected with chronic dosing with immunosuppressive biological products, therefore, both gout and RA safety datasets were examined for occurrences of malignancies. Table 23 lists all cases of malignancies and neoplasms observed in both gouty arthritis and RA programs. The majority of the observed malignancies were reported in the RA program.

Two cases of malignancy were reported in the gouty arthritis program: Subject H2251-0010-00002 (68 year old male) received a single 300 mg dose of canakinumab in study H2251 and was diagnosed with prostate cancer on Day 106, and Subject H2251-0520-00001 (45 year old male) from the colchicine group was diagnosed with renal cancer on Day 109. Subject H2251-0010-00002 had a history of a stable hypoechogenic lesion in the left zone of prostate and stable mild elevation of PSA since 2005; the unchanged hypoechogenic lesion was biopsied and the patient was diagnosed with prostate adenocarcinoma in April 2009 when the subject was in the trial follow up period. It is unlikely that canakinumab treatment contributed to development of adenocarcinoma in this subject.

In the RA program, except for gammopathy and the skin neoplasm, all malignancies were diagnosed after 24 weeks of treatment with canakinumab and in the open-label trials. One patient was diagnosed with two malignancies (non-Hodgkin's lymphoma and squamous cell carcinoma of the skin) after 48 weeks of treatment with canakinumab. No discernable pattern of malignancies was observed.

Table 23: Malignancies in the gout and RA clinical development programs

MedDRA Preferred Term	Gouty Arthritis Trials		RA controlled trials		All RA
	Can--mab N=691	Colch N=108	Can--mab N=332	Placebo N=121	Can--mab N=441
Subjects with ≥ 1 Malignancy	**1 (0.1%)**	**1(0.9%)**	**1(0.3)**	**0**	**7(1.6%)**
Basal cell carcinoma	0	0	0	0	2 (0.6%)
Gammopathy	0	0	0	0	1(0.2%)
Neoplasm Skin	0	0	1(0.3)	0	0
Thyroid Neoplasm	0	0	0	0	1(0.2%)
Lung Adenocarcinoma	0	0	0	0	2 (0.6%)
Non-Hodgkin's lymphoma	0	0	0	0	1(0.2%)
Squamous Cell Carcinoma of the Skin	0	0	0	0	1(0.2%)
Renal cancer	0	1(0.9%)	0	0	0
Prostate cancer	1 (0.1%)	0	0	0	0

Source: Table 2.5-9C, Appendix 1, Summary of Clinical Safety.

While the data show that the incidence of malignancies is not increased upon single injection treatment with canakinumab administered for gouty arthritis, the available data do not allow an estimation of the potential risk for malignancies upon chronic repetitive "on demand" canakinumab treatment in the gout population.

Adverse Events Causing Discontinuation

The adverse events by System Organ Class and Preferred Term that resulted in patients discontinuing from the controlled trials in gouty arthritis (H2251, H2255, H2356/56E1, H2357/57E1) and the controlled trials in RA are shown in Table 24. The findings from the H2251E1 extension are similar to the other trials and are not shown here. Overall, the proportions of patients who discontinued trial participation due to an AE were generally small but numerically higher in the canakinumab groups, with the highest rate occurring among patients who received 200 mg or greater in the gout program.

Review of the AEs leading to discontinuation in both the gout and RA clinical development programs generally mirrored AEs seen in the SAE analysis, and included serious infections and leucopenia. Of interest were occurrences of severe dizziness, lip edema, and two occurrences of renal failure. These events are discussed later in this briefing document.

In gouty arthritis trials, while none of the hepatic events were reported as serious or severe, two events led to study drug discontinuation. Subject H2251-0502-00005 with previously abnormal AST, ALT, and GGT developed worsening of these parameters after receiving 25 mg of canakinumab subcutaneously and Subject H2251-0520-00006 with mildly elevated ALT and GGT at baseline was found to have more increases in ALT, GGT (>2 ULN), and newly appearing elevation of AST (1.5 ULN) concomitantly with clinical finding of hepatomegaly on Day 31 after receiving one dose of canakinumab at 200mg.

Table 24: Discontinuations due to adverse events in the gout and RA controlled trials

MedDRA System Organ Class/ Preferred Term	Can-mab ≤ 100mg N=278	Can-mab split 150mg, N=53	Can-mab 150mg N=253	Can-mab ≥ 200mg N=107	Triam N=286	Colch N=108	Can-mab N=332	Placebo N=121
	Gouty Arthritis Controlled Trials						RA Controlled Trials	
Number of Subjects with ≥ 1 AE Leading to Discontinuation:	**4 (1.4%)**	**0**	**2 (0.8%)**	**7 (6.5%)**	**1(0.3%)**	**3(2.8)**	**11(3.3%)**	**4(3.3%)**
Blood and Lymphatic System Disorders								
Leucopenia	0	0	0	0	0	0	2(0.6%)	0
Anemia	0	0	0	0	0	0	1(0.3%)	0
Cardiac Disorders:								
Myocardial Infarction	0	0	0	0	0	1(0.9)	0	0
Palpitations	0	0	0	1(0.9%)	0	0	0	0
Hepatobiliary Disorders:								
Hepatomegaly	0	0	0	1(0.9%)	0	0	0	0
Gastrointestinal Disorders:								
Enteritis	0	0	0	1(0.9%)	0	0	0	0
Gastritis	0	0	0	0	0	0	1(0.3%)	0
Upper GI hemorrhage	0	0	0	0	0	0	0	1(0.8%)
General Disorders and Administrative Site Conditions:								
Non-cardiac chest pain	0	0	0	0	0	0	0	1(0.8%)
Immune System Disorders:								
Lip edema	0	0	0	0	0	0	1(0.3%)	0
Infections and Infestations								
Abscess limb	0	0	0	0	0	0	1(0.3%)	0
Cellulitis	0	0	0	0	0	0	1(0.3%)	0
Soft Tissue Infection	0	0	0	0	0	0	1(0.3%)	0
Urosepsis	0	0	0	0	0	0	1(0.3%)	0
Sepsis	0	0	0	1(0.9%)	0	0	0	0
Erysipelas	1(0.4%)	0	0	0	0	0	0	0
Investigations								
ALT Incr.	0	0	0	0	0	0	1 (0.3%)	0
Amylase & Lipase Incr.	0	0	1(0.4%)	0	0	0	0	0
LFT Abnormal	1(0.4%)	0	0	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders:								
Rheumatoid Arthritis	0	0	0	0	0	0	1(0.3%)	2(1.7%)
Arthralgia	0	0	0	0	0	0	0	1(0.8%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps):								
Renal Cancer	0	0	0	0	0	1(0.9%)	0	0
Nervous System Disorders								
Headache	0	0	0	1(0.9%)	0	0	0	0
Hemorrhage Intracr.	0	0	1(0.4%)	0	0	0	0	0
Dizziness	0	0	0	0	0	0	1(0.3%)	0
Metabolism and nutrition Disorders:								
Diabetes Mellitus	0	0	0	0	0	1(0.9%)	0	0
Renal and Urinary Disorders:								
Hematuria	1 (0.4%)	0	0	0	0	0	0	0
Renal Failure	0	0	0	2 (1.9%)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders:								
Pulmonary Embolism	0	0	0	0	1(0.3%)	0	0	0
Skin and Subcutaneous Tissue Disorders:								
Rash	1 (0.4%)	0	0	0	0	0	0	0
Vascular Disorders:								
BP* Inadequately Controlled	0	0	0	1(0.9)	0	0	0	0

*BP-Blood Pressure

Source: Tables 2.1-4A and 2.1-4B, Appendix 1 of the Summary of Clinical Safety

Common Adverse Events

About half of the patients in each combined treatment group (49%- 62.5%) experienced an adverse event during the gouty arthritis trials. The incidences of the adverse events observed in these trials by System Organ Class and treatment group are shown in Table 25. Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Investigations, and Metabolism and Nutrition Disorders were the most common types of adverse events observed. Infections and Infestations were also the most common MedDRA AE SOC observed among RA patients.

When comparing the AEs that occurred in patients treated with the proposed dose 150 mg s.c. canakinumab and in patients treated with 40 mg i.m. triamcinolone acetonide, the incidences of adverse event categories were slightly higher in the canakinumab group for the majority of MedDRA SOCs; but often times were driven by numerically small differences. The numeric imbalances in the Investigations SOC were primarily due to increases in triglycerides and occurrences of neutropenia and thrombocytopenia; the imbalances in the Nervous System Disorders SOC reflected occurrences of dizziness, vertigo, and headache.

Table 25: Common adverse events in the gout safety database

MedDRA System Organ Class	Can—mab ≤ 100 mg N=278	Can—mab split 150 mg, N=53	Can—mab 150 mg N=253	Can—mab ≥ 200 mg N=107	Total Can—mab N=961	Triam N=286	Colch N=108
Number of Subjects with a ≥ 1AE:	**137 (49%)**	**38 (58.5%)**	**152 (62.5%)**	**57 (53%)**	**383 (55%)**	**145 (51%)**	**58 (54%)**
Infections and Infestations, N(%)	42(15)	10(19)	49 (19)	19(18)	120 (17)	37 (13)	13 (12)
Musculoskeletal and Connective Tissue Disorder, N(%)	41(15)	5(9)	41(16)	18(17)	105 (15)	44(15)	18 (17)
Investigations, N(%)	19(7)	1(2)	31(12)	8(7.5)	59 (8.5)	27(9)	10(9)
Metabolism and Nutrition Disorders, N(%)	16(6)	3(6)	30(12)	6(6%)	55 (8)	24(8)	4(4)
Nervous System Disorders, N(%)	27(10)	5(9)	28(11)	11(10)	71(10)	24 (8)	7(6.5)
Gastrointestinal Disorders, N(%)	26(9)	4(7.5)	27 (11)	10(9)	67 (10)	20 (7)	10(9)
Vascular Disorders, N(%)	11(4)	2(4)	18(7)	11(10)	42(6)	16 (6)	1(<1)
Gen. Disorders and Admin. Site Conditions, N(%)	13(5)	0	18(7)	2(2)	33(5)	12(4)	4(4)
Cardiac Disorders, N(%)	5(2)	0	13(5)	7(6.5)	25(4)	14 (5)	2(2)
Respiratory, Thoracic and Mediastinal Disorders, N(%)	12(4)	292)	11(4)	7(6.5)	31(4.5)	8(3)	4(4)
Injury, Poisoning and Procedural Complications, N(%)	14(5)	2(4)	11(4)	5(5)	32(5)	18(6)	5(6)
Skin and Subcutaneous Tissue Disorders, N(%)	16(6)	7(13)	10(4)	6(6)	39(6)	12(4)	6(6)
Blood and Lymphatic System Disorders, N(%)	5(2)	1(2)	10(4)	2(2)	18(3)	6(2)	3(3)
Renal and Urinary Disorders, N(%)	7(2.5)	0	9(4)	2(2)	18(3)	8(3)	1(<1)
Psychiatric Disorders, N(%)	7(2.5)	0	8(3)	2(2)	17(2.5)	8(3)	1(<1)
Hepatobiliary Disorders, N(%)	3(1)	0	6(2)	2(2)	11(2)	2(<1)	1(<1)
Eye Disorders, N(%)	3(1)	1(2)	5(2)	0	9(1)	2(<1)	0
Ear and Labyrinth Disorders, N(%)	4(1)	1(2)	3(1)	2(2)	10(1)	2(<1)	0
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps), N(%)	0	0	2(<1)	1(<1)	3(<1)	0	1(<1)
Immune System Disorders, N(%)	1(<1)	0	1(<1)	1(<1)	3(<1)	1(<1)	0
Reproductive System and Breast Disorders, N(%)	4(1)	1(2)	0	3(3)	8(1)	0	0
Congenital, Familial and Genetic Disorders, N(%)	0	0	0	0	0	1(<1)	1(<1)
Endocrine Disorders, N(%)	0	0	0	0	0	1(<1)	0
Social Circumstances, N(%)	0	0	0	0	0	1(<1)	0
Surgical and Medical Procedures, N(%)	0	0	0	0	0	0	1(<1)

Adapted Sponsor's Table 2.1-6A Appendix 1, of the Summary of Clinical Safety.

