



FDA Arthritis Advisory Committee Meeting June 21, 2011

Supplemental Biologic License Application (sBLA) 125319/25

Canakinumab (Ilaris[®]) for the Treatment of Gouty Arthritis Attacks

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Canakinumab

- Recombinant human monoclonal antibody against interleukin 1 β (IL-1 β)
- Prolonged half-life and pharmacodynamic effects
- Currently approved for the rare genetic disorder Cryopyrin-Associated Periodic Syndromes (CAPS)
 - Dosing is every 2 months for this indication
- Proposed gout indication would greatly expand the potential population of canakinumab users

Clinical Program for Gout

- Two identical pivotal studies with blinded and open-label extensions
 - H2356: 228 patients, entirely ex-US
 - H2357: 226 patients, mostly US
- Two dose-ranging studies
 - H2255 in acute gout flares, single dose, 10 to 150 mg, triamcinolone 40 mg IM comparator
 - H2251 in prophylactic treatment, 25 to 300 mg; only one arm had multiple doses; colchicine 0.5 mg qd comparator
- Proof of concept study in 6 patients with gout flare

Efficacy Claim

- Proposed indication:
 - *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*
- Proposed dosage and administration:
 - 150 mg SC as a single dose



Efficacy: Co-Primary Endpoints for H2356 and H2357

Change in Pain Intensity at 72 hours (100 mm VAS)

	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	

Time to First New Flare

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)	

Safety Considerations

After a single dose:

- Infections and serious infections
- Neutropenia and leukopenia
- Hyperlipidemia (hypertriglyceridemia)
- Uric acid elevation
- Imbalances in occurrence of renal decline
- Hypertension adverse events

Also noted on re-treatment

Dose-Ranging, in Retrospect

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)	
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)

- 150 mg was statistically superior to triamcinolone
- Superiority to triamcinolone was not an Agency requirement
- Results suggest lower doses could have been efficacious; it is possible that lower doses could have had a more favorable risk:benefit profile

Purpose of Proceedings before an Advisory Committee (21 CFR 14.5)

- a) An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
- b) The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee

Risk-Benefit Considerations

- Canakinumab appeared to have extended effects after a single injection
 - Safety on recurrent use is limited, and is not available for chronic use in gout patients
- Symptomatic benefit vs. increased risk of serious infection and laboratory abnormalities after single injection
- Patient population for whom treatment would be indicated may not be considered refractory
- Data are mostly from 150 mg dose; it is not known whether a lower dose would have had a better risk-benefit profile



Canakinumab (Ilaris[®])

For Treatment of Gouty Arthritis Attacks in Patients who cannot
Obtain Adequate Response with NSAIDs or Colchicine

Arthritis Advisory Committee Meeting, June 21, 2011

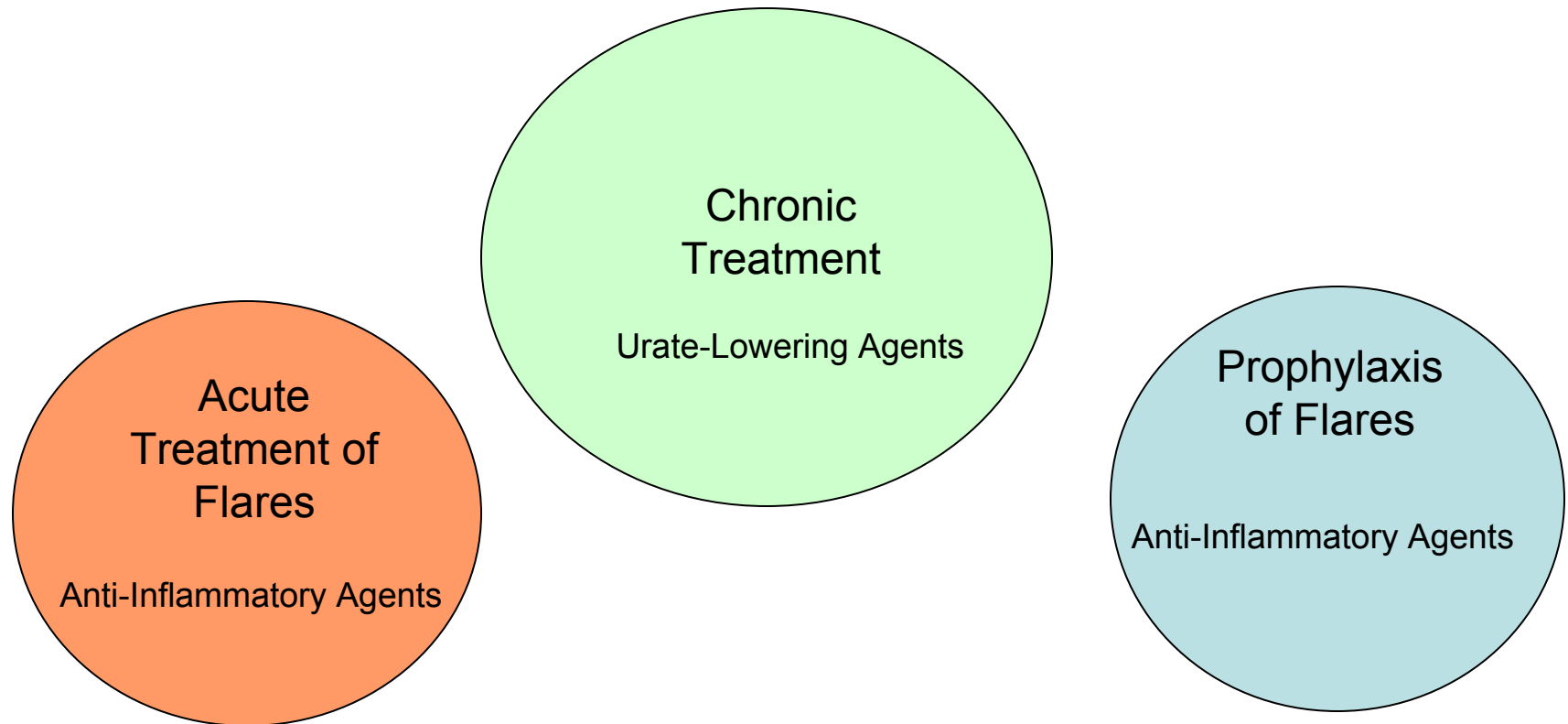
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Overview

