

**ILARIS® (canakinumab)  
sBLA No: 125,319**

**Arthritis Drugs  
Advisory Committee Meeting  
June 21, 2011**

**Novartis Pharmaceuticals Corporation**



# Introduction

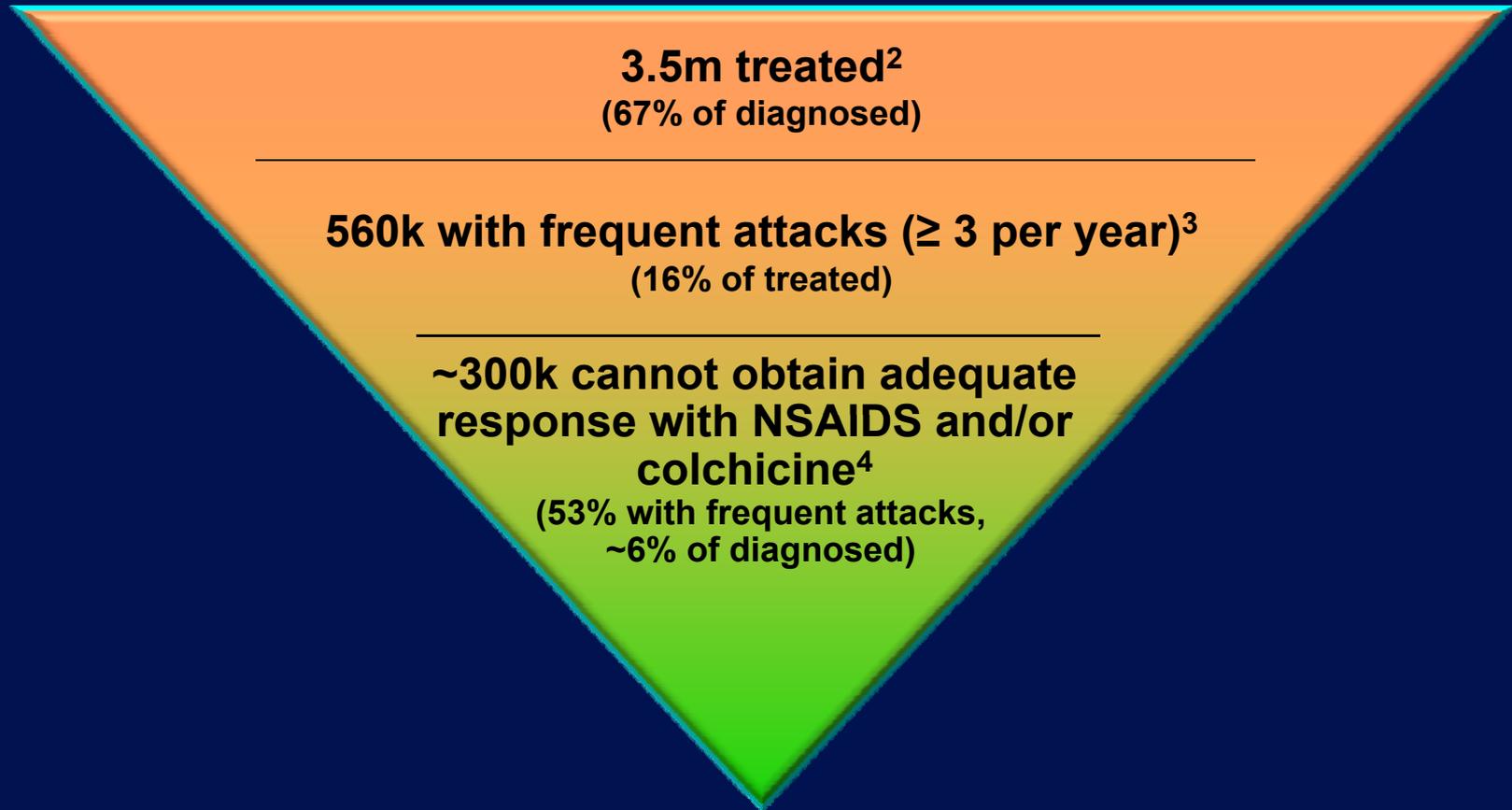
**Trevor Mundel, MD, PhD**

*Global Head of Development  
Novartis Pharma AG*

## **ILARIS (canakinumab)**

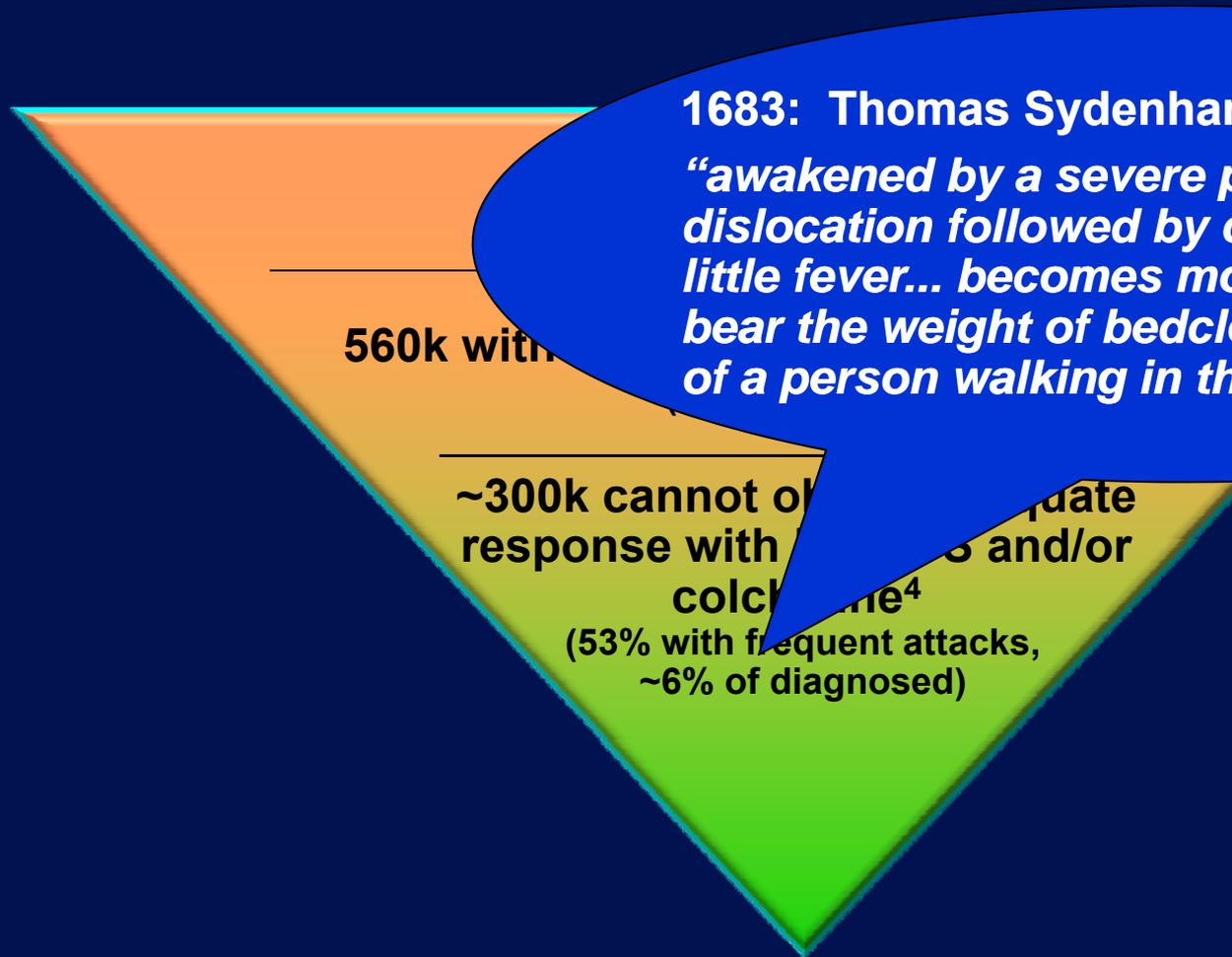
- **Canakinumab is a novel, targeted and potent anti-inflammatory agent for gouty arthritis attacks**
- **Human monoclonal antibody that neutralizes Interleukin-1 $\beta$**
- **First new class of therapies in almost a half century to directly treat the pain and inflammation of one of the oldest recognized diseases in medical history**
- **A single injection provides relief of the pain and inflammation of an attack and reduces the risk of subsequent attacks**

# Approx. 6% of Diagnosed GA Patients are Candidates for Canakinumab Therapy



<sup>1</sup> NHANES III, Decision Resource; <sup>2</sup> Decision Resources, M&J; <sup>3</sup> MR – patient case studies 2009, US quant research 2009, TPP research 2010; <sup>4</sup> Claims data.