Table 26 below lists common adverse events by Preferred Terms reported by ≥ 2% patients in any treatment group. Headache, hypertension, arthralgia, and back pain were the most commonly occurring adverse events that occurred more frequently among patients treated with canakinumab. Given that over 50% of the enrolled subjects had concomitant hypertension and over 10% subjects had diabetes, the appearance of hypertension as one of the most common adverse events is not unexpected in this patient population. The incidence of hypertension with canakinumab seems slightly higher than the incidence observed with the corticosteroid triamcinolone and appears more imbalanced in comparison with colchicine. More events of hypertension seem to be

reported with higher doses of canakinumab in the safety dataset (Table 26); hypertension appears as the most frequent adverse event upon a separate analysis of the controlled data from the two pivotal trials H2356 and H2357 (Table 27). Despite the frequent reporting of hypertension in the gout program, no meaningful changes have been observed upon analysis of mean changes or occurrences of > 25% shifts in systolic or diastolic BP measurements in the safety database or combined Phase 3 trials. Given that patients with hypertension were equally distributed between the treatment groups at the baseline, the increase in occurrence of events of hypertension or escape from previous blood pressure control in the canakinumab groups is notable and can not be immediately explained by known effects of canakinumab.

Table 26: Common AEs occurring at >2% frequency in any treatment group in the gout controlled trials, by preferred term

MedDRA System Organ Class/ Preferred Term	Can—mab ≤ 100 mg N=278	Can—mab split 150 mg, N=53	Can—mab 150 mg N=253	Can—mab ≥ 200 mg N=107	Total Can—mab N=961	Triam N=286	Colch N=108
Back Pain	9(3)	0	13(5)	3(3)	25(4)	2(<1)	4(4)
Hypertension	10(4)	2(4)	12(5)	9(8)	33(5)	13(4.5)	1(<1)
Headache	15(5)	3(6)	12(5)	8(7.5)	38(5.5)	12(4)	6(6)
Arthralgia	15(5)	294)	10(4)	5(5)	32(5)	11(4)	3(3)
Hypertriglyceridemia	2(<1)	0	9(4)	3(3)	14(2)	2(0.7)	0
GGT increased	4(1)	0	8(3)	1<1)	13(2)	5(2)	2(2)
Osteoarthritis	1(<1)	0	7(3)	1<1)	9(1)	2(<1)	3(3)
Hypercholesterolemia	1(<1)	0	6(2)	0	7(1)	0	0
Nasopharyngitis	13(5)	3(6)	6(2)	0	22(3)	7(2)	1(<1)
Diarrhea	8(3)	0	5(2)	4(4)	17 (2.5)	6(2)	2(2)
Dizziness	3(1)	1(2)	5(2)	3(3)	12(2)	1(0.3)	0
Fatigue	1(<1)	0	5(2)	1(<1)	7(1)	2(<1)	1(<1)
Sinusitis	0	0	5(2)	0	5(<1)	2(<1)	0
Upper Respiratory Tract Infection	6(2)	3(6)	5(2)	4(4)	18(3)	4(1)	4(4)
Bronchitis	2(<1)	3(4)	4(2)	0	8(1)	2(0.7)	0
Nausea	9(3)	1(2)	4(2)	0	14(2)	5(2)	1(<1)
AST increased	6(2)	0	3(1)	1(<1)	10(1)	1(0.3)	1(<1)
Ear infection	0	2(4)	3(1)	0	5(0.7)	0	0
Muscle spasm	1(<1)	0	3(1)	0	4(<1)	7(2)	1<1)
Edema Peripheral	6(2)	0	3(1)	1<1)	10(1)	4(1)	2(2)
Pain in Extremity	7(2.5)	2(4)	3(1)	2(2)	14(2)	11(4)	0
ALT increased	6(2)	0	2(<1)	1(<1)	9 (1)	2(<1)	1(<1)
Cough	5(2)	0	2(<1)	3(3)	10(1)	4(1)	0
Pruritis	4(1)	2(4)	2(<1)	1(<1)	9(1)	0	1(<1)
Blood CPK increased	5(2)	0	1(<1)	1(<1)	7(1)	6(2)	0
Gout	1(<1)	0	1(<1)	0	2(<1)	9(3)	0
Sinus congestion	2(<1)	0	1(<1)	3(3)	6(<1)	0	1(<1)
Rash	2(<1)	3(6)	0	0	5(<1)	4(1)	1(<1)

Adopted Sponsor's Table 2.1-1A; Appendix 1 of the Summary of Clinical Safety.

The numeric imbalances in occurrence of events recorded as hypertriglyceridemia or hypercholesterolemia can also be seen with 150 mg s.c. canakinumab treatment compared with 40 mg i.m. triamcinolone acetonide. The effect of IL-1 blockade on lipid parameters is known and described in labels of other IL-1 blocking agents. The effect of canakinumab on lipid parameters is discussed later in this briefing document.

Table 27: Common AEs occurring at >2% frequency in any treatment group in H2356 and H2357

MedDRA Preferred Term	Canakinumab 150 mg N=225 N (%)	Triamcinolone acetonide 40 mg N=229 N (%)
Any Preferred Term	124 (55)	102 (45)
Hypertension all* Hypertension	15 (6.7) 10 (4.4)	12 (5.2) 9 (3.9)
Headache	9 (4)	7 (3)
Back Pain	9 (4)	1 (0.4)
Hypertriglyceridemia	6 (2.7)	1 (0.4)
Arthralgia	6 (2.7)	1 (0.4)
Nausea	3 (1.3)	5 (2.2)
Hypoaesthesia	3 (1.3)	2 (0.9)
Muscle Spasm	1 (0.4)	6 (2.6)
Gout	1 (0.4)	7 (3)

Source: Tables 14.3.1-1.2. Trial reports H2356 and H2357
*In addition to events coded as "hypertension" this PT includes events coded as "essential hypertension", "blood pressure increased", "systolic blood pressure increased", "hypertensive crisis" from trial report H2356, Table 14.3.1-1.2.

AEs of Special Interest

Renal function

As noted previously, three non-fatal serious adverse events of renal failures were observed in the gouty arthritis dataset; all in the canakinumab-treated subjects. Table 28 summarizes occurrences of renal failure and depicts on-treatment elevations of creatinine and declines in glomerular filtration rate observed in the gouty arthritis trials. As shown, three subjects treated with canakinumab for gouty arthritis developed renal failures compared to no cases of renal failure in the active control arms. All three subjects had elevated serum creatinine at baseline and multiple co-morbidities including history of renal insufficiency and hypertension. According to the case report forms, none of the subjects required hemodialysis and the worsening of renal function appeared reversible.

As shown in Table 28, a greater proportion of subjects treated with 150 mg of canakinumab developed elevation in serum creatinine >1.5 ULN compared to subjects treated in the control groups (4.8% vs 2.8%). When the data in the overall dataset were examined for 25% decline from baseline in creatinine clearance, by Cockroft-Gault equation, a slightly higher proportion of subjects in the 150 mg canakinumab group had a decline in creatinine clearance compared to the triamcinolone group. The applicant also examined for decline in the glomerular filtration rate (GFR) based on the modification of diet in renal disease (MDRD) formula. Based on the MDRD analysis, greater proportion of subjects in the triamcinolone acetonide group showed <75-50 % decline in GFR below the lower limit of normal defined as 90 ml/min. However, according to the same MDRD analysis, a slightly greater proportion of patients treated in 150 mg canakinumab group had > 50 % decline in GFR (7.9%) compared to triamcinolone (6.7%) and colchicine (2.8%) groups.

Table 28: AEs of renal failure and renal function changes in the gout controlled trials

MedDRA Preferred Term	Can--mab ≤100mg N=278	Can--mab split 150mg N=53	Can--mab 150mg N=253	Can--mab ≥200 N=107	Can—mab all N=691	Triam N=286	Colch N=108
Number of Subjects with Renal Failure	0	0	1(0.4%)	2(1.9)	3 (0.4%)	0	0
Renal failure (PT)	0	0		2(1.9)	2(0.3)	0	0
Renal failure chronic (PT)	0	0	1 (0.4)	0	1(0.1)	0	0
Oliguria (PT)	0	0	0	0	0	0	0
Subjects with measured laboratory parameters	N=273	N=53	N=252	N=106	N=684	N=284	N=108
Creatinine Elevation ≥ 1.5 ULN N(%)	3(1.1)	1(1.9)	12(4.8)	3(2.8)	19 (2.8)	8(2.8)	3(2.8)
Creatinine Elevation ≥ 3 ULN, N(%)	0	0	1(0.4)	0	1 (0.1)	1(0.4)	0
≥ 25 % decline from baseline in Creatinine Clearance by Cockroft Gault, N(%)	21 (7.7)	3(5.7)	27 (10.7)	9 (8.4)	60 (8.8)	25 (8.7)	4 (3.7)
Decline in GFR by MDRD*, 75-50 % LLN (90 ml/min), N(%)	47 (17.2)	14 (26.4)	44(17.5)	30 (28.3)	135 (19.5)	67 (23.6)	23(21.3)
Decline in GFR by MDRD*, <50 % LLN (90 ml/min) N(%)	8(2.9)	2(3.8)	20 (7.9)	1(0.9)	31 (4.5)	19 (6.7)	3(2.8)

Source: Table 3.4-2A, Appendix 1 of Clinical Summary of Safety; Tables 14.3-2.7 in trial reports H2356/E1, H2357/E1, H2251, and H2255.
*GFR was calculated by the applicant based on the Modification of Diet in Renal Disease study (MDRD) formula, according to Levey, et al 2007, as follows:
GFR [mL/min/1.73m2] = 175*(C-1.154)*(A-0.203)*G*R; where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 if gender is female or G=1 if gender is male, and R=1.21 if race is black or R=1 otherwise.

Since the MDRD approach uses the cut off of the lower limit of normal and does not take into account individual's baseline renal function, this approach does not seem to take into account subjects who had a decline in renal function from the higher end of the normal range. It does, however, take into account subjects who had renal decline < 25 % of their baseline but who crossed the threshold of 67.5 ml/min (25% decrease from LLN of 90 ml/min).

Similar findings were observed in study H2251E: more patients previously treated with canakinumab in the core H2251 study were noted to have > 25% decline in creatinine clearance (4/75--5.3% in group A, 9/181--5% in group B, compared to 2/60--3.3% in group D).

In the pivotal trials and their extensions, a higher proportion of patients on canakinumab treatment in both trials, at both 12 week and 24 week time points, had an at least 25%

decrease in creatinine clearance (Table 29). The magnitude of the difference between groups was relatively small—3 to 5% in H2356/56E1 and 1 to 2% in H2357/57E1.

Table 29: Proportion of patients experiencing ≥25% decrease in creatinine clearance in the pivotal gout trials and extensions (H2356/H2356E1 and H2357/H2357E1)

Creatinine clearance by Cockroft-Gault	H2356/56E1		H2357/57E1		Combined H2356/56E1 and H2357/57E1	
	Can--mab N=109	Triam. N=113	Can--mab N=112	Triam. N=113	Can--mab N=222	Triam. N=225
≥ 25 % decrease from baseline, n (%) at Week 12	9 (8.3)	6 (5.3)	11(9.8)	8(7.1)	20 (9)	14(6)
≥ 25 % decrease from baseline, n (%) at Week 24	14 (12.8)	8 (7.1)	13 (11.6)	12 (10.6)	27 (12)	20 (9)

Source: Tables 14.3-2.7 Trial Reports H2356 and H2357

Although higher proportions of patients had elevation in creatinine and creatinine clearance decline with 150 mg canakinumab treatment compared triamcinolone acetonide 40 mg i.m., the magnitude of the treatment effect is not large, and it is not clear what clinical impact these changes may have over time.

Cardiovascular events

The occurrence of cardiovascular events would not be unexpected in the gouty arthritis program because the majority of the enrolled patients had significant co-morbidities predisposing them to development of CV events. To examine the incidence of cardiac adverse events the applicant used the definition of potential Major Adverse Cardiac Events (MACE) which included the following:

- Cardiovascular (CV) Death (includes 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

Cardiovascular events that occurred in two pivotal trials and their extensions H2356/56E1 and H2357/57E1 were reviewed and adjudicated by the Cardiovascular and Cerebrovascular (CCV) Safety Committee established for these trials.