- Regulatory history and clinical development program for canakinumab in gout
- Dose selection considerations
- Summary of Efficacy
- Summary of Safety
- Risk-Benefit considerations

Treatment of Gout



Clinical Development Program for Canakinumab in Gouty Arthritis

- Treatment of gout flares:
 - Phase 1 proof-of-concept trial, A 2212
 - Phase 2 dose-ranging trial, H2255
 - Phase 3 controlled trials, H2356 and H2357
 - Phase 3 extensions
 - Double-blind H2356E1 and H2357E1, 12 weeks
 - Open-label H2356E2 and H2357E2, ongoing
- Prophylaxis of gout flares upon initiation of urate-lowering agent allopurinol:
 - Phase 2 dose-ranging trial 2251
 - Phase 2 open-label extension trial 2251E1

Canakinumab in Gout: Brief Overview of Regulatory History

- End of Phase 2 meeting in November 2009
 - Two co-primary efficacy endpoints for Phase 3 trials
 - Comparator treatment and analysis
 - Corrections for multiple comparisons for secondary endpoints
- Pre-sBLA meeting in June 2010
 - Phase 3 trials designed to employ canakinumab for treatment of gouty arthritis flares

Canakinumab in Gout: Proposed Indication

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

Overview

- Regulatory history and Clinical Development Program for canakinumab in gout
- Dose selection considerations
- Summary of efficacy
- Summary of safety
- Risk-benefit considerations

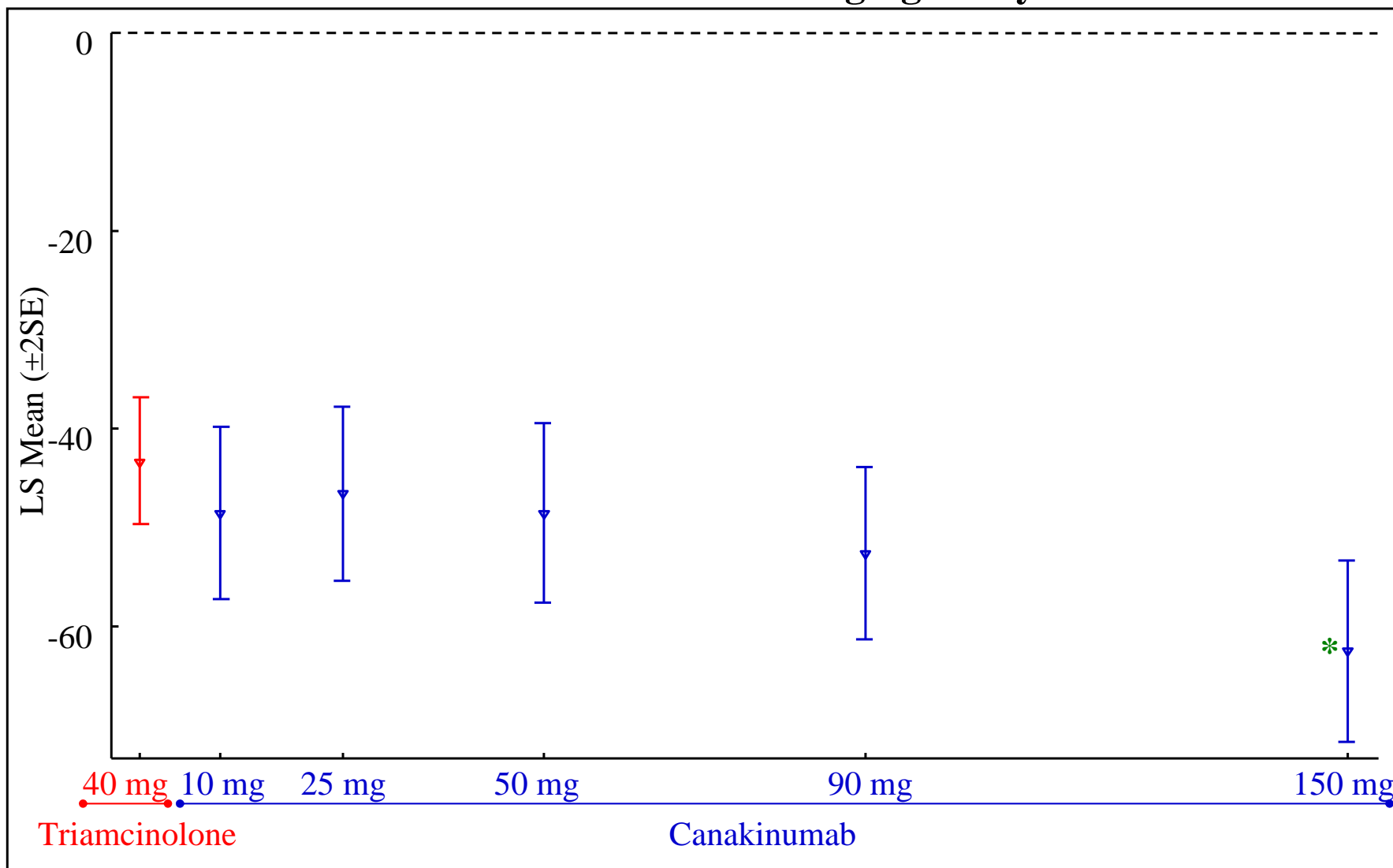
Outline

- Dose-ranging considerations (Study 55)
 - Role of statistical significance in dose-ranging
- Summary of Efficacy (Studies 56 and 57)
 - Co-Primary Efficacy Endpoints
 - Subgroup analysis in patients unable to use NSAIDs and colchicine
 - Efficacy Results by Use of Urate-Lowering Therapy
 - Secondary Endpoints

Dose-Ranging Study

- Objective: To determine the dose of canakinumab that leads to the same efficacy as triamcinolone for the treatment of acute flares in gout patients who are refractory or contraindicated to NSAIDs and/or colchicine
- 1:1:1:1:1:2 randomization to
 - canakinumab 10 mg s.c. (28 patients)
 - canakinumab 25 mg s.c. (29 patients)
 - canakinumab 50 mg s.c. (29 patients)
 - canakinumab 90 mg s.c. (29 patients)
 - canakinumab 150 mg s.c. (28 patients)
 - triamcinolone acetonide 40 mg i.m. (57 patients)
- Patient-blinded treatment of acute flare upon enrollment (study day 1)
- Primary endpoint
 - Pain intensity in the target joint at 72 hours (study day 4) post-dose measured on a 0-100 mm VAS