# Approx. 6% of Diagnosed GA Patients are Candidates for Canakinumab Therapy



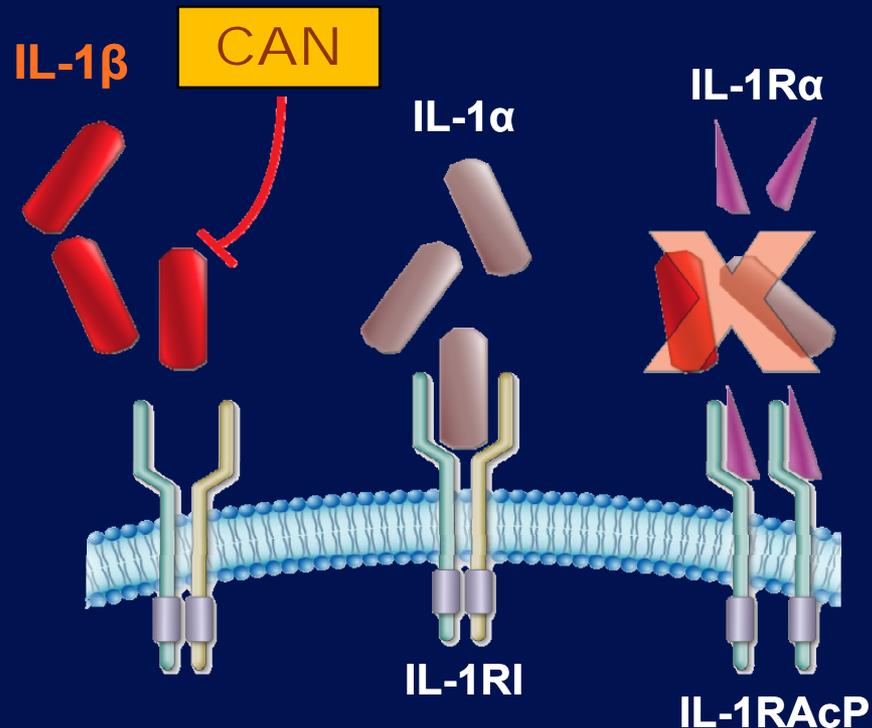
1683: Thomas Sydenham's own description  
*"awakened by a severe pain... like a dislocation followed by chills, shivers and a little fever... becomes more intense... cannot bear the weight of bedclothes... nor the jar of a person walking in the room"*

<sup>1</sup> NHANES III, Decision Resource; <sup>2</sup> Decision Resources, M&J; <sup>3</sup> MR – patient case studies 2009, US quant research 2009, TPP research 2010; <sup>4</sup> Claims data.

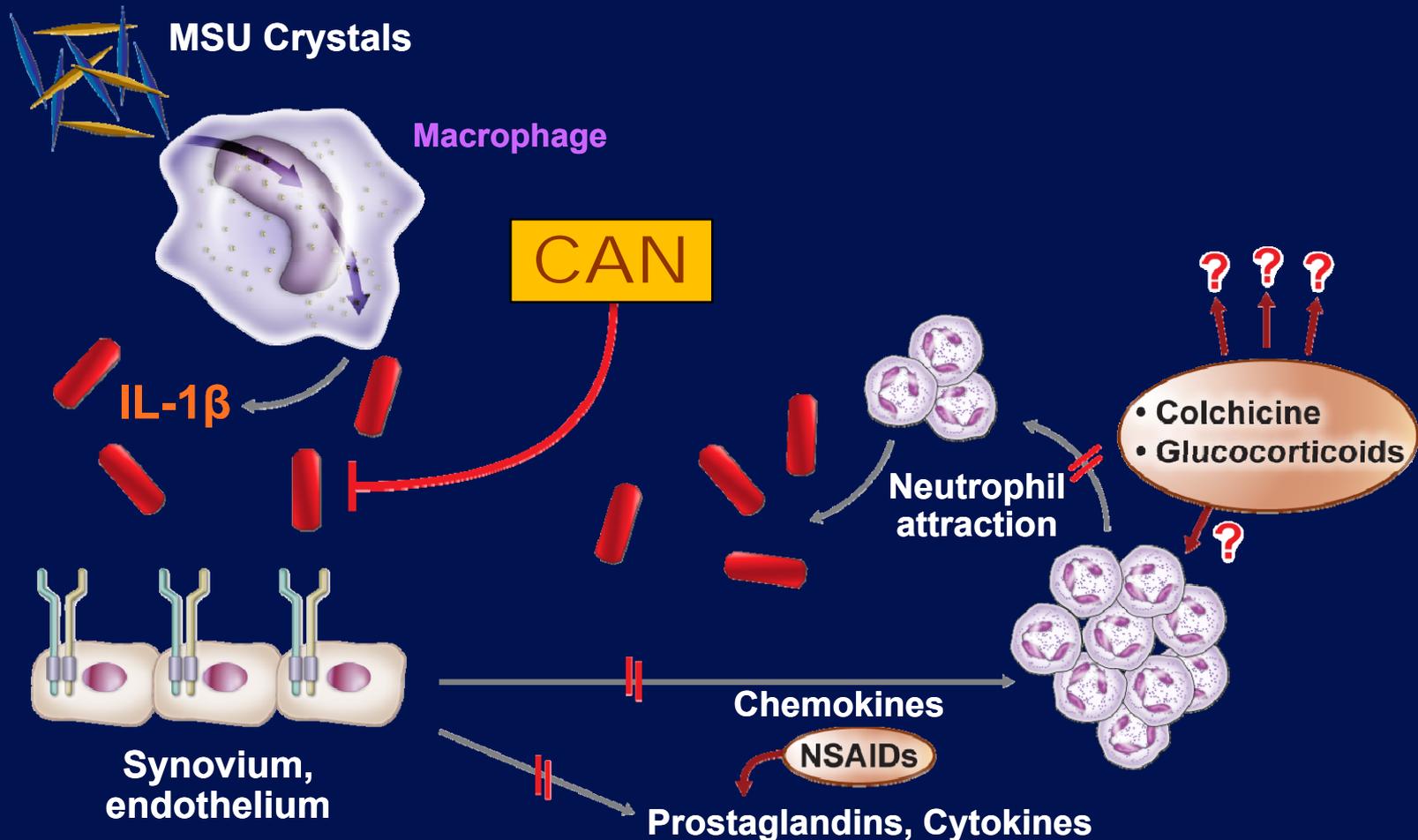
# Targeted Therapy with Canakinumab (CAN)

Specifically targets signaling by IL-1 $\beta$ , but not IL-1 $\alpha$  or IL-1 Receptor antagonist

Highly specific binding to IL-1 $\beta$

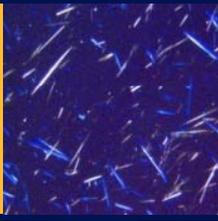


# Canakinumab (CAN) Selectively Interrupts the Inflammatory Cascade



Source: Martinon et al., Clin Invest. 116(8): 2073–75; Martinon, Immunol Rev. (2010) 233(1):218-32; Nuki, Curr Rheumatol Rep. (2008) 10(3):218-27; Ben-Chetrit et al, Rheumatology (Oxford). (2006) 45(3):274-82; Phelps, Arthritis Rheum. (2008) 58(2 Suppl):S25-33