Table 30 lists cardiovascular events in the gouty arthritis dataset. Overall, the incidence of the cardiovascular events was low and appeared comparable between canakinumab-treated groups and the active comparator-treated groups.

Table 30: Potential expanded MACE events in the gout controlled trials.

MedDRA System Organ Class	Can—mab ≤ 100 mg N=278	Can—mab split 150 mg, N=53	Can—mab 150 mg N=253	Can—mab ≥ 200 mg N=107	Total Can—mab N=961	Triam N=286	Colch N=108
Number of Subjects with ≥ 1AE:	**1 (0.4)**	**0**	**2 (0.8)**	**1(0.9)**	**4(0.4)**	**2(0.6)**	**2(1.9)**
CV Death (Myocardial Infarction)	**0**	**0**	**0**	**0**	**0**	**0**	**1(0.9)**
[1]Stroke or TIA	**1(0.4)**	**0**	**2(0.8)**	**0**	**3 (0.4)**	**2 (0.6)**	**0**
Carotid Artery Stenosis	1(0.4)	0	0	0	1(0.1)	0	0
Transient Ischemic Attack	0	0	1(0.8)	0	1(0.1)	0	0
Cerebrovascular Accident	0	0	1(0.8)	0	1(0.1)	0	0
Intracranial Hemorrhage	0	0	1(0.8)	0	1(0.1)	0	0
Cerebrovascular Disorder	0	0	0	0	0	1(0.3)	0
Ischemic Stroke	0	0	0	0	0	1(0.3)	0
Myocardial Infarction	**0**	**0**	**0**	1(0.9)	1(0.1)	**0**	**2(1.9)**
Acute MI[2]	0	0	0	1(0.9)	1(0.1)	0	1(0.9)
ECG ST segment elevation	0	0	0	0	0	0	1(0.9)

Source: derived from Sponsor's Tables 2.5-19A, Appendix 1 and Table 2-35 of Summary of Clinical Safety and the respective narratives of cases.
[1]Vertebrobasilar insufficiency and elevated CPK are not included
[2]combines Preferred Terms of Acute Myocardial Infarction and Myocardial Infarction.

Hypersensitivity Reactions and Anaphylaxis

Table 31 below lists the relevant events found through the applicant's search of MedDRA Standard Medical Queries for (1) anaphylactic reactions, (2) angioedema, (3) severe cutaneous adverse reactions, (4) immunology and allergy investigations and the corresponding Preferred Terms in both the gouty arthritis and RA programs.

Overall, small proportions of subjects in both gout and RA programs developed non-serious hypersensitivity reactions; all events occurred within the first 24 weeks of dosing. As shown in Table 31, there were 2/691 (0.3%) cases of non-serious events of urticaria observed in the gout program, and 5/441(1.1%) events of facial or lip swelling, or urticaria observed in the RA program. One subject, CACZ885A2204, enrolled in the RA program was treated with canakinumab and methotrexate (MTX) and developed urticaria 2 weeks after receiving 600 mg of canakinumab (Day 1) intravenously and MTX orally (Day 1 and Day 8) in trial A2204. According to the respective CRF, the episode of urticaria lasted several days and resolved with cetirizine hydrochloride treatment; the event was considered non-serious. This same subject later received two more doses of canakinumab 600 mg IV (Day 15 and Day 43) and one dose of concomitant methotrexate (Day 51), after which 4 hours later she developed a serious event of "lip edema" of moderate severity requiring an emergency clinic visit and treatment with intravenous betamethasone sodium phosphate and chlorphenamine maleate. The event was considered resolved on the following day and the subject was discontinued from the trial.

Upon FDA's request, the applicant retrospectively assessed whether any of the adverse events met clinical criteria for diagnosis of anaphylaxis, as per the Second Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network

(FAAN). None of the subjects who developed the hypersensitivity events listed in Table 31 met the criteria.[15]

Table 31: Summary of hypersensitivity reactions in the gout and RA programs

MedDRA SMQ HGLT/ Preferred Term	Can--mab N=691 N(%)	Triamc N=286 N(%)	Colch N=108 N(%)	Can--mab N=332 N(%)	Placebo N=121 N(%)	Can--mab all RA N=441 N(%)
	Gout Program			RA program		
Angioedema (SMQ)	**2(0.3)**	**0**	**0***	**3 (0.9)**	**1 (0.8)**	**5 (1.1)**
Eyelid edema (PT)				1(0.3)		2 (0.5)
Face edema (PT)						1(0.3)
Lip edema (PT)				1(0.3)		1(0.3)
Lip swelling (PT)				1(0.3)		1(0.3)
Urticaria (PT)	2(0.3)			1(0.3)		1(0.3)
Swelling face (PT)					1(0.8)	0

Source: Source Tables 2.5-1A, 2.5-1B, 2.5-1C, Appendix 1 of the Summary of Clinical Safety
*one event related to bee sting is not included

Vertigo/dizziness

Events of vertigo and dizziness have been previously reported in patients treated with canakinumab: occurrence of vertigo has been reported in 9-14% patients in the Cryopyrin-Associated Periodic Syndromes (CAPS) studies, primarily in patients with Muckle-Wells Syndrome. The adverse reaction of vertigo is included in the current labeling for canakinumab. No pathogenetic mechanisms have been confirmed to explain occurrence of vertigo with canakinumab treatment.

Table 32 summarizes adverse events of dizziness and vertigo in the gouty arthritis controlled trials. Overall, a small proportion of subjects treated with canakinumab in the gout program developed events of dizziness and vertigo (16/691- 2.3%) compared to isolated occurrences among triamcinolone-treated patients and no events among patients treated with colchicine. Upon examining the dose-response, slight increases in rates of dizziness are observed with higher doses of canakinumab.

Table 32: Events of dizziness and vertigo in the gout controlled trials

MedDRA System Organ Class/Preferred Term	Can-mab ≤ 100mg N=278	Can--mab split 150mg, N=53	Can--mab 150mg N=253	Can--mab ≥ 200mg N=107	Can--mab All N=691	Triam N=286	Colch N=108
Number of Subjects with ≥ 1 AE of Vertigo or Dizziness	**5(1.8%)**	**1(1.9%)**	**6(2.4%)**	**4(3.7%)**	**16(2.3%)**	**2(0.7%)**	**0**
Number of Subjects with ≥ 1 AE of Dizziness	**3(1.1%)**	**1(1.9%)**	**5(2%)**	**3(2.8%)**	**12(1.7%)**	**1(0.3%)**	**0**
Number of Subjects with ≥ 1 AE of Vertigo	**2(0.7%)**	**0**	**1(0.4%)**	**1(0.9%)**	**4(0.6%)**	**1(0.3%)**	**0**

Source: Summary of Clinical Safety, Appendix 1, Tables 2.5-4A, 2.5-4B, 2.5-4C.

In RA clinical trials, the proportions of patients developing events of dizziness and vertigo were similar between canakinumab- and placebo-treated patients (6.4% vs

[15] Sampson et al., J Allergy Clin Immunol, 2006, 117(2) :391-397.

10.7%), however, one subject in RA program was discontinued from canakinumab treatment because of 3 episodes of dizziness, occurring between days 1-21 of treatment period and lasting 2-3 days each, after receiving canakinumab 600 mg intravenously and 300 mg intravenously, 16 days apart. The overall incidence of dizziness was 14/441 (3.2%) and the incidence of vertigo was 16/441 (3.6%) among all RA patients exposed to canakinumab.

Injection Site Reactions

Local injection site reactions occurred in 26/691 (3.8%) of patients with gouty arthritis treated with subcutaneous injections; the reactions occurred in slightly higher rates among patients receiving canakinumab when compared to patients receiving subcutaneous placebo in the triamcinolone or colchicine comparator groups (Table 33). There were no severe reactions in any of the groups; the most common reactions in canakinumab-exposed patients were symptoms of redness reported in 9 (1.3%) patients and local pain reported in 6 (0.9%) patients. Other reactions reported with canakinumab included hemorrhage, induration, swelling, itching, and tenderness. There appeared to be no dose-response with occurrence of local reactions.

Table 33: Injection site reactions reported in the gout controlled trials

MedDRA Primary SOC/ Preferred term	Can-mab All N=691	Can-mab ≤ 100 mg N=278	Can-mab split 150 mg, N=53	Can-mab 150 mg N=253	Can-mab ≥ 200 mg N=107	Triam (sc pbo) N=286	Colch (sc pbo) N=108
Total number of patients with any injection site symptoms	**26(3.8%)**	**16 (5.8%)**	**2(3.8%)**	**3(1.2%)**	**5(4.7%)**	**3(1%)**	**4(3.7%)**
Symptom severity							
Mild	24(3.5%)	15(5.4%)	2(3.8%)	2(0.8%)	5(4.7%)	3(1%)	4(3.7%)
Moderate	2(0.3%)	1(0.4%)	0	1(0.4%)	0	0	0

Source: Table 7.1-2A, Summary of Clinical Safety.

Immunogenicity

Of the 961 patients exposed to canakinumab in the gouty arthritis program, 8 patients (1 in trial H2251 and 7 in trial H2251E) tested positive for anti-canakinumab antibodies in low titers. None of the RA patients tested positive for the anti-product antibodies. Of the 8 patients from the gout program, one patient tested positive after receiving four injections of canakinumab (split 150 mg dose q 4 weeks) and another patient tested positive after receiving two 150 mg injections of canakinumab. The remaining 6 subjects received single injections of canakinumab ranging between 50 mg and 150 mg. None of these eight subjects were reported to develop any associated adverse events; however, with so few patients being anti-product antibody positive, the risk for adverse events related to immunogenicity could not be estimated.

Laboratory Findings

Hematology parameters

Table 34 below summarizes the frequencies of newly occurring post-baseline notable abnormalities in the hematology parameters in the gouty arthritis dataset. Overall, leucopenia, neutropenia, thrombocytopenia, and eosinophilia occurred more frequently in patients treated with canakinumab compared to patients treated with triamcinolone acetonide or colchicine. The analyses of mean changes revealed mean decreases in white blood cells, neutrophils and platelets in the canakinumab groups compared to triamcinolone and colchicine. The rates of shifts to abnormal appeared to be lower with smaller doses of canakinumab; the highest rates were observed with the 150 mg dose (Table 34). One fifth of subjects treated with 150 mg canakinumab developed Grade 1 neutropenia compared to 5.3% subjects treated with triamcinolone acetonide (Table 35). The majority of those who developed leucopenia and neutropenia had these changes occurring within the first 2-12 days following canakinumab injection; the changes were lasting generally for the duration of canakinumab's pharmacodynamic effect, appeared reversible and, in some patients, recurred with subsequent injections.

Table 34: Shifts from normal to abnormal in selected hematology parameters in the gout controlled trials

MedDRA Primary SOC/ Preferred term	All N=691	≤ 100 mg N=278	split 150 mg, N=53	150 mg N=253	200 mg N=107	Triam N=286	Colch N=108
WBC ≤ 0.8 X LLN	35(5%)	10/273 (3.7%)	2/53 (3.8%)	17/252 (6.7%)	6/106 (5.7%)	4/284 (1.4%)	3/108 (2.8%)
Abs neutrophils ≤ 0.9 X LLN	80(11.6%)	15/273 (5.5%)	6/53 (11.3%)	44/252 (17.5%)	15/106 (14.2%)	6/284 (2.1%)	7/108 (6.5%)
Abs eosinophils > 1.1 ULN	33(4.7%)	10/273 (3.7%)	2/53 (3.8%)	15/252 (6%)	6/106 (5.7%)	6/284 (2.1%)	4/108 (3.7%)
Platelets < LLN-75X10^9/L	75(10.9%)	22/273 (8.1%)	8/53 (15.1%)	32/251 (12.7%)	13/106 (12.3%)	22/284 (7.7%)	6/107 (5.6%)

Source: Table 3.3-2A, Appendix 1 of Summary of Clinical Safety.