Change from Baseline in Pain Intensity (0 to 100 mm VAS) at Day 4 Post-Treatment in Dose-Ranging Study



* p -value < 0.05 for comparison to Triamcinolone using ANCOVA with treatment, baseline VAS & BMI



Selected Secondary Endpoints

Endpoint	Can-mab					Triam.
	10 mg SC	25 mg SC	50 mg SC	90 mg SC	150 mg SC	40 mg IM
VAS pain (change from baseline to 6 hours post-dose in mm) p-value (relative to Triam.)	-10 0.6	-5 0.1	-14 0.6	-11 0.8	-20 0.051	-12
Days to 50% reduction in pain achieved by 50% of patients p-value (relative to Triam.)	3 0.8	3 1.0	1 0.4	1 0.3	1 0.0006	2
Number (%) of patients using rescue medication up to day 7 p-value (relative to Triam.)	13 (46%) 0.4	16 (55%) 0.9	16 (57%) 1.0	14 (48%) 0.5	6 (22%) 0.01	31 (55%)

Patient Population in Phase 3 Studies

Canakinumab groups:

- Tophaceous gout
 - 39% in H2356
 - 18% in H2357
- Treated with ULT
 - 50% in H2356
 - 29% in H2357
- Not able to use both NSAIDs and colchicine
 - 19% in H2356
 - 48% in H2357

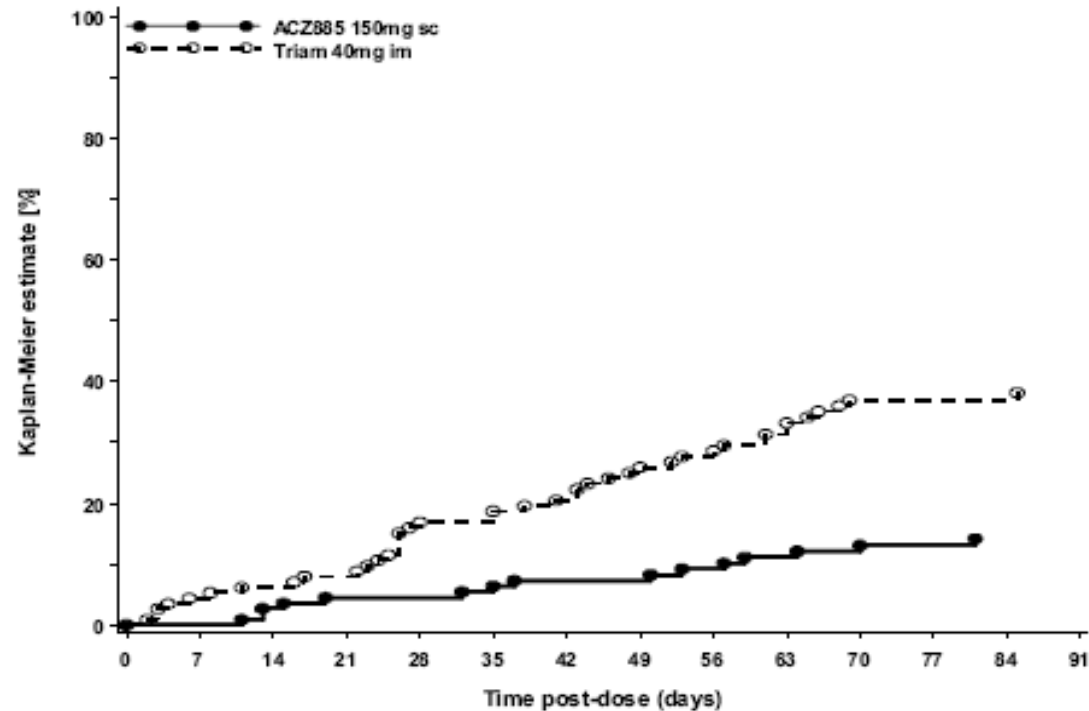
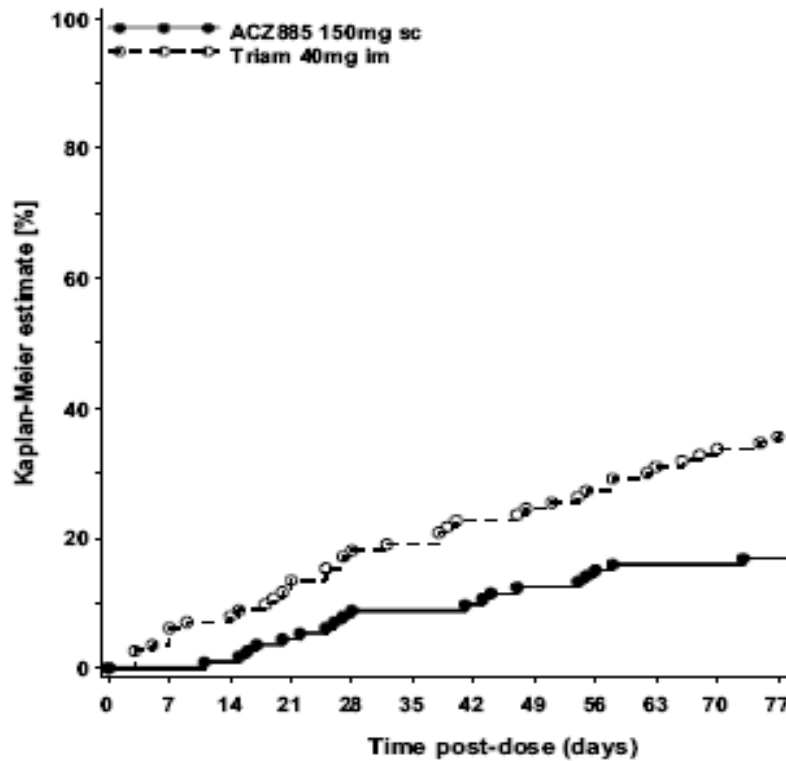
Pain Intensity on Visual Analogue Scale