# Canakinumab Targeting IL-1 $\beta$ Mediated Inflammatory Diseases

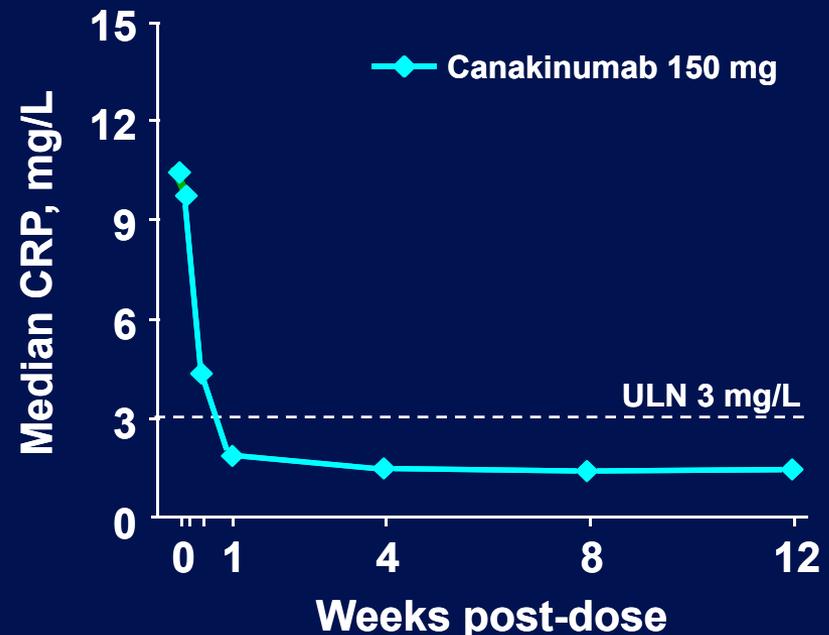
<p><b>Approved</b></p>	<p>Cryopyrin-Associated Periodic Syndrome</p>		<p>Rationale: Genetic mutation drives overproduction of IL-1<math>\beta</math></p> <ul style="list-style-type: none"> <li>• Significant clinical improvement demonstrated</li> </ul>
<p><b>Under Review</b></p>	<p>Gouty Arthritis (Acute)</p>		<p>Rationale: gouty arthritis is IL-1<math>\beta</math> mediated</p> <ul style="list-style-type: none"> <li>• Monosodium urate crystals activate inflammasome and provide basis for inflammatory pain</li> </ul>
<p><b>Supportive Program</b></p>	<p>Rheumatoid Arthritis</p>		<p>Rationale: Rheumatoid arthritis mediated by IL-1<math>\beta</math></p> <ul style="list-style-type: none"> <li>• This program provides supporting safety data in arthritis</li> </ul>
<p><b>Phase 3</b></p>	<p>Systemic Juvenile Idiopathic Arthritis</p>		<p>Rationale: SJIA is significantly driven by IL-1<math>\beta</math></p> <ul style="list-style-type: none"> <li>• 50% of patients have persistent disease extending to adulthood, and 20% develop destructive arthritis</li> </ul>

- Additional programs in Cardiovascular risk reduction in post-MI subjects, diabetes and ophthalmology

# Biological Characteristics of Canakinumab

- Exhibits strong anti-inflammatory effects
- Pharmacokinetic properties are typical of human IgG1-type immunoglobulins:
  - Half-life of ~26 days, distribution volume consistent with total blood volume
- No clinically relevant changes in PK due to renal impairment

**CRP Levels Were Rapidly Reduced and Normalized (Gouty Arthritis – H2356)**



CRP, C-reactive protein; ULN, upper limit of normal.

## **Proposed Indication**

**ILARIS (canakinumab) is an interleukin-1 $\beta$  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**

# US Regulatory History/Summary

- **Cryopyrin-Associated Periodic Syndrome (CAPS)**
  - June 2009, Priority Review Approval (orphan indication)
- **Gouty arthritis**
  - Nov 2009, End of Phase II – Agreement on program
    - Population, design, dose and safety database
  - June 2010, Pre-sBLA meeting
  - Feb 2011, sBLA submission
  - May 2011, 120 day safety update

# Agenda

## Introduction

**Trevor Mundel, MD, PhD**  
*Global Head of Development,  
Novartis Pharma AG*

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## Gouty Arthritis: Unmet Medical Need

**N. Lawrence Edwards, MD**  
*Professor of Medicine, Rheumatology  
University of Florida*

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## Dose Selection and Efficacy

**Marjorie Gatlin, MD**  
*VP, Head CVMI Medical Unit  
Novartis Pharmaceuticals Corp*

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## Integrated Safety Review

**Michael Shetzline, MD, PhD**  
*Global Program Head  
Novartis Pharmaceuticals Corp*

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## Benefit-Risk: Clinical Perspective

**Robert Wortmann, MD, FACP, MACR**  
*Professor of Medicine, Rheumatology  
Dartmouth Medical School*

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# Scientific Experts

- **N. Lawrence Edwards, MD**

Professor of Medicine, Rheumatology and Clinical Immunology  
University of Florida, Gainesville, FL

- **Gary Koch, PhD**

Professor of Biostatistics, University of North Carolina (Chapel Hill)

- **Vibeke Strand, MD**

Clinical Professor, Adjunct  
Division of Immunology/Rheumatology, Stanford University

- **Robert L. Wortmann, MD, M.A.C.R.**

Professor of Medicine, Rheumatology Section,  
Dartmouth Medical School

# **Gouty Arthritis: Unmet Medical Need**

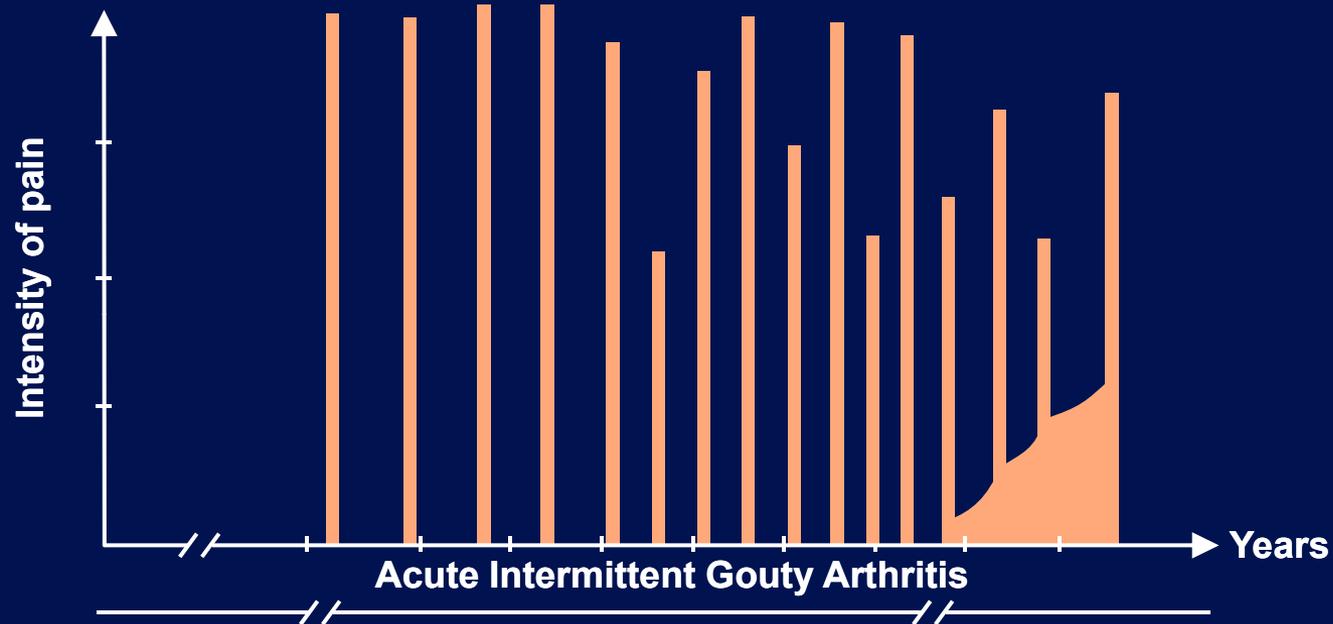
**N. Lawrence Edwards, MD**

*Professor of Medicine and Rheumatology  
University of Florida*

# Overview of Gouty Arthritis

- **Gouty arthritis (GA) is the most common form of inflammatory arthritis**
  - **Affects approximately 8.3 million US adults<sup>1</sup>**
- **Features acute attacks characterized by agonizing pain and progressive debilitation**
- **A subset of patients with frequent GA attacks is unable to obtain adequate response to NSAIDs or colchicine**
  - **Due to relative or absolute contraindications, intolerance, or lack of efficacy**
  - **Corticosteroids may be the only available option, however there exist concerns with frequent use**
- **Thus, there is a need for a new mechanism of action to directly manage the pain and inflammation of frequent GA attacks**