Two patients in the canakinumab-treated groups developed associated adverse events of infections. Subject H2251-0075-00002 developed an acute respiratory infection concurrently with neutrophil count of 1.96 X 10E9 (lowest recorded WBC was 3.7 X 10E9/L). Subject H2356-0121-00001 received a single dose of canakinumab 150 mg subcutaneously in the pivotal trial H2356 and developed leucopenia (4.0 X 10^9/L) and neutropenia (1.9 X 10^9/L) within the first few days following study drug administration; on Day 29 this subject was diagnosed with submandibular (jaw) abscess requiring surgical treatment and antibiotics. The event was recorded as serious. Both subjects subsequently recovered from the infections.

Table 35: Selected abnormal hematology values by Common Toxicity Criteria (CTC) grades (ver.3)

MedDRA Primary SOC/ Preferred term	≤ 100 mg N=278	150 mg N=253	200 mg N=107	Triam N=286	Colch N=108
WBC, N(%)					
Grade 1 < LLN—3X10^9/L	24(8.8)	**58(23)**	19(17.9)	**19(6.7)**	7(6.5)
Grade 2 <3.0--2.0 X10^9/L	7(2.6)	**9(3.6)**	2(1.9)	**1(0.4)**	2(1.9)
Grade 3 <2.0--1.0 X10^9/L	1(0.4)	**0**	1(0.9)	**0**	1(0.4)
Absolute neutrophils, N(%)					
Grade 1 < LLN—1.5X10^9/L	26(9.5)	**52(20.6)**	17(16)	**15(5.3)**	7(6.5)
Grade 2 <1.5--1.0 X10^9/L	7(2.6)	**20(7.9)**	3(2.8)	**2(0.7)**	3(2.8)
Grade 3 <1.0—0.5 X10^9/L	1(0.4)	**5(2)**	0	**0**	0
Grade 4 <0.5 X10^9/L	0	**0**	2(1.9)	**0**	0

Source: April 14, 2011, IR response, Part 2.

In the RA program, three canakinumab-treated subjects developed leucopenia and neutropenia with subsequent occurrence of severe influenza (1), severe bacterial skin infection (1), and a left knee prosthetic infection (1). Two other subjects receiving canakinumab at 300 mg subcutaneously every two weeks were discontinued from the trial for persistent leucopenia (Subject A2201-0023-00006: WBC = 2.7X10 9 /L and Subject A2201-0023-00009: WBC 2.3X 10 9/L); both subjects had normal white blood cell counts at baseline. None of the placebo-treated subjects had leucopenia or neutropenia recorded as AEs or had any events of infections associated with low white blood cell count in the RA program.

More subjects treated with canakinumab were observed to develop Grade 1 thrombocytopenia (LLN-75X109/L) according to the Common Toxicity Criteria, v3.0; 6 subjects treated with canakinumab and one subject treated with colchicine were reported to have adverse events of thrombocytopenia without any associated bleeding events. More subjects treated with 150 mg canakinumab had shifts to higher eosinophil counts compared to subjects treated with 40 mg triamcinolone acetonide (6% vs. 2.1%).

Lipid Parameters

Increases in total cholesterol and triglycerides were also observed with canakinumab treatment. For triglyceride values, a mean increase was observed with 150 mg canakinumab treatment compared to mean decrease with 40 mg triamcinolone acetonide treatment (+0.382+/-1.87mmol/L vs -0.035+/-2.06 mmol/L). As shown in Table 36, more subjects treated with canakinumab 150 mg s.c compared to traimcinolone acetonide 40 mg i.m. had shifts to different degrees of increase for triglycerides (40% vs 26%), LDL cholesterol (8.1% vs 6.9%), and total cholesterol (9% vs 5% for ≥1.5 ULN).

Table 36: Shifts from normal to abnormal lipid parameters in the gout controlled trials

Lipid Parameters	Can-mab All N=691	Can-mab ≤ 100 mg N=278	Can-mab split 150 mg, N=53	Can-mab 150 mg N=253	Can. 200 mg N=107	Triam N=286	Colch N=108
N patients with measured lab parameters	0	0	0	N=211	0	N=218	N=108
HDL cholesterol, N(%)							
>ULN*	ND**	ND	ND	**6 (2.8)**	ND	**8(3.7)**	ND
LDL cholesterol, N(%)							
>ULN	ND**	ND	ND	**17 (8.1)**	ND	**15 (6.9)**	ND
N patients with measured lab parameters	N=684	N= 273	N=53	N=252	N=106	N=218	N=108
Total Cholesterol, N(%)							
> ULN	158 (23)	63(23)	13(24)	**60(24)**	22(21)	**65(23)**	27(25)
> 1.5 X ULN	56(8)	22(8)	6(11)	**23(9)**	5(5)	**15(5)**	4(4)
Triglycerides							
> ULN, N(%)	249 (36)	87(32)	23(43)	**101(40)**	38 (36)	**75 (26)**	29(27)
≥ 1.5 X ULN	166 (24)	61(22)	14 (26)	**63(25)**	28 (26)	**39(14)**	17 (16)
≥ 2.5 X ULN	63(9)	24 (9)	5(9)	**26 (10)**	8(7.5)	**9(3)**	8(7)
≥ 5 X ULN	18 (3)	9(3)	2(4)	**6(2)**	1(0.9)	**2(0.7)**	6(6)

Source: Table US6-1 applicant's response to IR, May 9, 2011
*ULN- Upper Limit of Normal
**HDL cholesterol was measured only in pivotal trials H2356/56E1 and H2357/57E1; LDL cholesterol was calculated according to Cleeman et al, 2001: LDL=Total Cholesterol –HDL-[TG/5] with ULN=130mg/dL or 3.367mmol/L.

Liver enzymes

The proportions of subjects who developed hepatic AEs in the gouty arthritis and rheumatoid arthritis controlled trials are summarized in Table 37. In the gout population, the incidence of these events was higher among patients treated in the canakinumab groups, with the highest rate observed in 150 mg canakinumab-treated group (6.3%) compared to the traimcinolone-treated group (3.1%). Six patients treated with canakinumab (3 from H2351, 1 from trial H2355, 1 from H2356, and 1 from H2357) were found to have elevated transaminases concomitantly with hypertriglyceridemia. Hepatic AE rates were comparable in the RA population. The vast majority of the reported hepatic adverse changes were asymptomatic.

Two subjects treated for gouty arthritis were noted to have concurrent elevations in bilirubin and AST and/or ALT. Subject H2251-0018-00005 (53 y/o female) had baseline LFT abnormalities including bilirubin ≥2 x ULN, AST >3 x ULN, ALT > ULN, and GGT was >4 x ULN. This patient received one dose of canakinumab (100 mg) and continued to have fluctuation in the LFT parameters in the same range without clinically meaningful worsening. Because they were present at the baseline, these LFT abnormalities are unlikely to be related to the study drug.

Subject H2357-0031-00002 (32 y/o male) had past medical history of hepatic steatosis and mildly elevated ALT and GGT (both <1.5 X ULN) at baseline. This subject was treated with one dose of canakinumab 150 mg subcutaneously and on Day 29 was found to have ALT>3ULN, AST >2 ULN, bilirubin ≥1.5 x ULN, and GGT > UNL while remaining asymptomatic. On Day 85, bilirubin normalized, ALT decreased to <2 ULN, and GGT and ALT decreased to slightly above normal. Although this subject had prior history of liver disorder, worsening of the LFTs and increase in bilirubin coincided with

canakinumab exposure (half-life ~27 days), therefore, the contributing role of the drug can not be excluded in this case.

Table 37: Changes in liver enzyme tests from baseline to end of study in gout and RA programs

Liver Function	Can--mab ≤100mg N=278	Can--mab split 150mg N=53	Can--mab 150mg N=253	Can--mab ≥200 N=107	Can—mab all N=691	Triam N=286	Colch N=108	Can—mab RA N=344	Placebo RA N=121
N (%) of Subjects with at Least 1 AE of liver dysfunction	12(4.3)	1(1.9)	16 (6.3)	5(4.7%)	34 (4.9%)	9 (3.1%)	3(2.8%)	11(3.2%)	5(4.1%)
N of Subjects with laboratory measurements	N=273	N=53	N=252	N=106	N=684	N=284	N=108	N=344	N=121
N (%) Subjects with at Least 1 elevation of ALT									
> ULN	**71(26)**	**14(26)**	**57(22.6)**	**24(22.6)**	**166 (24)**	**54(19)**	**28 (26)**	**ND**	**ND**
≥ 3 ULN	**7 (2.6)**	**1(1.9)**	**4(1.6)**	**5(4.7)**	**17 (2.5)**	**7(2.5)**	**2(1.9)**	**8(2.3)**	**1(0.8)**
≥ 5 ULN	**3(1.1)**	**0**	**0**	**1(0.9)**	**4 (0.6)**	**0**	**0**	**2(0.6)**	**0**
≥ 10 ULN	**1(0.4)**	**0**	**0**	**0**	**1(0.1)**	**0**	**0**	**0**	**0**
N (%) Subjects with at Least 1 elevation of AST									
> ULN	57 (20.9)	10(19)	49 (19)	21(20)	137 (20)	33(11.6)	13(12)	ND	ND
≥ 3 ULN	5(1.8)	1(1.9)	2(0.8%)	2(1.9)	10 (1.5)	7(2.5)	1(0.9)	4(1.2)	1(0.8)
≥ 5 ULN	1(0.4)	1(1.9)	0	0	2(0.3)	2(0.7)	0	0	0
≥ 10 ULN	1(0.4)	0	0	0	1(0.1)	1(0.4)	0	0	0
N(%) Subjects with at Least 1 elevation of GGT									
≥ ULN	45(16.5)	14(26.4)	36 (14)	14 (13)	109 (15.9)	27 (9.5)	20(18.5)	ND	ND
≥ 3 ULN	23(8.4)	2(3.8)	17 (6.7)	6(5.7)	48 (7)	16 (5.6)	6(5.6)	1/102*(1)	1 (2.8)
N (%) Subjects with at Least 1 elevation of bilirubin									
≥ ULN	22(8.1)	4(7.5)	20 (7.9)	3(2.8)	49 (7.2)	26(9.2)	6(5.6)	5(1.5)	3(2.5)
≥ 1.5 ULN	4 (1.5)	0	3(1.2)	0	7(1)	3(1.1)	0	0	1(0.8)
≥ 2 ULN	1(0.4)	0	2(0.8)	1(0.9)	4(0.6)	0	0	0	0
≥ 1.5 ULN and ALT and/or AST ≥ 3 ULN	1(0.4)*	0	1(0.4)	0	2(0.3)	0	0	0	0
≥ 2 ULN and ALT and/or AST ≥ 3 ULN	1(0.4)	0	0	0	1(0.1)	0	0	0	0
N (%) Subjects with at Least 1 elevation of Alk Phosphatase									
≥ ULN, N subjects (%)	4(1.5)	0	8(3.2)	2(1.9)	14(2)	4(1.4)	6(5.6)	ND	ND
≥ 1.5 ULN	0	0	0	0	0	4(1.4)	1(0.9)	8(2.3)	2(1.7)

ND-not determined
*Subject H2251-0018-00003 had mild (< 1.5 ULN) elevation in bilirubin occurring not concurrently with AST and ALT elevation.
Source: Table 3.4-2A; Table 2.5-5A of Clinical Summary of Safety; Table US2.10-1 from applicant's response to IR#2; respective case summaries.

One subject (H2251-0018-00003) was found to have transaminase elevations in the range of 10 X ULN. This subject was a 55 year old Caucasian male who had normal LFTs at baseline and throughout the study after being treated with 25 mg of canakinumab subcutaneously. On Day 178, the subject was found to have both ALT and AST ≥10 x ULN and GGT >4 x ULN. No relevant medical history was reported for this patient, however, on day 204, follow-up LFTs normalized except for GGT remaining <2ULN. These changes were unlikely related to the study drug as they occurred out of the temporal window of canakinumab exposure.

Overall, primarily mild elevations in LFTs were observed in patients with gouty arthritis exposed to canakinumab. LFT elevations were observed as both de novo occurrences and declines of pre-existing liver dysfunction.