Pain intensity at 72 hours (mm)	H2356		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
LS Mean (SE)	28 (2.4)	40 (2.4)	22 (2.3)	32 (2.4)
Diff to triamcinolone (95% CI)	-11 (-18, -5)		-10 (-16, -3)	
One-sided p-value	p=0.0005		p=0.002	

Time to First New Flare

New Gout Flare	H2356		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
Kaplan Meier est. of flare probability (12 wks) (95% CI)	19% (13%, 27%)	36% (28%, 46%)	14% (9%, 22%)	38% (30%, 48%)
Hazard Ratio to triam. (95% CI)	0.45 (0.26, 0.76)		0.32 (0.18, 0.58)	
One-sided p-value	p=0.001		p=0.0001	

Time to First New Flare





Subgroup Efficacy Analysis (Studies 56 & 57 pooled)

Co-Primary Efficacy Endpoints	Subjects who were not able to use both NSAIDs and colchicine (H2356 and H2357 pooled)	
	Can-mab 150 mg SC N=76	Triam. ac. 40 mg IM N= 84
LS Mean pain intensity at 72 hours post-dose, VAS 0-100 (mm)	23	36
Between group difference at 72 h post-dose (95% CI)	-13 (-21, -4)	
Kaplan Meier estimate of flare probability (12 wks) (95% CI)	13% (8%, 24%)	45% (34%, 56%)
Hazard ratio to triam (95% CI)	0.2 (0.1, 0.5)	



Co-Primary Efficacy by Use of ULT (Studies 56 & 57 pooled)

Co-Primary Efficacy Endpoints	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 (95% CI)	-9 (-16, -1)		-13 (-19, -7)	
Trt-by-ULT-use Interaction	p=0.4			
Kaplan Meier estimate of flare probability (12 wks) (95% CI)	20% (13%, 31%)	26% (19%, 36%)	14% (9%, 21%)	47% (39%, 57%)
Hazard ratio to triam (95% CI)	0.73 (0.40, 1.32)		0.23 (.13, .39)	
Trt-by-ULT-use Interaction	p=0.005			



First Set of Secondary Efficacy Endpoints	H2356		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
Proportions of patients taking rescue medication during the first week				
N (%)	35 (31)	60 (52)	49 (44)	65 (57)
p-value	0.002		0.02	
Median time to at least 50% reduction of baseline pain intensity				
Kaplan-Meier estimate (hrs)	48	72	25	48
p-value	0.01		0.08	
Time to complete resolution of pain				
Kaplan-Meier estimate of rates of complete resolution (%)	34	31	57	43
SF-36 (Physical Component) at end of study, 12 weeks				
LS Mean (SE), mm	72 (3)	71 (3)	81 (3)	79 (3)

Summary

- Dose-ranging considerations (Study 55)
 - Requiring statistically significant differences for choice of dose is not necessary.
- Summary of Efficacy (Studies 56 and 57)
 - Statistically significant results achieved for both co-primary efficacy endpoints (VAS pain and time to next flare)
 - Subgroup analysis of the co-primary efficacy endpoints in patients unable to use NSAIDs and Colchicine revealed a similar treatment effect to those who could use either NSAIDs, Colchicine, or both.
 - Significant treatment-by-ULT-use interaction identified for time-to-next-flare, indicating that that the treatment effect may be smaller in those using ULT therapy than those not using ULT.
 - Among the secondary endpoints corrected for multiple endpoints, there were none that revealed significant difference between treatment groups in both studies.

Efficacy Conclusions and Considerations of Treatment Benefits

- Two Phase 3 trials demonstrated efficacy of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m. in treatment of acute flares of gouty arthritis
 - Δ VAS = 10-11mm at 72 hours post-dose
 - time to the new flare could not be estimated from the core trials
 - fewer flares over 12 weeks with canakinumab treatment would not be unexpected in light of prolonged pharmacodynamic effects
 - these represent symptomatic clinical benefits
- Subgroup analyses in patients unable to use both NSAIDs and Colchicine were generally consistent with the overall efficacy results
- Only a minority of enrolled patients had tophaceous gout

Overview

- Regulatory history and Clinical Development Program for canakinumab in gout
- Dose selection considerations
- Summary of Efficacy
- **Summary of Safety**
- Risk-Benefit considerations

Safety Data

- Safety database of gout population contained double-blind safety data generated from trials H2255, H2251, H2356, H2356E1, H2357, and H2357E1, N=691
- Supportive safety data on re-treatment:
 - core H2356 and H2357 trials and their double-blinded extensions E1 and open-label extensions E2, N=118
 - open-label extension trial H2251E1, N=75
- Additional supportive safety data were provided from the terminated RA program, N=441

Exposure in Gout Safety Database

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%)

Safety Considerations with Canakinumab in Gout Population

- Infections and Serious Infections
- Neutropenia and leukopenia
- Hyperlipidemia (hypertriglyceridemia)
- Uric acid elevation
- Imbalances in occurrence of renal decline
- Frequent reporting of HTN
- Safety upon re-treatment

Adverse Events by MedDRA System Organ Class in Gout Safety Database

MedDRA System Organ Class	Can—mab ≤ 100 mg N=278	Can—mab split 150mg N=53	Can— mab 150 mg N=253	Can— mab ≥ 200 mg N=107	Total Can— mab N=961	Triam. ac. 40mg N=286	Colch 0.5 mg N=108
Number of Subjects with a > 1AE:	137	38	152	57	383	145	58
	(49%)	(58.5%)	(62.5%)	(53%)	(55%)	(51%)	(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)

Non-Fatal Serious Infections in Gout Safety Database

MedDRA Primary SOC/ Preferred term	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. ac. 40 mg N=286	Colch. 0.5 mg N=108
Infections and infestations	11 (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

Serious adverse events include events that are: fatal, life-threatening, result in hospitalization, result in significant disability/ incapacity, or constitute a congenital anomaly

Infections and Leukopenia with Canakinumab Treatment

- Gouty arthritis program:
 - acute respiratory tract infection (1)
 - SAE of jaw abscess (1)
- RA program:
 - skin infection (1)
 - severe influenza (1)
 - left knee prosthetic infection (1)