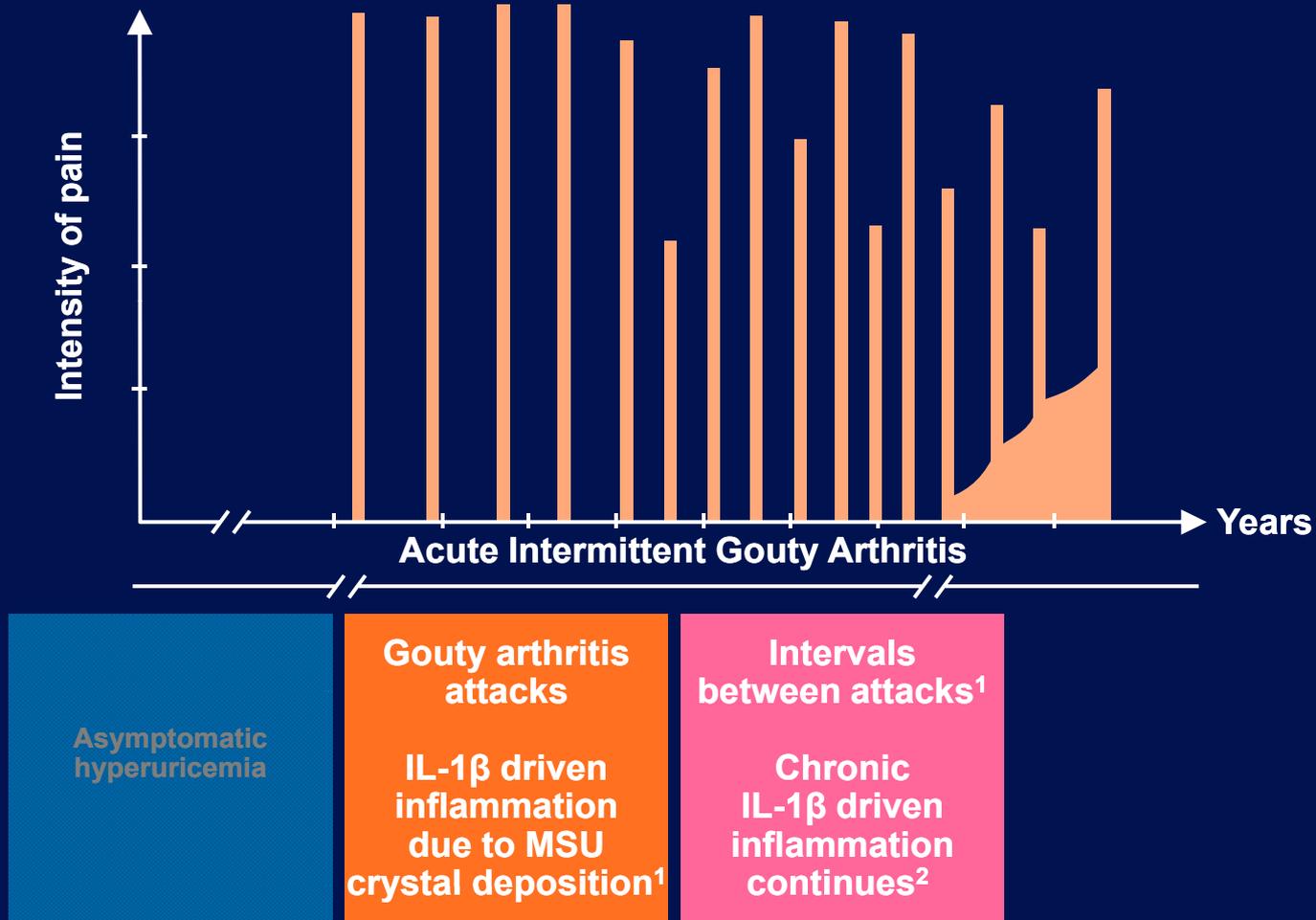
# Gouty Arthritis Is a Chronic Progressive Disease Characterized by Acute Inflammation



Asymptomatic  
hyperuricemia

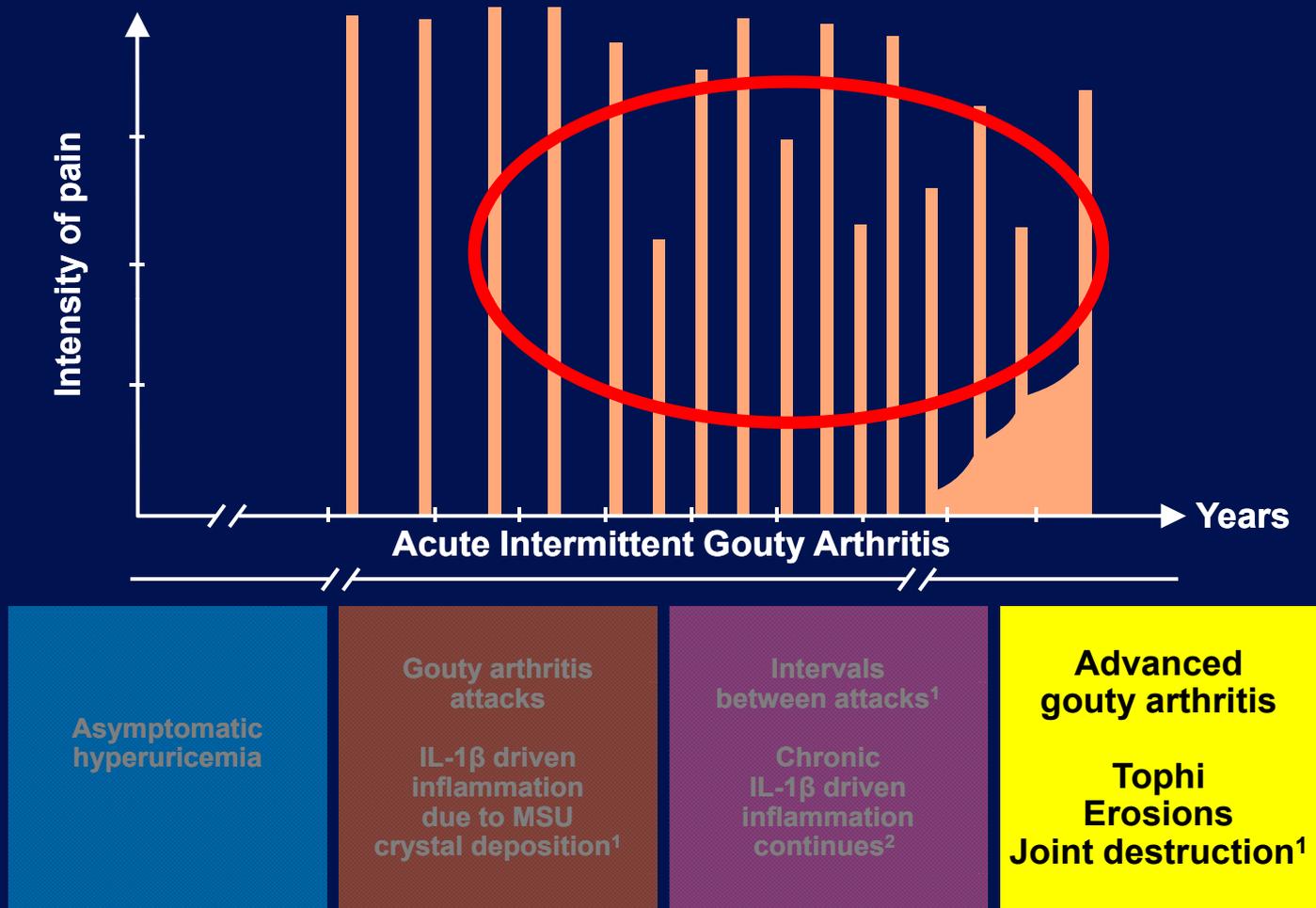
1. Edwards NL. Gout; clinical features. Also Choi HK. Gout; epidemiology, pathology, and pathogenesis. In: Klippel JH et al, eds. *Primer on the Rheumatic Diseases*. 13th ed. 2008:241-257.