Effect on serum uric acid

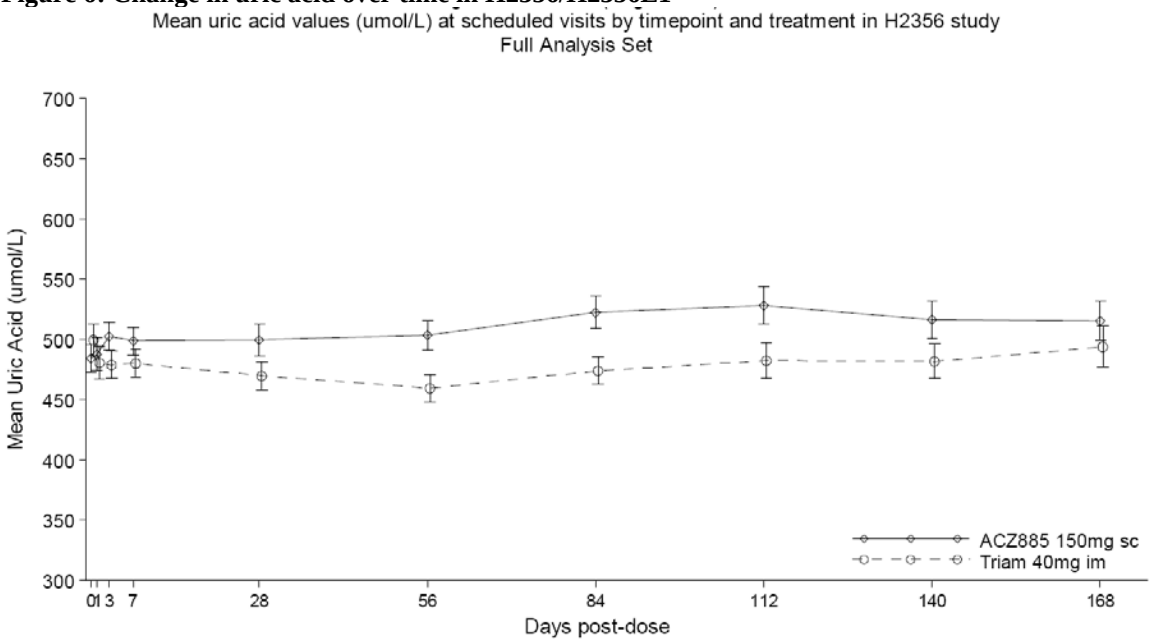
Serum uric acid was measured at pre-specified time intervals in patients enrolled in the controlled trials and their extensions H2356/56E1 and H2357/57E1. Given that this was the gout population, serum uric acid levels were increased in both treatment groups at baseline (Table 6—baseline disease characteristics). With treatment, the mean serum uric acid levels increased in subjects treated with canakinumab and remained stable in subjects treated with triamcinolone acetonide. Table 38 summarizes the mean changes in serum uric acid levels in patients treated in the pivotal trials up to 12 weeks of observation. The mean changes in serum uric acid in trials H2356/H2356E1 and H2357/H2357E1 are represented graphically in Figure 6 and Figure 7. Overall, patients treated with canakinumab had rapid increases in serum uric acid from baseline occurring within the first week of treatment and declining by the 56-84 day time point. A similar pattern of recurrent elevations in serum uric acid was observed upon re-treatment. According to the applicant's analysis, patients who were switched from triamcinolone acetonide to canakinumab during the second extensions of trials H2356E2 and H2357E2 were also observed to have increases in serum uric acid with canakinumab treatment.

Table 38: Mean changes in serum uric acid from baseline to selected timepoints in trials H2356/56E1 and H2357/57E1

	Day 2 post-dose	Day 4	Day 29	Day 57	Day 85 (12 weeks)
Trial H2356					
Canakinumab	+6 (40) µmol/L 0.1 (0.7) mg/dL	+18 (68) µmol/L 0.3(1.1) mg/dL	+ 17 (121) µmol/L 0.3 (2.0) mg/dL	+ 25 (120) µmol/L 0.4 (2.0) mg/dL	+ 35 (144) µmol/L 0.6 (2.4) mg/dL
Triamcinolone	-14 (42) µmol/L 0.2 (0.7) mg/dL	-19 (73) µmol/L 0.3 (1.2) mg/dL	-25 (104) µmol/L 0.4 (1.7) mg/dL	-29 (139) µmol/L 0.4 (2.3) mg/dL	-19 (128) µmol/L 0.3 (2.1) mg/dL
Trial H2357					
Canakinumab	+ 3(40) µmol/L 0.05 (0.7) mg/dL	+ 22 (57) µmol/L 0.4 (0.9) mg/dL	+38 (97) µmol/L 0.6 (1.6) mg/dL	+ 49 (110) µmol/L 0.8 (1.8) mg/dL	+ 41 (119) µmol/L 0.7 (2.0) mg/dL
Triamcinolone	- 27 (42) µmol/L 0.45(0.7) mg/dL	-15 (64) µmol/L 0.3 (1.1) mg/dL	+10 (71) µmol/L 0.17 (1.2) mg/dL	+ 20 (99) µmol/L 0.4 (1.7) mg/dL	+ 15 (92) µmol/L 0.3 (1.7) mg/dL

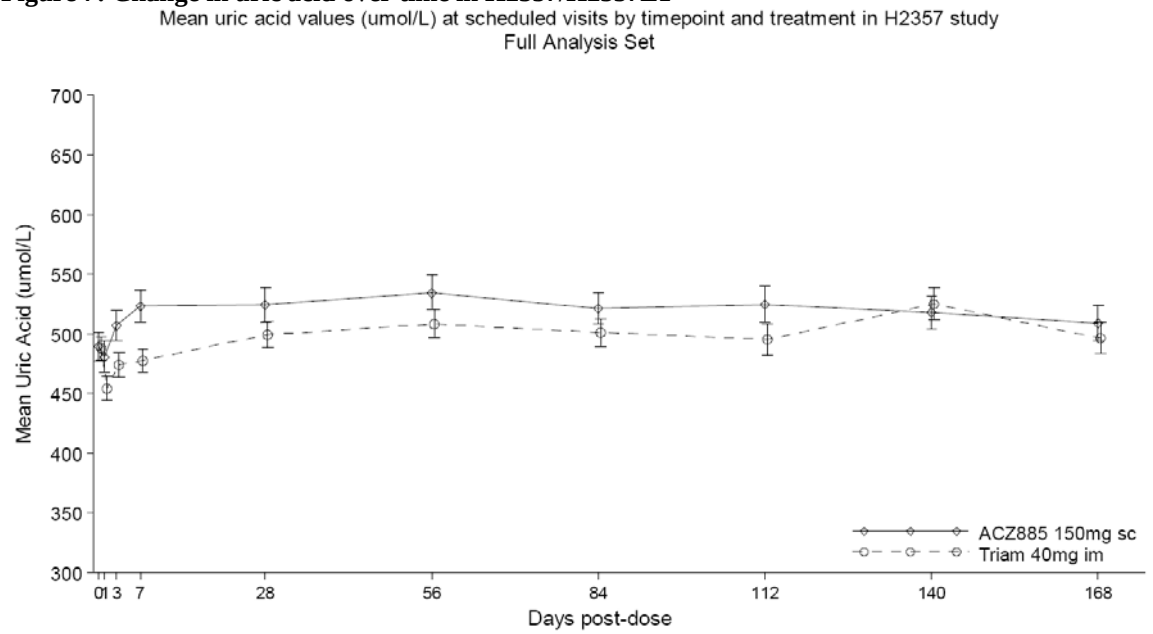
Source: Tables 14.3-2.2 in trials H2356, H2356E1 and H2357, H2357E1.

Figure 6: Change in uric acid over time in H2356/H2356E1



Source: Figure US3.2-1a1 of the response to 5-5-11 information request

Figure 7: Change in uric acid over time in H2357/H2357E1



Source: Figure US3.2-1b1 of the response to 5-5-11 information request

Given the variability observed with the measurements of mean differences, the proportions of patients in trials H2356 and H2357 with uric acid increases of >0.5 mg/dL, >1 mg/dL and >2 mg/dL were evaluated, as summarized in Table 39. Canakinumab treatment was associated with a higher proportion of patients in each elevation category compared to triamcinolone. Although the majority of canakinumab patients experienced elevations of > 0.5 mg/dL, approximately one-third of patients experienced an elevation of over 2 mg/dL.

Table 39: Proportions of patients with increases in serum uric acid in trials H2356 and H2357

N(%) subjects experiencing increase in serum uric acid during the first 12 weeks of treatment	H2356		H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg SC N=109	Triam. ac. 40 mg IM N=112	Can-mab 150 mg SC N=112	Triam. ac. 40 mg IM N=113	Can-mab 150 mg SC N=221	Triam. ac. 40 mg IM N=225
>0.5 mg/dL	83(76)	63(56)	93(83)	65 (57.5)	176 (80)	128 (57)
Odds ratio (95% CI)	2.5 (1.4, 4.4)		3.6 (2.0, 6.7)		3.0 (2.0, 4.5)	
>1 mg/dL	66 (60)	39 (35)	72(64)	49 (43)	138 (62)	88 (39)
Odds ratio (95% CI)	2.9 (1.7, 5.0)		2.4 (1.4, 4.0)		2.6 (1.8, 3.8)	
>2 mg/dL	39 (36)	15(13)	30 (27)	26 (23)	69 (31)	41(18)
Odds ratio (95% CI)	3.6 (1.8, 7.0)		1.2 (0.7, 2.2)		2.0 (1.3, 3.1)	

Source: Table US3. 2-3a_1b, US3. 2-3b_1b, US3. 2-3c_1b, US3. 2-4a_1b, US3. 2-4b_1b, US3. 2-4c_1b, US3. 2-5a_1b, US3. 2-5b_1b, US3. 2-5c_1b.

When levels of serum uric acid were analyzed in relation to urate-lowering therapy use, increases in mean serum uric acid were observed in the canakinumab-treated patients regardless of ULT treatment status, whereas primarily mean decreases in serum uric acid were observed in subjects treated with triamcinolone acetonide (Table 40).

Table 40: Mean change in serum uric acid over time by subgroups on or off urate lowering therapy, pooled data from H2356 and H2357

	Day 2 post-dose	Day 4	Day 29	Day 57	Day 85 (12 weeks)
On ULT, Mean (SD)					
Canakinumab	-0(42) µmol/L 0 (0.7) mg/dL	+5 (67) µmol/L 0.1(1.1) mg/dL	+10 (126)µmol/L 0.2(2.1) mg/dL	+34 (130)µmol/L 0.6(2.2) mg/dL	+55 (156)µmol/L 0.9 (2.6) mg/dL
Triamcinolone	-10 (39) µmol/L 0.2 (0.7) mg/dL	-15 (65) µmol/L 0.25 (1.1) mg/dL	-7(90) µmol/L 0.1 (1.5) mg/dL	+2 (122) µmol/L 0.03 (2.05) mg/dL	+6 (110) µmol/L 0.1 (1.8) mg/dL
Not on ULT, Mean (SD)					
Canakinumab	+8 (39) µmol/L 0.1(0.7) mg/dL	+29 (57) µmol/L 0.5 (1) mg/dL	+39 (97) µmol/L 0.7(1.6) mg/dL	+39 (106) µmol/L 0.7 (1.8) mg/dL	+27 (113)µmol/L 0.5 (1.8) mg/dL
Triamcinolone	-28 (43) µmol/L 0.5 (0.7) mg/dL	- 18 (70) µmol/L 0.3 (1.2) mg/dL	-6 (91) µmol/L 0.1 (1.5 mg/dL)	-10 (124) µmol/L 0.2 (2.1) mg/dL	-12 (117) µmol/L 0.2 (2) mg/dL

Source: Table 3.4-3A, Appendix 1, Summary of Clinical Safety.
1mg/dL= 59.48 µmol/L

The observed changes in serum uric acid are notable and concerning, particularly for patients with underlying hyperuricemia. The recurrent and sustained character of the serum uric acid increases and the observed incremental changes raise concerns regarding uric acid control on urate-lowering therapy, as well as the possibility of increased tophi formation in patients with baseline high levels of uric acid.

Overview of safety profile of canakinumab in re-treated patients

Some patients enrolled in the double-blind Phase 3 trials and their double-blind extensions H2356/56E1 and H2357/57E1 were re-treated with the study medication on demand if they developed a new flare. In addition, patients initially treated in study

H2251 upon start of allopurinol treatment were enrolled in the extension trial H2251E and treated with 150 mg canakainumab s.c. regardless of their original treatment assignment in H2251, if they developed a gouty arthritis flare.