Leukopenia and Neutropenia in Gout Safety Database

MedDRA Primary SOC/ Preferred term	Can-mab ≤ 100 mg N=278	Can-mab 150 mg N=253	Can-mab ≥200 mg N=107	Triam. ac. 40 mg N=286	Colch. 0.5 mg 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

CTC grading, v.3

Hypertriglyceridemia in Gout Safety Database

Lipid Parameters	Can-mab All N=684	Can-mab ≤ 100 mg N=273	Can-mab split 150 mg, N=53	Can-mab 150 mg N=252	Can-mab 200 mg N=106	Triam. ac. 40 mg N=218	Colch 0.5 mg N=108
Triglycerides, N (%)							
> ULN	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)

Mean changes in TG:

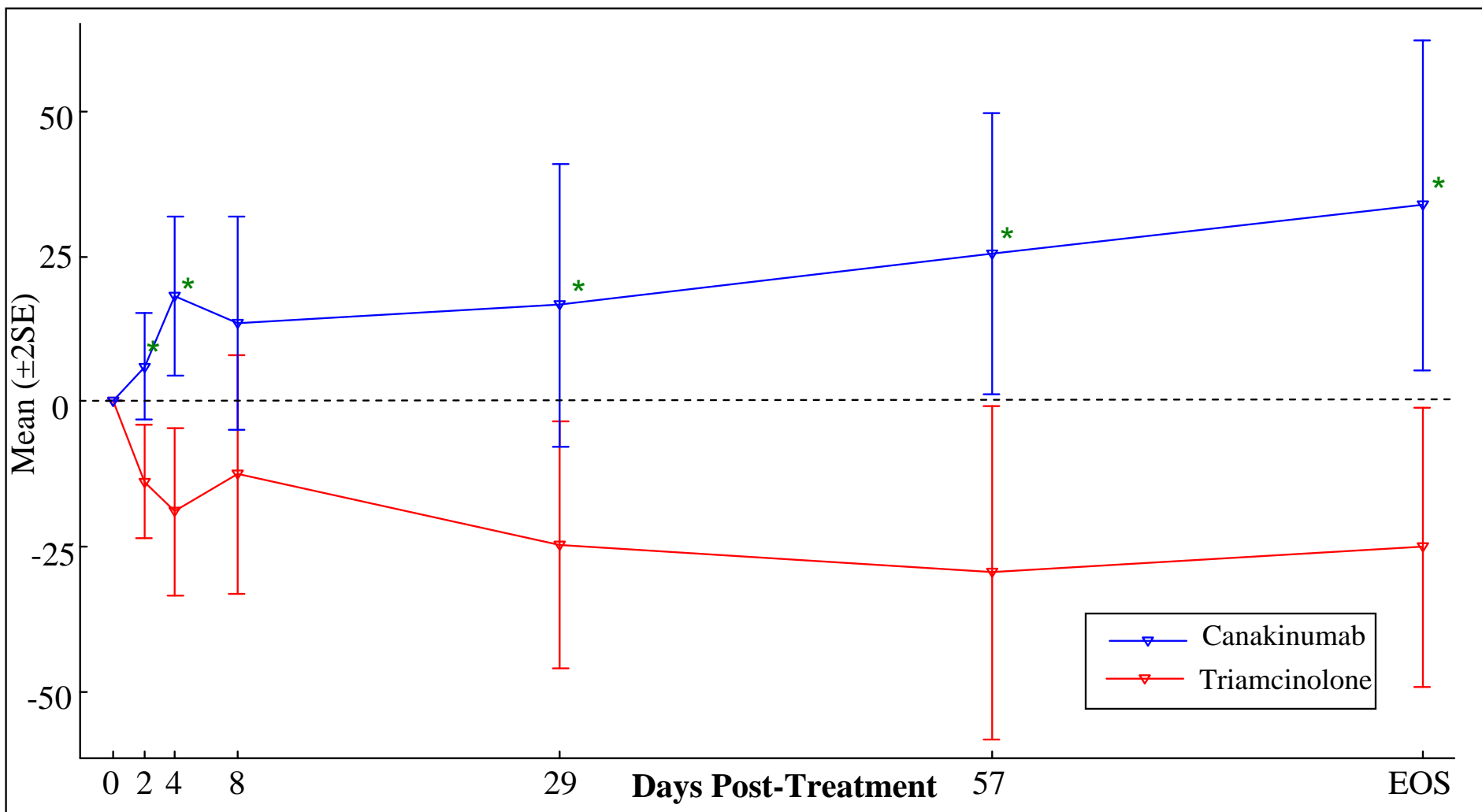
Canakinumab 150 mg, Δ in TG mean +/- SD:

+33 +/- 165 mg/dL

Triamcinolone acetonide 40 mg, Δ in TG mean +/- SD:

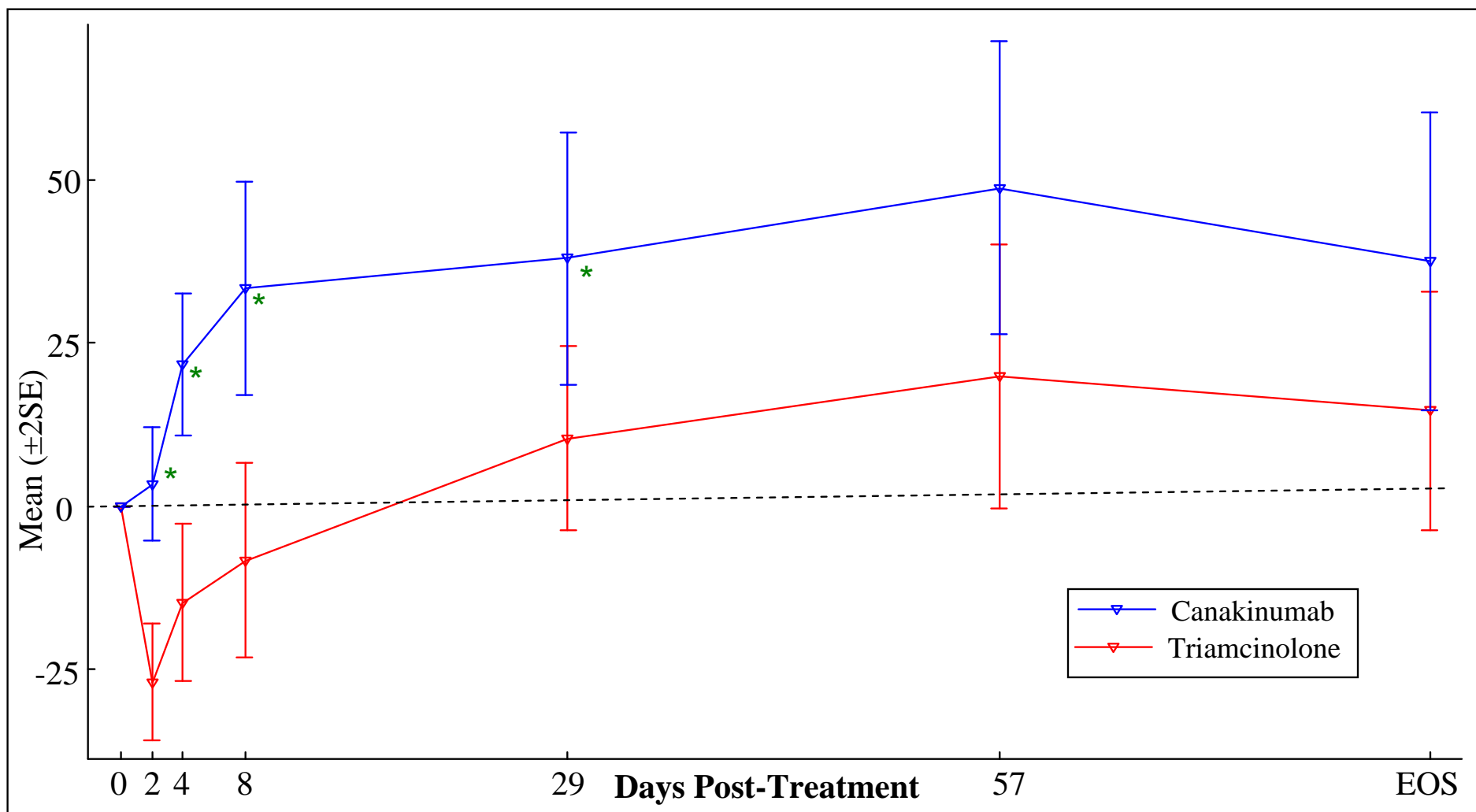
-3 +/- 24 mg/dL

Change from Baseline in Uric Acid in Study 56 (umol/L)



*denotes a p-value < 0.05 for difference between treatment groups using ANCOVA with treatment and baseline uric acid as covariates at each time point

Change from Baseline in Uric Acid in Study 57 (umol/L)



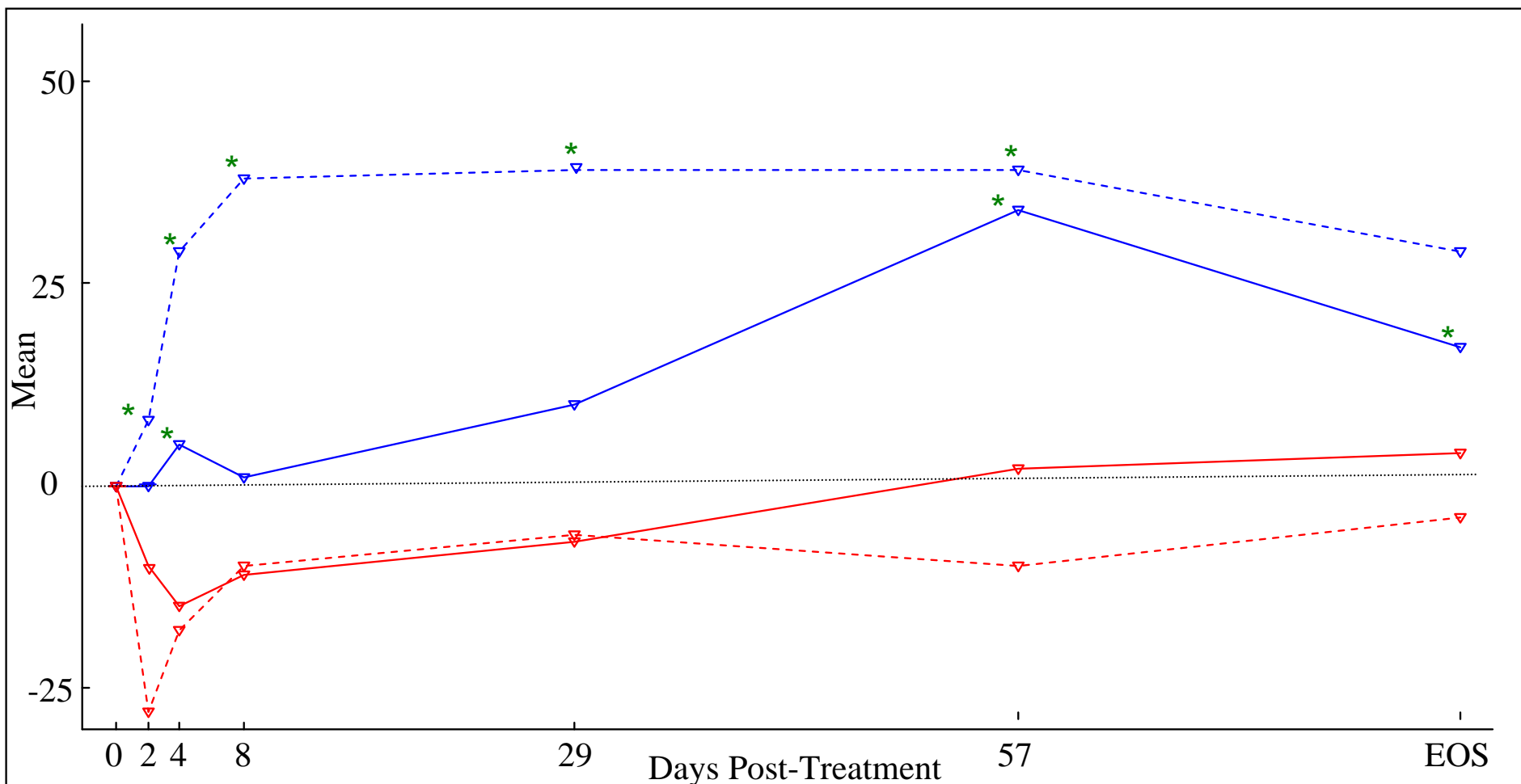
*denotes a p-value < 0.05 for difference between treatment groups using ANCOVA with treatment and baseline uric acid as covariates at each time point