# Gouty Arthritis Is a Chronic Progressive Disease Characterized by Acute Inflammation



1. Edwards NL. Gout; clinical features. Also Choi HK. Gout; epidemiology, pathology, and pathogenesis. In: Klippel JH et al, eds. *Primer on the Rheumatic Diseases*. 13th ed. 2008:241-257. 2. Pascual E et al. *Ann Intern Med*. 1999;131:756-759.

# Gouty Arthritis Is a Chronic Progressive Disease Characterized by Acute Inflammation



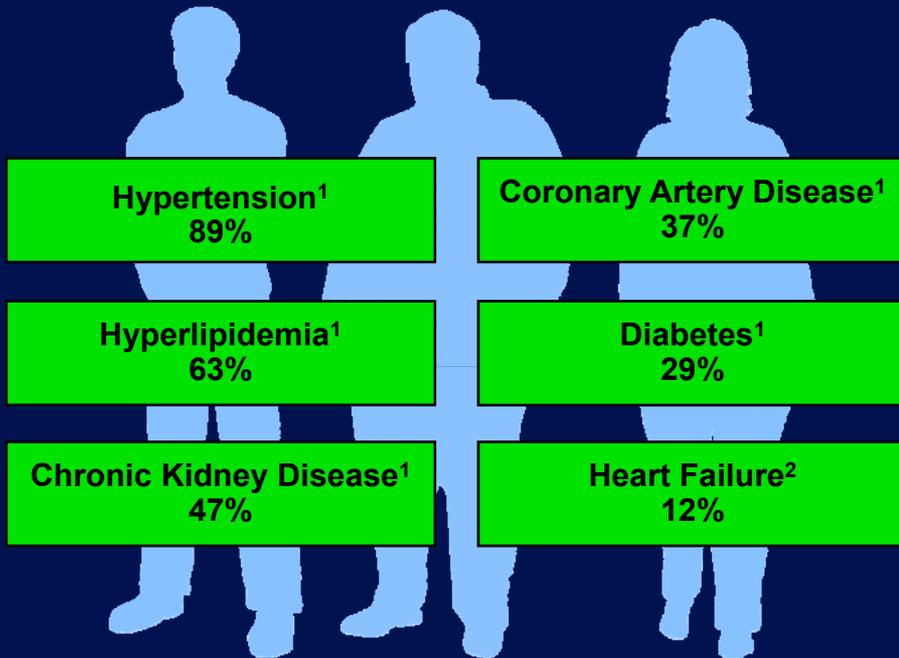
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# Gouty Arthritis Is a Serious Inflammatory Disease, Leading to Agonizing Pain and Debilitation

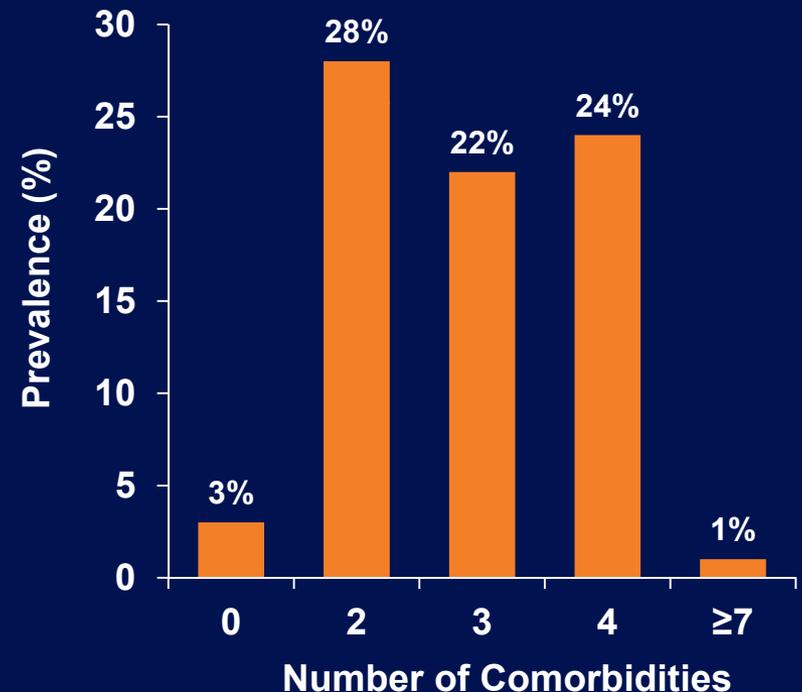
- In a study of 298 patients with GA, 62% described the pain of a typical attack as severe, very severe, or as bad as imaginable<sup>1</sup>
  - “Severe” pain is associated with an average VAS score of 75 mm<sup>2</sup>
- In a survey of 1,000 GA patients, 69% described attacks as “miserable”<sup>3</sup>
  - Severe burn (34%)
  - Breaking a bone (28%)
  - Shattered glass piercing the skin (23%)



# Comorbidities are Common in Gouty Arthritis and May Influence Treatment



Prevalence of having 0 to  $\geq 7$  comorbidities in patient population with gouty arthritis<sup>1</sup>