As mentioned earlier, there were 60 patients re-treated with canakinumab in the pivotal trials and their double-blinded extensions (E1) and 75 patients re-treated in the H2251E extension trial (Table 16, Table 17, above). Upon submission of the 120-day safety update, the applicant included interim analyses of the ongoing open-label extensions of both trials, H2356E2 and H2357E2. The side-by-side comparison of the proportions of subjects who received ≥ 1 injection of canakinumab of those originally randomized to canakinumab treatment from the original submission and from the 120-day safety update is shown in Table 41 below.

Table 41: Canakinumab re-treatment exposure in the pivotal gout trials and extensions (E1-double-blind, E2-open label)

N of injections:	Canakinumab 150mg N=225 re-treated in 2356/56E1 2357/57E1 Original submission	Canakinumab 150mg N=225 re-treated in trials 2356/56E1/56E2 2357/57E1/57E2 120-day safety update
1	165(73%)	107(47%)
2	47 (19%)	75(33%)
3	11(4%)	25(11%)
4	2 (1%)	15(7%)
≥5	0	3(2%)

Source: applicant's Table 3-19, 120-day safety update.

The subjects re-treated in the pivotal trials and their E1 extensions represent the groups re-treated in the double-blinded setting and will be examined for occurrence of adverse events. The data displayed below represent an overview of adverse events occurring in groups of re-treated vs non-retreated subjects enrolled in the pivotal trials and their double-blinded extensions H2356/56E1 and H2357/57E1. The vast majority of these subjects were followed for 24 weeks.

A comparison of selected disease characteristics of the subjects re-treated vs. not re-treated with canakinumab in trials H2356/56E1 and H2357/57E1 are shown in Table 42 below. As shown, more subjects with polyarticular tophaceous gout and with higher average number of flares during the previous year required re-treatment. In this non-randomized comparison, the baseline co-morbidities of hypertriglyceridemia and stable hypertension appeared to be distributed equally between the re-treated and non-retreated subjects.

Table 42: Comparison of selected disease characteristics among re-treated and non-retreated patients in trials H2356/56E1, H2357/57E1 and H2251E1

	Trial H2356/56E1		Trial H2357/57E1	
Disease Characteristics	Re-treated N=60	Non-retreated N=165	Re-treated N=89	Non-retreated N=140
Number of joints affected by acute attack of gout within the last five days				
1	22(37)	106 (64)	50(56)	82(59)
2	14(23)	28(17)	20(22)	29(21)
3	4(7)	11(7)	7(8)	11(8)
4	6(10)	5(3)	3(3)	6(4)
>4	14(23)	15(9)	9(10)	12(9)
Mean number of flares in the last year	8.1	6	6	7
Known presence of tophi	28 (47)	36(22)	30(34)	38(27)
N(%) Subjects with contraindications, intolerance, or lack of efficacy to				
NSAIDs	56(93)	148(90)	81(91)	128(91)
Colchicine	21(35)	73(44)	42(47)	56(40)
Both NSAIDs and Colchicine	17(28)	59(36)	35(39)	49(35)
Subjects with reported cardiovascular contraindications to NSAIDs, N(%)				
Cardiovascular diseases	2(3.3)	12(7)	1(1)	7(5)
Uncontrolled hypertension	3(5)	2(1.2)	2(2)	5(4)
Subjects with any cardiovascular reasons for intolerance of NSAIDs, N(%)				
Hypertension	3(5)	9(5.5)	5(6)	12 (9)
Selected baseline co-morbidities, N(%)				
Hypertriglyceridemia	8(13)	24(14)	10 (11)	27(19)
High blood pressure or on antihypertensive treatment	14(23)	56(34)	23(26)	38(27)
Hypercholesterolemia	14 (23)	41(24)	24(27)	40(29)
Stable Hypertension	28 (47)	103 (62)	49 (55)	90(64)
Study H2251E1				
Selected baseline co-morbidities, N(%)	Group A N=75	Group B N=181	Group C N=25	Group D N=60
Hypertension	32(43)	89 (49)	13(52)	31(52)
Essential Hypertension	2(3)	6(3)	0	4(7)
Hypertriglyceridemia	2(3)	6(3)	0	3(5)

Source: Tables 1.6-1A and 1.8-1A, Appendix 1 of Summary of Clinical Safety

The rates of adverse events by MedDRA SOC in the two pivotal trials and their extensions E1 are shown in Table 43. As shown, for within canakinumab treatment comparison, the re-treated subjects had more adverse events occurring at any time during the observation period compared to the non-retreated subjects. A higher proportion of patients re-treated with canakinumab experienced adverse events compared with the subjects who were re-treated with triamcinolone acetonide.

Table 43: Incidence of adverse events in retreated and non-retreated patients by System Organ Class

	ACZ885 150 mg		Triamcinolone	
Primary system organ class	Retreated N=60 n (%)	Non-retreated N=165 n (%)	Retreated N=89 n (%)	Non-retreated N=140 n (%)
Total number (%) of patients with any AE	48 (80.0)	101 (61.2)	51 (57.3)	70 (50.0)
Infections and infestations	15 (25.0)	31 (18.8)	13 (14.6)	15 (10.7)
Investigations	14 (23.3)	15 (9.1)	9 (10.1)	16 (11.4)
Musculoskeletal and connective tissue disorders	13 (21.7)	27 (16.4)	15 (16.9)	23 (16.4)
Metabolism and nutrition disorders	13 (21.7)	15 (9.1)	11 (12.4)	13 (9.3)
Nervous system disorders	10 (16.7)	17 (10.3)	11 (12.4)	8 (5.7)
Vascular disorders	10 (16.7)	8 (4.8)	10 (11.2)	6 (4.3)
Gastrointestinal disorders	9 (15.0)	18 (10.9)	10 (11.2)	8 (5.7)
General disorders and administration site conditions	6 (10.0)	11 (6.7)	7 (7.9)	3 (2.1)
Respiratory, thoracic and mediastinal disorders	6 (10.0)	4 (2.4)	4 (4.5)	3 (2.1)
Skin and subcutaneous tissue disorders	6 (10.0)	3 (1.8)	7 (7.9)	4 (2.9)
Cardiac disorders	4 (6.7)	8 (4.8)	4 (4.5)	7 (5.0)
Injury, poisoning and procedural complications	4 (6.7)	6 (3.6)	8 (9.0)	7 (5.0)
Renal and urinary disorders	4 (6.7)	5 (3.0)	2 (2.2)	4 (2.9)
Psychiatric disorders	3 (5.0)	5 (3.0)	3 (3.4)	4 (2.9)
Hepatobiliary disorders	3 (5.0)	2 (1.2)	1 (1.1)	1 (0.7)
Eye disorders	3 (5.0)	2 (1.2)	1 (1.1)	0
Blood and lymphatic system disorders	2 (3.3)	8 (4.8)	3 (3.4)	1 (0.7)
Ear and labyrinth disorders	1 (1.7)	2 (1.2)	1 (1.1)	1 (0.7)
Immune system disorders	0	1 (0.6)	1 (1.1)	0

Applicant's Table 5-10, Summary of Clinical Safety.

As shown in Table 44 below, the most frequent preferred terms reported in the canakinumab retreatment group of trial H2356/56E1 included hypertension (12%), back pain (10%), headache (8%), arthralgia (8%), and dyslipidemia (7%). In trial H2357/57E1, hypertension is also the most commonly reported AE (10%), followed by headache (6%), arthralgia (3%) and vomiting (3%).

Table 44: Incidence of adverse events occurring in ≥5% patients, retreated vs. non-retreated

Adverse Events by MedDRA Preferred Term	H2356/56E1		H2357/57E1	
	Re-treated with canakinumab 150 mg s.c. N=60	Non-retreated with canakinumab 150 mg s.c. N=165	Re-treated with triamcinolone acetonide 40 mg i.m. N=89	Non-retreated with triamcinolone acetonide, 40 mg i.m. N=140
Hypertension*	7 (12)	5(3)	9(10)	4(3)
Back Pain	6(10)	7(4.2)	1(1)	8(3)
Headache	5(8)	6(3.6)	5(6)	3(2)
Arthralgia	5(8)	4(2.4)	3(3)	1(0.7)
Dyslipidemia	4(7)	0**	1(1)	0**
Hypertriglyceridemia	4(7)	5(3)	1(1)	1(0.7)
Ear infection	3(5)	0**	0	0**
Vomiting	3(5)	1(0.6)	3(3)	0

Source: Table 2.1-6A6, Appendix 1, Summary of Clinical Safety
*includes PT of hypertensive crisis
** not reported in the source table 2.1-6A6 for non-retreated subjects.

To examine the safety of re-treatment with canakinumab when administered concurrently with allopurinol, data from open-label trial H2251E1 were examined. As described earlier, patients enrolled in the Phase 2 core trial H2255 were originally treated with a range of canakinumab doses upon initiation of allopurinol treatment; they could receive re-treatment with 150 mg dose on demand in an open-labeled fashion if they developed a gout flare in the H2255E1 extension study. All patients enrolled in the H2255E1 extension study were then retrospectively divided into the following four groups:

- Group A- received canakinumab both in the core trial and in the extension study, N=75;
- Group B- received canakinumab in the core trial only and no treatment in the extension study, N=181;
- Group C- received colchicine in the core trial and received canakinumab in the extension study, N= 25;
- Group D- received colchicine in the core trial and no treatment in the extension study, N=60.

Therefore Group A and B are of relevance in the assessment of re-treatment with canakinumab. As shown in Table 45 below, the overall proportion of patients experiencing adverse events was similar in patients who were retreated (Group A) or not retreated (Group B). The most frequently reported MedDRA SOCs were Musculoskeletal and Connective Tissue Disorders and Infections and Infestations. When assessed by Preferred Term (Table 46 below), the most frequently reported adverse events in retreated patients were hypertension (14.7%), upper respiratory tract infection (13.3%) and arthralgia (13.3%). While the medical history of hypertension was reported in equal proportions of subjects in groups A and B at baseline (Table 42), the higher occurrence of adverse events of hypertension in re-treated subjects is again noted.

Table 45: Incidence of adverse events in retreated vs. non-retreated patients in trial H2251E1

Adverse Events by MedDRA Primary SOC	Re-treated (Group A) N=75	Non-retreated (Group B) N=248
Total number of patients with any AE	45(60)	152 (61)
Musculoskeletal and Connective Tissue Disorders, N(%)	24(32)	46 (18.5)
Infections and Infestations, N(%)	22(29)	54 (22)
Gastrointestinal Disorders, N(%)	14 (19)	28 (11)
Vascular Disorders, N(%)	13 (17)	18 (7)
Nervous System Disorders, N(%)	11(15)	30 (12)
Metabolism and Nutrition Disorders, N(%)	10 (13)	15 (6)
Respiratory, Thoracic and Mediastinal Disorders, N(%)	9 (12)	10 (4)
Skin and Subcutaneous Tissue Disorders, N(%)	7 (9)	20 (8)
Investigations, N(%)	6(8)	19(8)
Gen. Disorders and Admin. Site Conditions, N(%)	5(7)	10 (4)
Blood and Lymphatic System Disorders, N(%)	5(7)	4(2)
Psychiatric Disorders, N(%)	4(5)	5(2)
Injury, Poisoning and Procedural Complications, N(%)	4 (5)	18 (7)
Reproductive System and Breast Disorders, N(%)	3(4)	7(3)
Renal and Urinary Disorders, N(%)	2(3)	8(3)
Eye Disorders, N(%)	2(3)	4(2)
Cardiac Disorders, N(%)	1(1)	14 (6)
Immune System Disorders, N(%)	1(1.3)	1(0.4)
Hepatobiliary Disorders, N(%)	1(1)	6(2)
Ear and Labyrinth Disorders, N(%)	1(1)	5(2)
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps), N(%)	0	1(0.4)

Source: PT-Table 14.3.1-1.2, Study H2251E.