Serum Uric Acid Elevation

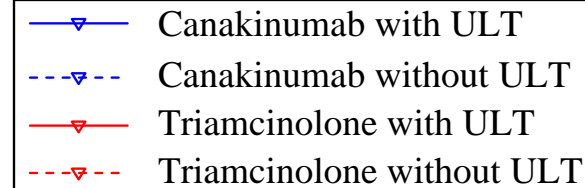
N(%) subjects experiencing increase in serum uric acid during the first 12 weeks of treatment	H2356		H2357		Pooled Data from Trials H2356 and H2357	
	Can-mab 150 mg SC N=109	Triam. ac. 40 mg IM N=112	Can-mab 150 mg SC N=112	Triam. ac. 40 mg IM N=113	Can-mab 150 mg SC N=221	Triam. ac. 40 mg IM N=225
>0.5 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.

Change from Baseline in Uric Acid by Urate Lowering Therapy Use in Studies 56 and 57 Pooled (umol/L)



*denotes a p-value < 0.05 for difference between treatment groups within ULT-use subgroup using ANCOVA with treatment, study, and baseline uric acid as covariates at each time point



Renal Failure Events in Gout Safety Database

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

Changes in Renal Function in H2356/56E1* and H2357/57E1*

Serum Creatinine elevation and Creatinine Clearance decline by Cockcroft-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
Serum Creatinine ≥ 1.5 ULN, n (%) at Week 12	2 (1.8)	2(1.8)	5(4.5)	1(0.9)	7(3.1)	3(1.3)
Serum Creatinine ≥ 1.5 ULN, n (%) at Week 24	3(2.7)	2(1.8)	5(4.5)	3 (2.7)	8 (3.6)	5(2.2)
≥ 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)

*Canakinumab – 150 mg s.c., Triamcinolone acetonide – 40 mg i.m.



Hypertension: Common Adverse Events in Gout Safety Database

MedDRA System Organ Class/ Preferred Term	Can—mab ≤ 100 mg N=278 n(%)	Can—mab split 150 mg N=53 n(%)	Can— mab 150 mg N=253 n(%)	Can— mab ≥ 200 mg N=107 n(%)	Total Can— mab N=961 n(%)	Triam. ac. 40 mg N=286 n(%)	Colch. 0.5 mg N=108 n(%)
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)	2(4)	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)

Hypertension: Common Adverse Events by MedDRA PT in Core Trials 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*	15 (6.7)	12 (5.2)
Hypertension	10 (4.4)	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-

Safety Upon Re-treatment: Exposure to Canakinumab

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%)
<u>≥5</u>	0	3(2%)

Safety Upon Re-treatment with Canakinumab: Re-treated vs Not Re-treated Patients in H2356/56E1 and H2357/57E

- The most common adverse events by MedDRA SOC, more frequently reported in re-treated patients:
 - Infections and Infestations (25% vs 19%)
 - Investigations (23% vs 9%)
 - Musculoskeletal and Connective Tissue (22% vs 16%)
- The most common adverse events by MedDRA PT, more frequently reported in re-treated patients:
 - Hypertension (12% vs 3%)
 - Back Pain (10% vs 4%)
 - Headache (8% vs 4%)

Safety Upon Re-treatment with Canakinumab: (H2356/56E1/E2 and H2357/57E1/E2)

Adverse Events n (IR/100 patient years)	Can-mab 150 mg Not re-treated N=107	Can-mab 150 mg Re- treated N=118	Canakinumab 150 mg re-treated, N=118			
			Before 1st re- treatment N=118	After 1st re-treatment N=118	After 2nd re- treatment N=43	After 3rd re- treatment N=18
Any AE	63 (59)	90(76)	77(65)	56(47)	20(47)	6(33)
MedDRA SOC						
Infections and Infestations	24(45)	65(66)	37(68)	28 (63)	11 (87)	3(85)
MedDRA PT						
Hypertension	5(9)	16 (16)	7(13)	9(20)	3(24)	0
Laboratory changes, n (%)						
WBC $\leq 0.09 \times \text{LLN}$, n (%)	12(11)	21(18)	12(10)	13(11)	4(9)	2(11)
Neutroph., abs $\leq 0.09 \times \text{LLN}$, n(%)	20(19)	26 (22)	21(18)	16(14)	4(9)	1(6)
Creatinine $> 1.5 \text{ ULN}$, n (%)	3(3)	9(8)	5(4)	7(6)	2(5)	2(11)
GFR $\geq 25\%$ decrease from baseline, n (%)	9(9)	22 (19)	13(11)	17 (15)	5(12)	5(28)

Safety Conclusions and Considerations of Risks

- Safety profile of canakinumab in gout population includes the following observed effects:
 - Infections and serious infections
 - Cytopenias
 - Lipid parameter changes
 - Elevations in serum uric acid
 - Frequent adverse events of hypertension
 - Possible decline in renal function
- Other observed signals (not included in the slide presentation)
 - Hypersensitivity reactions
 - Vertigo and dizziness
 - Changes in liver enzymes

Overview

- Regulatory history and Clinical Development Program for canakinumab in gout
- Dose selection considerations
- Summary of Efficacy
- Summary of Safety
- Risk-Benefit considerations