1. Keenan RT, et al. *Am J Med.* 2011;124:155-163. 2. Pandya B, et al. *Arthritis Rheum.* 2010;62(suppl 10):879.

# Gouty Arthritis Attacks Lead to ER Visits and Hospitalizations

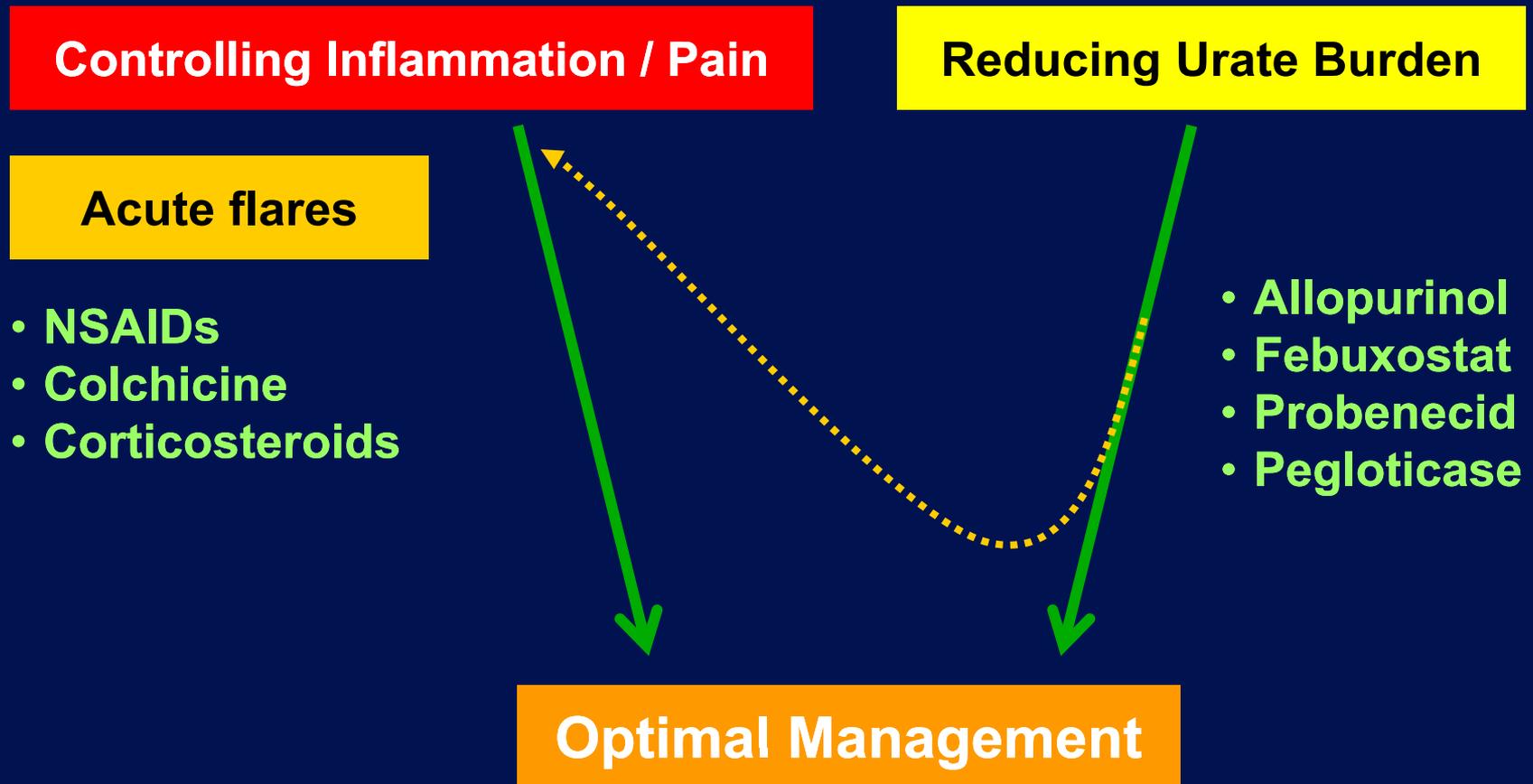
Healthcare utilization in GA patients with frequent attacks ( $\geq 3$ /year)<sup>1</sup>

	<b>% with ER Visits Due to GA</b>	<b>% Hospitalized Due to GA</b>
<b>Total US (n=304)</b>	<b>25%</b>	<b>15%</b>

- Hospitalizations for gouty arthritis are characterized by substantial length of stay (mean 4 days)<sup>2</sup>
- Gouty arthritis attacks add ~3 days to a hospital stay for another condition<sup>3</sup>

1. ChartTrends: Hard-To-Treat Gout study. 2. Mandell BF et al. *Cleve Clin J Med*. 2010;77:S2-25.  
3. Lin Y-H et al. *Cerebrovasc Dis*. 2009;28:391-396.

# A Critical Part of Treating Gouty Arthritis Is Effective Treatment of Pain and Inflammation



# Challenges With Current Therapies

	<b>Safety and Tolerability Concerns</b>	<b>Relevant Comorbidities</b>
<b>NSAIDs</b>	<ul style="list-style-type: none"><li>• Renal toxicity</li><li>• CV risk</li><li>• Bleeding risk</li></ul>	<ul style="list-style-type: none"><li>• HTN</li><li>• CKD</li><li>• CVD</li><li>• PUD/GI bleed</li></ul>
<b>Colchicine</b>	<ul style="list-style-type: none"><li>• Diarrhea</li><li>• Rhabdomyolysis</li><li>• Neuromuscular toxicity</li><li>• Myelosuppression</li></ul>	<ul style="list-style-type: none"><li>• CKD</li><li>• CLD</li></ul>
<b>Corticosteroids</b>	<ul style="list-style-type: none"><li>• Uncontrolled hypertension</li><li>• Worsening dysglycemia</li><li>• Worsening volume overload</li><li>• Other</li></ul>	<ul style="list-style-type: none"><li>• HTN</li><li>• DM</li><li>• CVD</li></ul>

HTN=hypertension, CKD=chronic kidney disease, CVD=cardiovascular disease, PUD=peptic ulcer disease, CLD=chronic liver disease, DM=diabetes mellitus

1. Keenan RT, et al. *Am J Med.* 2011;124:155-163. 2. Indocin (indomethacin) prescribing information. Merck & Co, Inc. 2007. 3. Colcrys (colchicine) prescribing information. URL Pharma Inc. 2010. 4. Prednisone prescribing information. Watson Pharma Inc. 2008.

# A Subset of Patients With Frequent Gouty Arthritis Attacks Need a New Treatment Option

- Those who **do not receive adequate relief** with NSAIDs or colchicine
- Patients who **cannot tolerate** NSAIDs or colchicine, due to the well-known side effects
- Patients with **absolute or relative contraindications** to NSAIDs or colchicine, most likely due to comorbidities
  - e.g., CKD, CVD, PUD/GI bleed<sup>1</sup>
- For many of these patients, **corticosteroids** may represent the only available treatment option
  - However, there exist **concerns with frequent use**

# Summary

- **Gouty arthritis is a chronic inflammatory disease which features agonizing pain and debilitation**
  - Greater frequency of attacks adds to the burden of disease
- **A subset of patients with frequent GA attacks is unable to obtain adequate response to NSAIDs or colchicine**
  - Due to relative or absolute contraindications, intolerance, or lack of efficacy
  - Corticosteroids may be the only available option, however there exist concerns with frequent use
- **Thus, there is a need for a new mechanism of action to directly manage the pain and inflammation of frequent GA attacks**