Table 46: Adverse events occurring in >3% of patients in H2251/H2251E, by re-treatment status

Adverse Events by MedDRA Preferred Term	Re-treated (Group A) N=75	Non-retreated (Group B) N=248
Hypertension	11(14.7)	15 (6.0)
Upper Respiratory Tract Infection	10 (13.3)	11(4.4)
Arthralgia	10 (13.3)	17 (6.9)
Diarrhea	9(12.9)	4(1.6)
Headache	7(9.3)	15 (6)
Cough	6(8)	4(1.6)
Back Pain	5(6.7)	8(3.2)
Pain in extremity	5(6.7)	7(2.8)
Tendonitis	5(6.7)	2(0.8)
Nasopharyngitis	4(5.3)	9(3.6)
Diabetes	4(5.3)	2(0.8)
Hypertriglyceridemia	2(2.7)	2(0.8)

Source: Table 14.3.1-1.4, Study H2251E.

Overall, retreatment safety data from trial H2251/H2251E are consistent with data from the rest of the gout development program. Patients experienced more adverse events in the majority of the system organ classes, and the numeric imbalances were primarily due to higher rates of infections, arthralgia and back pain, and reports of hypertension and hypertriglyceridemia.

Safety Conclusions

Canakinumab treatment, even with a single subcutaneous injection of 150 mg, appears to be associated with an increase in infections and serious infections. Neutropenia is a known effect of IL-1 inhibition and was observed with canakinumab treatment, again with as little as one subcutaneous injection. The risk of infections appears to be greater than that observed with the comparative treatment corticosteroid, triamcinolone acetonide.

Canakinumab treatment appeared to be associated with worsening of certain clinically relevant features in this patient population—namely, uric acid elevation, elevation in triglycerides, and possible decline in renal function. The clinical impact of these is difficult to assess with limited data regarding repeat exposure over time.

Limited data are available on the effects of retreatment; what data are available suggest that similar risks and effects are observed with retreatment as with the initial injection. There are also very limited data available on the effects of canakinumab given in lower doses; what data are available suggest a dose-effect relationship for some of the safety concerns.

Conclusion

Based on the efficacy and safety data provided, the Advisory Committee will be asked to consider whether the benefit-risk profile of canakinumab is acceptable for the treatment of acute flares of gout. This question is complicated by a number of issues to include:

- Canakinumab has a long half-life and extended pharmacodynamic effects. These are not characteristics typical of an acute treatment, and both efficacy and safety data suggest the effects of even a single subcutaneous 150 mg injection of canakinumab may be protracted.
- Canakinumab is associated with an increased risk of infection and serious infection. Given that it is expected to provide primarily a symptomatic benefit, is the magnitude of the risk of infection still outweighed by the clinical benefits?
- Canakinumab is associated with a number of laboratory abnormalities. The impact of decreased white blood cell counts may be considered with the risk of infection. However, canakinumab also appears to be associated with a mild decline in creatinine clearance, occurrence of hypertriglyceridemia, and elevated serum uric acid, all of which could be deleterious in the gout patient population. The available data do not allow assessment of whether these changes are likely to result in negative outcomes long-term, if canakinumab is given as a chronic recurrent treatment.

- Finally, although a fairly wide range of doses were studied early on, only the 150 mg dose of canakinumab was studied further in the gout clinical development program. Given that some of the safety findings suggest a dose-response, it may have been useful to have additional data from a lower dose, to assess whether adequate efficacy could have been provided with less undesirable effect on susceptibility to infection and laboratory abnormalities.

These are the issues that FDA asks the Advisory Committee to consider when discussing the sBLA for canakinumab in the acute treatment of gouty arthritis. FDA greatly appreciates the Advisory Committee's consideration and input.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ILARIS safely and effectively. See full prescribing information for ILARIS

ILARIS (canakinumab*)*

Injection for Subcutaneous use
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

ILARIS is an interleukin-1β blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS) (1)

----------DOSAGE AND ADMINISTRATION----------

150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Sterile, single-use 6-mL, glass vial containing 180 mg of ILARIS as a lyophilized powder for reconstitution. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- 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 initiate treatment with ILARIS in patients with active infection requiring medical intervention. (5.1)
- Live vaccines should not be given concurrently with ILARIS. Prior to initiation of therapy with ILARIS, patients should receive all recommended vaccinations. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported by patients with CAPS treated with ILARIS are nasopharyngitis, diarrhea, influenza, headache and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

No formal drug interaction studies have been conducted with ILARIS.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No Human data. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 06/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ILARIS (canakinumab) is an interleukin-1β blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Recommended Dose

The recommended dose of ILARIS is 150 mg for CAPS patients with body weight greater than 40 kg. For CAPS patients with body weight between 15 kg and 40 kg, the recommended dose is 2 mg/kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg.

ILARIS is administered every eight weeks as a single dose via subcutaneous injection.

2.3 Preparation for Administration

Using aseptic technique, reconstitute each vial of ILARIS by slowly injecting 1 mL of preservative-free Sterile Water for Injection with a 1 mL syringe and an 18 G x 2" needle. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for 5 minutes. Then gently turn the vial upside down and back again ten times. Avoid touching the rubber stopper with your fingers. Allow to stand for about 15 minutes at room temperature to obtain a clear solution. Do not shake. Do not use if particulate matter is present in the solution. Tap the side of the vial to remove any residual liquid from the stopper. The reconstituted solution should be essentially free from particulates, and clear to opalescent. The solution should be colorless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discoloration it should not be used. If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator at 2 to 8° C (36 to 46° F) and used within 4 hours. Slight foaming of the product upon reconstitution is not unusual.

Using a sterile syringe and needle carefully withdraw the required volume depending on the dose to be administered (0.2 mL to 1 mL) and subcutaneously inject using a 27 G x 0.5" needle.

Injection into scar tissue should be avoided as this may result in insufficient exposure to ILARIS.

ILARIS 180-mg powder for solution for injection is supplied in a single-use vial. Any unused product or waste material should be disposed of in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

ILARIS is supplied as a 180 mg white lyophilized powder for solution for subcutaneous injection. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug, resulting in a total volume of 1.2 mL reconstituted solution. The reconstituted ILARIS is a clear to slightly opalescent, colorless to a slight brownish yellow tint, essentially free from particulates, 150 mg/mL solution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

ILARIS may be associated with an increased risk 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. Treatment with ILARIS should not be initiated in patients with active infection requiring medical intervention. Administration of ILARIS should be discontinued if a patient develops a serious infection.

Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported with ILARIS. The observed infections responded to standard therapy. No unusual or opportunistic infections were reported with ILARIS. In clinical trials, ILARIS has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An

increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Taking ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections [*see Drug Interactions (7.1)*].

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ILARIS that block IL-1 increases the risk of TB or other atypical or opportunistic infections.

Prior to initiating immunomodulatory therapies, including ILARIS, patients should be tested for latent tuberculosis infection. ILARIS has not been studied in patients with a positive tuberculosis screen, and the safety of ILARIS in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ILARIS.

Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ILARIS.

5.2 Immunosuppression

The impact of treatment with anti-interleukin-1 (IL-1) therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

5.3 Immunizations

Live vaccines should not be given concurrently with ILARIS [*see Drug Interactions (7.2)*]. Since no data are available on either the efficacy or on the risks of secondary transmission of infection by live vaccines in patients receiving ILARIS, live vaccines should not be given concurrently with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS. No data are available on the effectiveness of vaccinations with inactivated (killed) antigens in patients receiving ILARIS. [*see Drug Interactions (7.2)*].

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ILARIS, adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current recommended immunization schedules at the website of the Centers for Disease Control, http://www.cdc.gov/vaccines/recs/schedules/).

6 ADVERSE REACTIONS

The data described herein reflect exposure to ILARIS in 104 adult and pediatric CAPS patients, (including 20 FCAS, 72 MWS, 10 MWS/NOMID (Neonatal Onset Multisystem Inflammatory Disorder) overlap, 1 non-FCAS non-MWS, and 1 mis-diagnosed in placebo-controlled (35 patients) and uncontrolled trials. Sixty-two patients were exposed to ILARIS for at least 6 months, 56 for at least 1 year and 4 for at least 3 years. A total of 9 serious adverse reactions were reported for CAPS patients. Among these were vertigo (2 patients), infections (3 patients), including intra-abdominal abscess following appendectomy (1 patient). 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. One patient discontinued treatment due to potential infection.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience

Approximately 833 subjects have been treated with ILARIS in blinded and open-label clinical trials in CAPS and other diseases, and healthy volunteers. A total of 15 patients reported serious adverse reactions during the clinical program.

Study 1 investigated the safety of ILARIS in an 8-week, open-label period (Part 1), followed by a 24-week, randomized withdrawal period (Part 2), followed by a 16-week, open-label period (Part 3). All patients were treated with ILARIS 150 mg subcutaneously or 2 mg/kg if body weight was greater than or equal to 15 kg and less than or equal to 40 kg (see Table 1).

Since all CAPS patients received ILARIS in Part 1, there are no controlled data on adverse events (AEs). Data in Table 1 are for all AEs for all CAPS patients receiving canakinumab. In study 1, no pattern was observed for any type or frequency of adverse events throughout the three study periods.

Table 1 Number (%) of Patients with AEs by Preferred Terms, in > 10% of Patients in Parts 1 to 3 of the Phase 3 Trial for CAPS Patients

Preferred Term	ILARIS N=35 n (%)
n % of Patients with Adverse Events	35 (100)
Nasopharyngitis	12 (34)
Diarrhea	7 (20)
Influenza	6 (17)
Rhinitis	6 (17)
Nausea	5 (14)
Headache	5 (14)
Bronchitis	4 (11)
Gastroenteritis	4 (11)
Pharyngitis	4 (11)
Weight increased	4 (11)
Musculoskeletal pain	4(11)
Vertigo	4(11)

6.2 Vertigo

Vertigo has been reported in 9 to 14% of patients in CAPS studies, exclusively in MWS patients, and reported as a serious adverse event in two cases. All events resolved with continued treatment with ILARIS.

6.3 Injection Site Reactions

In Study 1, subcutaneous injection site reactions were observed in 9% of patients in Part 1 with mild tolerability reactions; in Part 2, one patient each (7%) had a mild or a moderate tolerability reaction and, in Part 3, one patient had a mild local tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment.

6.4 Immunogenicity

A specific biosensor binding assay was used to detect antibodies directed against canakinumab in patients who received ILARIS. None of the 60 CAPS patients who had received ILARIS tested positive for treatment-emergent binding antibodies at the time points tested. Thirty-one of 60 CAPS patients had a duration of exposure to canakinumab >48 weeks. The data obtained in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, comparison of the incidence of antibodies to canakinumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Interactions between ILARIS and other medicinal products have not been investigated in formal studies.

7.1 TNF-Blocker and IL-1 Blocking Agent

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors in another patient population. Use of ILARIS with TNF inhibitors may also result in similar toxicities and is not recommended because this may increase the risk of serious infections [*see Warnings and Precautions (5.1)*].

The concomitant administration of ILARIS with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacological interactions between ILARIS and a recombinant IL-1ra, concomitant administration of ILARIS and other agents that block IL-1 or its receptors is not recommended.

7.2 Immunization

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving ILARIS. Therefore, live vaccines should not be given concurrently with ILARIS. It is recommended that, if possible, pediatric and adult patients should complete all immunizations in accordance with current immunization guidelines prior to initiating ILARIS therapy [*see Warnings and Precautions (5.3)*].

7.3 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Canakinumab has been shown to produce delays in fetal skeletal development when evaluated in marmoset monkeys using doses 23-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve [AUC] comparison). Doses producing exposures within the clinical exposure range at the MRHD were not evaluated. Similar delays in fetal skeletal development were observed in mice administered a murine analog of canakinumab. There are no adequate and well-controlled studies of ILARIS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Embryofetal developmental toxicity studies were performed in marmoset monkeys and mice. Pregnant marmoset monkeys were administered canakinumab subcutaneously twice weekly at doses of 15, 50 or 150 mg/kg (representing 23 to 230-fold the human dose based on a plasma AUC comparison at the MRHD) from gestation days 25 to 109 which revealed no evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since canakinumab does not cross-react with mouse or rat IL-1, pregnant mice were subcutaneously administered a murine analog of canakinumab at doses of 15, 50, or 150 mg/kg on gestation days 6, 11 and 17. The incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased in a dose-dependent manner at all dose levels tested.

8.3 Nursing Mothers

It is not known whether canakinumab is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILARIS is administered to a nursing woman.