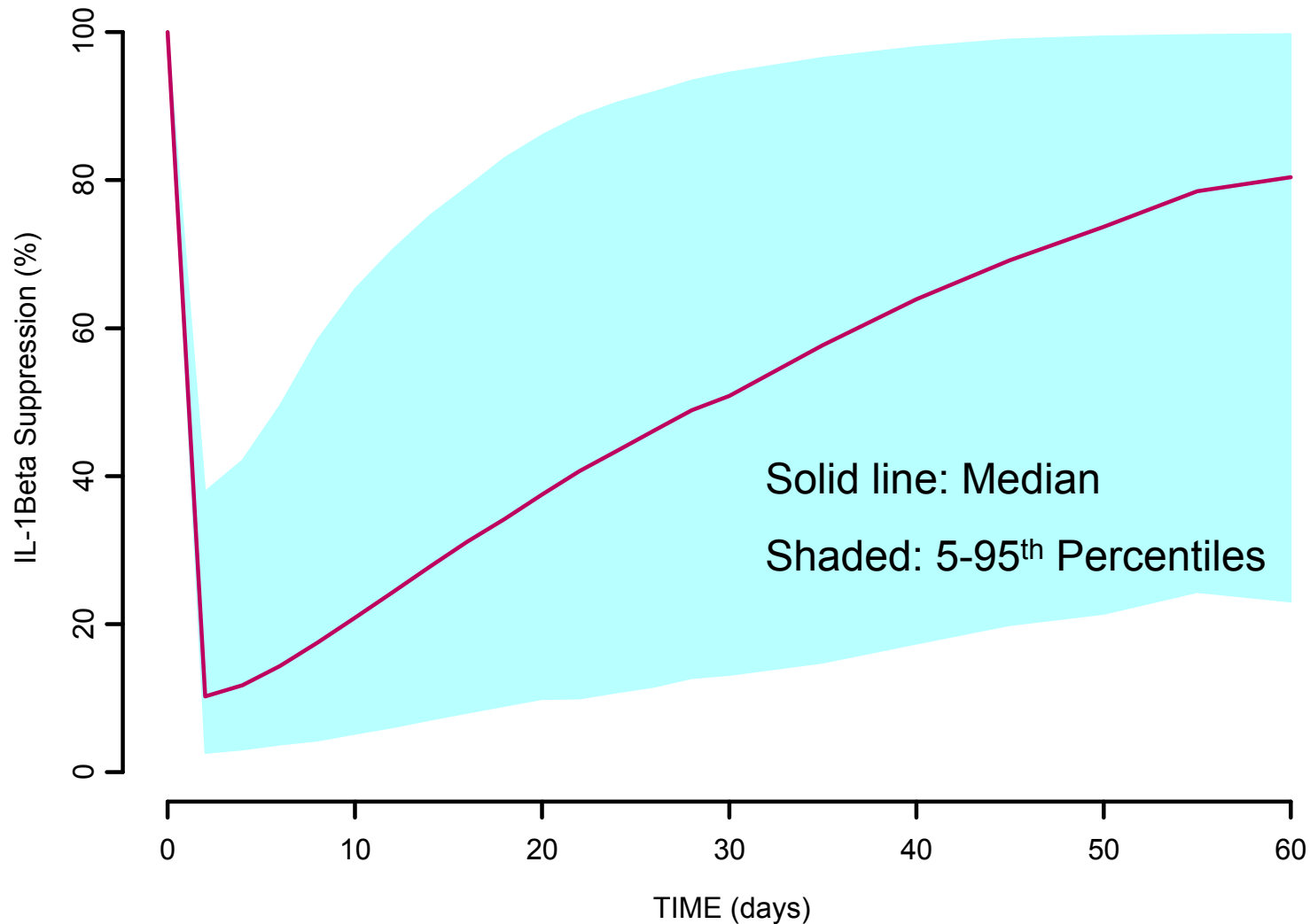
Risk-Benefit Considerations

- Canakinumab appeared to have extended effects after a single injection
 - Safety on recurrent use is limited, and is not available for chronic use in gout patients
- Symptomatic benefit vs. increased risk of serious infection and laboratory abnormalities
- Patient population for whom treatment would be indicated may not be considered refractory
- Data are mostly from 150 mg dose; it is not known whether a lower dose would have had a better risk-benefit profile



Q&A Slides Shown

IL-1beta Suppression Post Single 150 mg S.C. Dose



Exposure-Adjusted Incidence Rates of Infections and Serious Infections in Gout and RA

Adverse Events	Gout program							RA program	
	Can- mab All N=691	Can- mab \leq 100 mg N=278	Can- mab 150 mg, split N=53	Can- mab 150 mg N=253	Can- mab \geq 200 mg N=107	Triam. ac. 40 mg N=286	Colch N=108	Can-mab N=344	Placebo N=121
All Adverse Events of Infections Number of events (IR 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 (IR per 100-pt years)	13(6)	4(6)	2(12)	4(4)	3(9)	0	0	12 (10)	0



FDA Arthritis Advisory Committee Meeting June 21, 2011

Supplemental Biologic License Application (sBLA) 125319/25

Canakinumab (Ilaris[®]) for the Treatment of Gouty Arthritis Attacks

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Center for Drug Evaluation and Research
FDA/DHHS

Risk-Benefit Considerations

- Canakinumab appeared to have extended effects after a single injection
 - Safety on recurrent use is limited, and is not available for chronic use in gout patients
- Symptomatic benefit vs. increased risk of serious infection and laboratory abnormalities after single injection
- Patient population for whom treatment would be indicated may not be considered refractory
- Data are mostly from 150 mg dose; it is not known whether a lower dose would have had a better risk-benefit profile

Approval of an Application

-21 CFR 314.105 (c)

- “FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.”

Efficacy Standard

-21 CFR 314.125 Refusal to Approve an Application

(b)(5) “...substantial evidence consisting of adequate and well-controlled investigations...that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Safety Standard

-21 CFR 314.125 Refusal to Approve an Application

- (b)(2) "...do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."
- (b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."
- (b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Question 1: Discussion

- Discuss the efficacy data of canakinumab for gout considering the following:
 - The dose ranging data and whether doses lower than 150mg should be explored further.
 - Whether the proposed regimen (150 mg subcutaneously single-dose, with re-treatment on demand) represent acute treatment, or a more chronic treatment.
 - 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).

Question 2: Discussion

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

Question 3: Voting and Discussion

- 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)**
 - If not, what further efficacy data should be obtained?

Question 4: Voting and Discussion

- 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**)
 - If not, what further data should be obtained?₉

Question 5: Voting and Discussion

- Is the **safety** profile of canakinumab at a dose of 150 mg subcutaneously sufficient for approval for use as acute recurrent treatment of gout flares in the population of gout patients who cannot obtain adequate response with NSAIDs or colchicine? (**voting question**)
 - If not, what further safety data should be obtained?

Question 6: Voting

- 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 question**)

Question 7: Voting and Discussion

- 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 question)