# Dose Selection and Efficacy

**Marjorie Gatlin, MD**

*VP, Head CVMI Medical Unit  
Novartis Pharmaceuticals Corp*

# Introduction

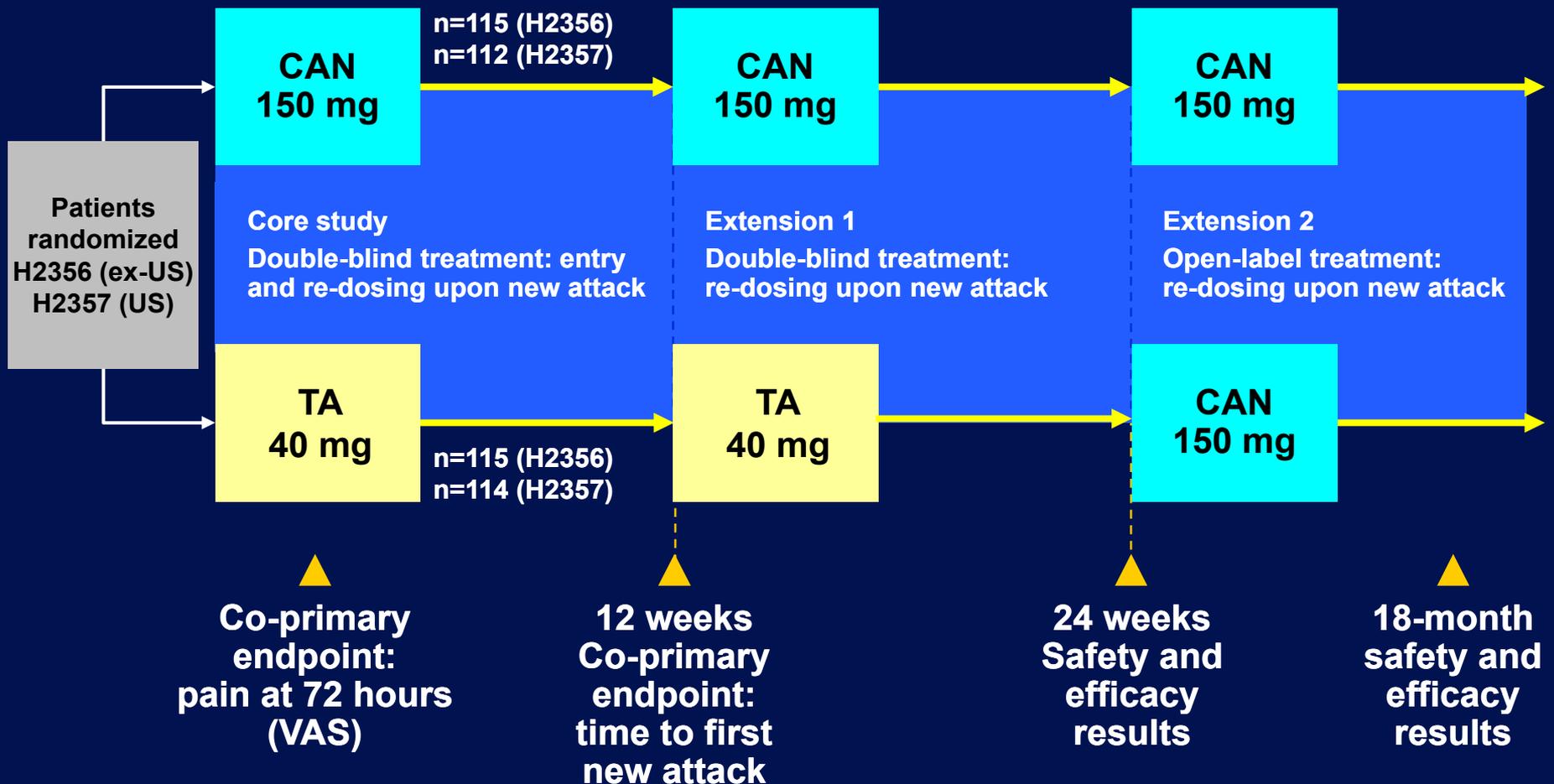
- **Canakinumab development program comprised of 3 trials with extensions**
- **Canakinumab 150 mg provides fast, effective relief of the pain and inflammation of an acute gouty arthritis attack**
- **Canakinumab is also effective in extending the time to the next attack and reducing the risk of subsequent attacks**
- **Canakinumab efficacy is predictable in patients requiring retreatment**

# Overview

- **Phase III Program Design**
- **Dose Rationale**
- **Primary Endpoints**
  - **Attack Pain**
  - **Efficacy in Delaying Subsequent Attacks**
- **Supportive Secondary Endpoints**
- **Efficacy in Re-treatment**

# Phase III Program Design

# β-RELIEVED: Two Phase 3 Studies of Patients With Frequent Attacks ( $\geq 3$ /year)



TA = triamcinolone acetonide

# Phase III Trial Design

- **Randomized, double-blind, active comparator**
- **Canakinumab or TA administered by study site personnel**
- **New attacks re-treated within 5 days from onset, but only after 14 days from last dose**
- **Rescue medication allowed:**
  - **After 6-hour post-dose pain assessment**
  - **Not less than 4 hours before an assessment**
- **Allowed rescue medications were oral steroids, paracetamol/acetaminophen, codeine**

# Key Inclusion/Exclusion Criteria for Phase III

- **Key Inclusion Criteria:**

- Adult male and female patients with chronic gouty arthritis
- $\geq 3$  gouty arthritis attacks in the previous year
- Experiencing an acute attack of  $< 5$  days since onset
- Pain intensity  $\geq 50$ mm on visual analogue scale (VAS)
- Contraindicated (relative or absolute) to, intolerant of, or lack of efficacy with NSAIDs and/or colchicine

- **Key Exclusion Criteria**

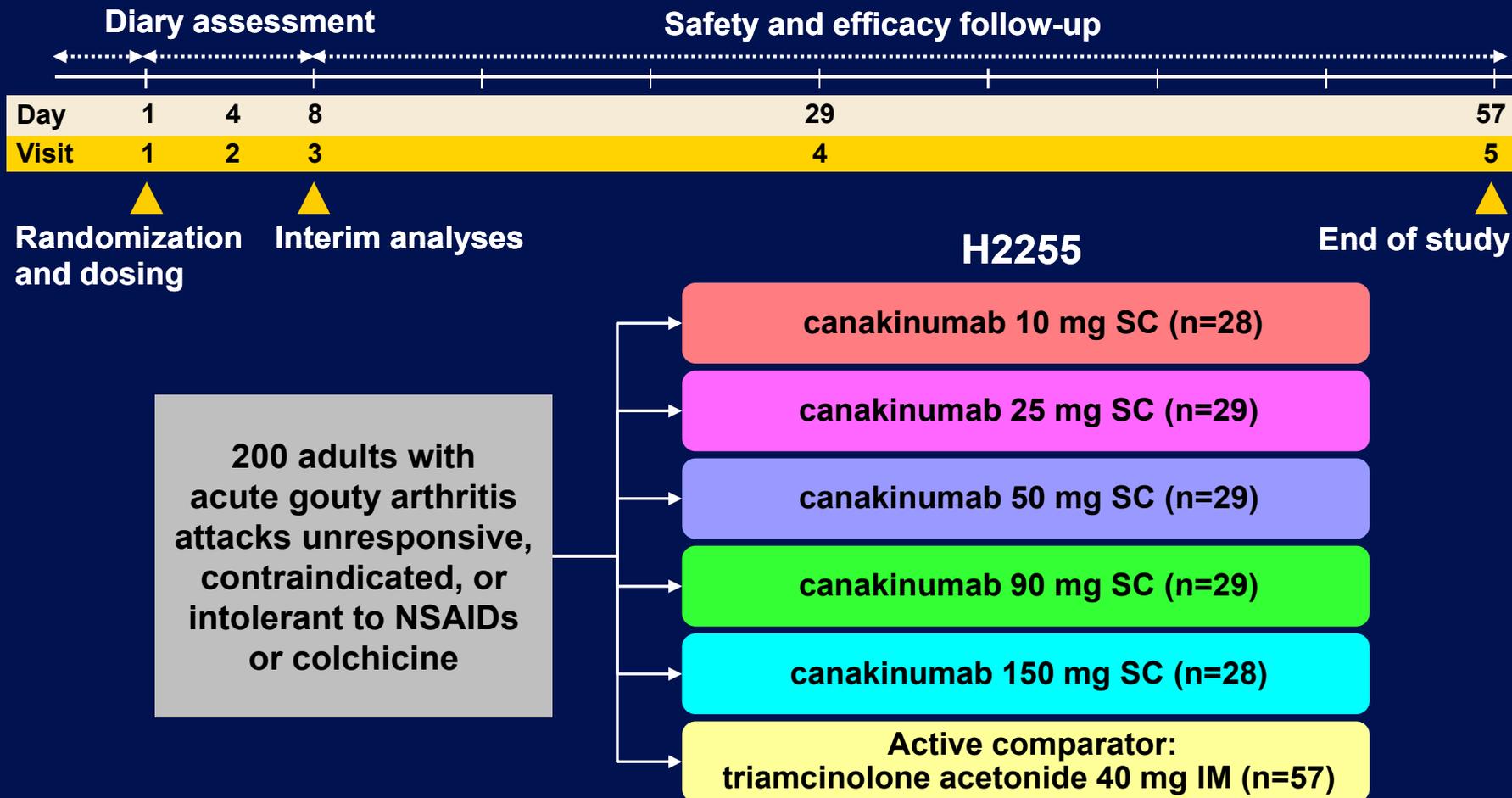
- Use of specific pain relief medications
- Use of anakinra, rilonacept or other biologics
- Severe renal impairment
- Active or recurrent infections