8.4 Pediatric Use

The CAPS trials with ILARIS included a total of 23 pediatric patients with an age range from 4 years to 17 years (11 adolescents were treated subcutaneously with 150 mg , and 12 children were treated with 2 mg/kg based on body weight greater than or equal to 15 kg and less than or equal to 40 kg). The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., Serum Amyloid A and C-Reactive Protein). Overall, the efficacy and safety of ILARIS in pediatric and adult patients were comparable. Infections of the upper respiratory tract were the most frequently reported infection. The safety and effectiveness of ILARIS in patients under 4 years of age has not been established [*see Pharmacokinetics (12.3)*].

8.5 Geriatric Use

Clinical studies of ILARIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported. In the case of overdose, it is recommended that the subject be monitored for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298 (Asn 298).

The biological activity of canakinumab is measured by comparing its inhibition of IL-1β-dependent expression of the reporter gene luciferase to that of a canakinumab internal reference standard, using a stably transfected cell line.

ILARIS is supplied in a sterile, single-use, colorless, 6 mL glass vial with coated stopper and aluminum flip-off cap. Each vial contains 180 mg of canakinumab as a white, preservative-free, lyophilized powder. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted canakinumab is a 150 mg/mL solution essentially free of particulates, clear to slightly opalescent, and is colorless or may have a slightly brownish-yellow tint. A volume of up to 1 mL can be withdrawn for delivery of 150 mg/mL canakinumab for subcutaneous administration. Each reconstituted vial contains 180 mg canakinumab, sucrose, L-histidine, L-histidine HCL monohydrate, polysorbate 80 and Sterile Water for Injection. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [CIAS1]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

The NLRP-3 gene encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Canakinumab is a human monoclonal anti-human IL-1β antibody of the IgG1/κ isotype. Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra).

12.2 Pharmacodynamics

C-reactive protein and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Following ILARIS treatment, CRP and SAA levels normalize within 8 days.

12.3 Pharmacokinetics

Absorption

The peak serum canakinumab concentration (Cmax) of 16 ± 3.5 μg/mL occurred approximately 7 days after subcutaneous administration of a single, 150-mg dose subcutaneously to adult CAPS patients. The mean terminal half-life was 26 days. The absolute bioavailability of subcutaneous canakinumab was estimated to be 70%. Exposure parameters (such as AUC and Cmax) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion or from 150 to 300 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1β. Canakinumab volume of distribution (Vss) varied according to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg. The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous dosing of 150 mg ILARIS every 8 weeks.

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender- or age-related pharmacokinetic differences were observed after correction for body weight.

Pediatrics

Peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric patients. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab.

The mutagenic potential of canakinumab was not evaluated.

As canakinumab does not cross-react with rodent IL-1β, male and female fertility was evaluated in a mouse model using a murine analog of canakinumab. Male mice were treated weekly beginning 4 weeks prior to mating and continuing through 3 weeks after mating. Female mice were treated weekly for 2 weeks prior to mating through gestation day 3 or 4. The murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous doses up to 150 mg/kg.

14 CLINICAL STUDIES

The efficacy and safety of ILARIS for the treatment of CAPS was demonstrated in Study 1, a 3-part trial in patients 9 to 74 years of age with the MWS phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received ILARIS 150 mg and patients weighing 15 to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received ILARIS. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients one week following initiation of treatment and in 97% of patients by Week 8 (see Figure 1 and Table 2). In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared as compared to none (0%) of the patients randomized to ILARIS. The 95% confidence interval for treatment difference in the proportion of flares was 53% to 96%. At the end of Part 2, all 15 patients treated with ILARIS had absent or minimal disease activity and skin disease (see Table 2).

In a second trial, patients 4 to 74 years of age with both MWS and FCAS phenotypes of CAPS were treated in an open-label manner. Treatment with ILARIS resulted in clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week.

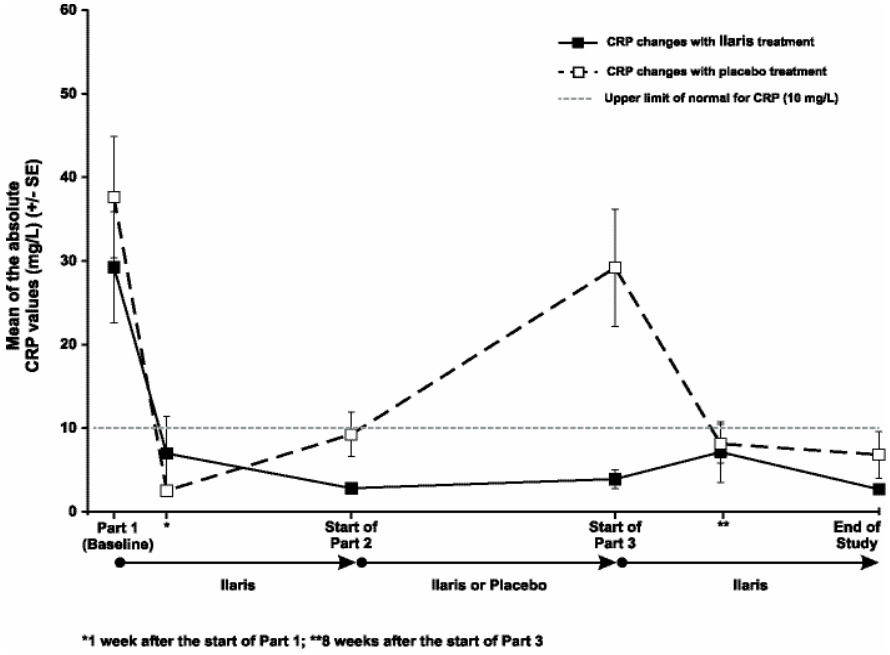
Table 2 Physician's Global Assessment of Auto-Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part 2 (Using LOCF, ITT Population)

		ILARIS N= 15		Placebo N= 16	
	Baseline	Start of Part 2 (Week 8)	End of Part 2	Start of Part 2 (Week 8)	End of Part 2
Physician's Global Assessment of Auto-Inflammatory Disease Activity - n (%)					
Absent	0/31 (0)	9/15 (60)	8/15 (53)	8/16 (50)	0/16 (0)
Minimal	1/31 (3)	4/15 (27)	7/15 (47)	8/16 (50)	4/16 (25)
Mild	7/31 (23)	2/15 (13)	0/15 (0)	0/16 (0)	8/16 (50)
Moderate	19/31 (61)	0/15 (0)	0/15 (0)	0/16 (0)	4/16 (25)
Severe	4/31 (13)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

		ILARIS N= 15		Placebo N= 16	
	Baseline	Start of Part 2 (Week 8)	End of Part 2	Start of Part 2 (Week 8)	End of Part 2
Assessment of Skin Disease – n (%)					
Absent	3/31 (10)	13/15 (87)	14/15 (93)	13/16 (81)	5/16 (31)
Minimal	6/31 (19)	2/15 (13)	1/15 (7)	3/16 (19)	3/16 (19)
Mild	9/31 (29)	0/15 (0)	0/15 (0)	0/16 (0)	5/16 (31)
Moderate	12/31 (39)	0/15 (0)	0/15 (0)	0/16 (0)	3/16 (19)
Severe	1/32 (3)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

Markers of inflammation CRP and SAA normalized within 8 days of treatment in the majority of patients. Normal mean CRP (Figure 1) and SAA values were sustained throughout study 1 in patients continuously treated with canakinumab. After withdrawal of canakinumab in Part 2 CRP (figure 1) and SAA values again returned to abnormal values and subsequently normalized after reintroduction of canakinumab in Part 3. The pattern of normalization of CRP and SAA was similar.

Figure 1. Mean C-Reactive Protein Levels at the End of Parts 1, 2 and 3 of Study 1



*1 week after the start of Part 1; **8 weeks after the start of Part 3

16 HOW SUPPLIED/STORAGE AND HANDLING

Carton of 1 vial…….NDC 0078-0582-61

Each 6 mL single-use vial of ILARIS contains a sterile, preservative free, white lyophilized powder containing 180 mg of canakinumab. Each vial is to be reconstituted with 1 mL of preservative-free Sterile Water for Injection in a 150 mg/mL solution.

Special Precautions for Storage

The unopened vial must be stored refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Store in the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ILARIS should be kept from light, and can be kept at room temperature if used within 60 minutes of reconstitution. Otherwise, it should be refrigerated at 2 to 8° C (36 to 46° F) and used within 4 hours of reconstitution. ILARIS does not contain preservatives. Unused portions of ILARIS should be discarded.

Keep this and all drugs out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling.

Patients should be provided the opportunity to read the Patient Information for ILARIS prior to the first treatment and any questions resulting from the patient's reading of the guide should be discussed.

17.1 Drug Administration

Healthcare providers should perform administration of ILARIS by the subcutaneous injection route.

17.2 Infections

Patients should be cautioned that ILARIS use has been associated with serious infections. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ILARIS. Treatment with ILARIS should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ILARIS, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ILARIS with other IL-1 blocking agents, such as rilonacept and anakinra is not recommended. Patients should be cautioned not to initiate treatment with ILARIS if they have a chronic or active infection, including HIV, Hepatitis B or C.

17.3 Vaccinations

Prior to initiation of therapy with ILARIS, physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ILARIS.

17.4 Injection-site Reactions

Physicians should explain to patients that a very small number of patients in the clinical trials experienced a reaction at the subcutaneous injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Healthcare providers should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

INFORMATION FOR PATIENTS

See patient information leaflet.

Patient Information

ILARIS® (i-LAHR-us)

(canakinumab)

Read the Patient Information that comes with ILARIS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is ILARIS? ILARIS is a prescription medicine injected just below the skin (subcutaneous) used in adults and children 4 years and older to treat auto-inflammatory diseases known as Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS),

It is not known if ILARIS is safe or effective in children under 4 years of age.

What should I tell my healthcare provider before taking ILARIS?

Before you take ILARIS, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have a history of infections that keep coming back

- have or have had HIV, Hepatitis B, or Hepatitis C
- have an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has or has had tuberculosis
- are scheduled to receive any immunizations (vaccines). You should not get 'live vaccines' if you take ILARIS.
- are pregnant or planning to become pregnant. It is not known if ILARIS will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking ILARIS.
- are breastfeeding or planning to breastfeed. It is not known if ILARIS passes into your breast milk. You and your healthcare provider should decide if you will take ILARIS or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take:

- Medicines that affect your immune system
- IL-1 blocking agents such as Kineret® (anakinra), Arcalyst® (rilonacept)
- Tumor Necrosis Factor (TNF) inhibitors such as Enbrel® (etanercept)
- Humira® (adalimumab), or Remicade® (infliximab)
- medicines that can affect enzyme metabolism. Ask your healthcare provider if you are not sure.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ILARIS?

- Do not receive ILARIS if you have an infection.
- ILARIS is given by your healthcare provider every 8 weeks
- Your healthcare provider may change your dose if needed.

What are the possible side effects of ILARIS?

ILARIS can cause serious side effects including:

- serious infections
- decrease your body's ability to fight infections (immunosuppression)
- feeling like you are spinning (vertigo)

Call you healthcare provider right away if you have any of these signs of an infection:

- a fever lasting longer than 3 days
- a cough that does not go away
- redness in one part of your body
- warm feeling or swelling of your skin

The most common side effects include:

- cold symptoms
- diarrhea
- flu (influenza)
- runny nose
- nausea
- headache
- injection site reaction (such as redness, swelling, warmth, itching)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ILARIS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ILARIS

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use ILARIS for a condition for which it was not prescribed.

This leaflet summarizes the most important information about ILARIS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ILARIS that was written for health professionals. For more information about ILARIS, call 1-877-452-7471 or visit www.ILARIS.com.

What are the ingredients in ILARIS?

Active ingredients: canakinumab

Inactive ingredients: sucrose, L-histidine, L-histidine HCl monohydrate, polysorbate 80, preservative-free Sterile Water for Injection.

What is CAPS Disease?

In patients with CAPS, the body produces excessive amounts of a chemical messenger called interleukin-1 beta (IL-1β). This may lead to symptoms such as fever, headache, fatigue, skin rash, painful joints and muscles. In some patients, more severe outcomes such as hearing impairment are observed.

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