# Primary Endpoints

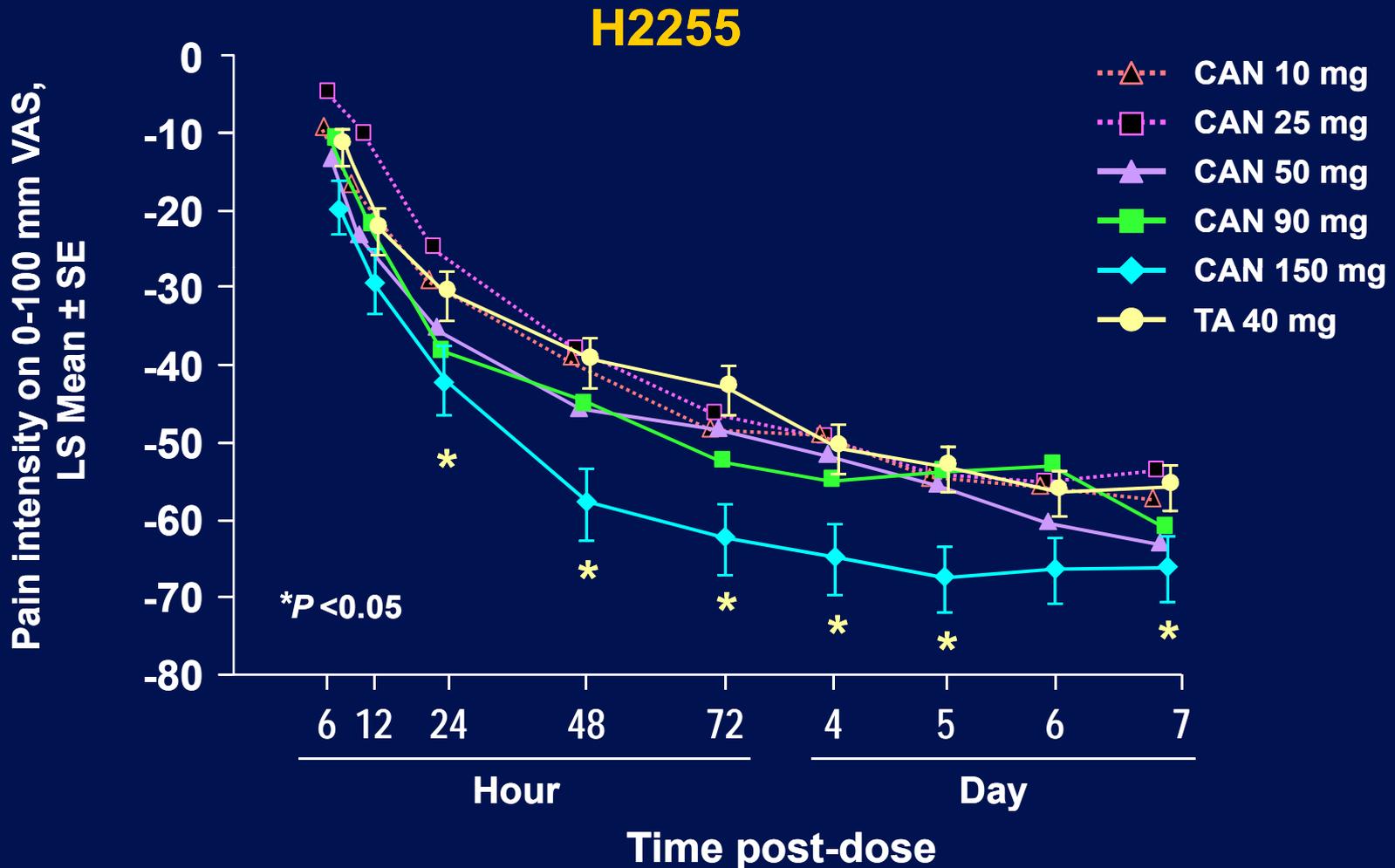
- **Co-Primary endpoints:**
  - Pain intensity in the most affected joint at 72 hours (0-100mm VAS)
    - Study powered to detect 12 mm treatment difference
  - Time to the first new attack
    - Study powered to detect relative risk of 0.415
- **Success required statistical significance for both primary endpoints**
  - Overall power for each study was > 90%

# Dose Rationale for Phase III

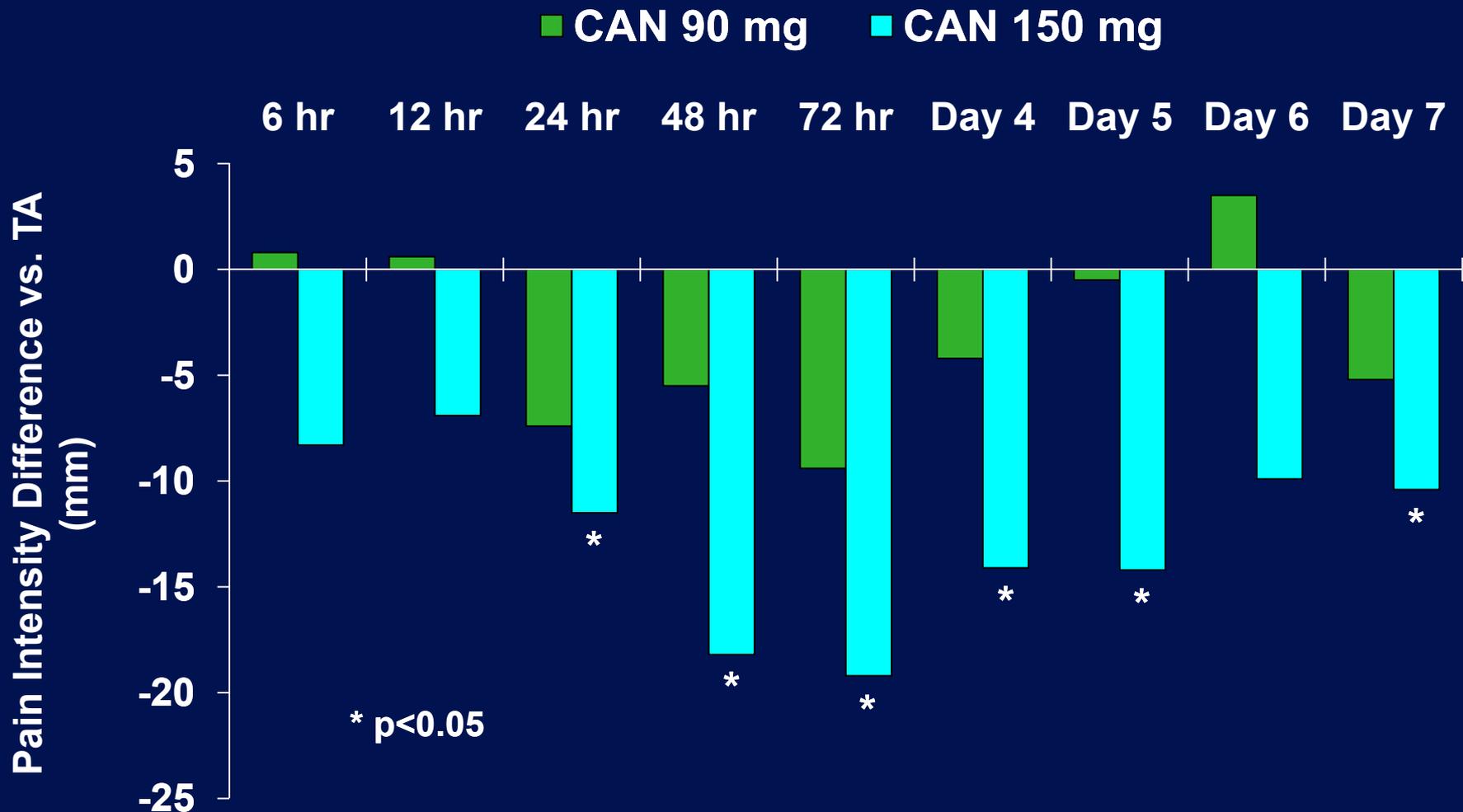
# Efficacy of Canakinumab vs. Triamcinolone



# Canakinumab 150 mg Provided Superior Pain Relief vs. Triamcinolone Acetonide 40 mg



# Study H2255: Estimated Difference in VAS Pain Intensity for CAN 90 mg and 150 mg vs. TA



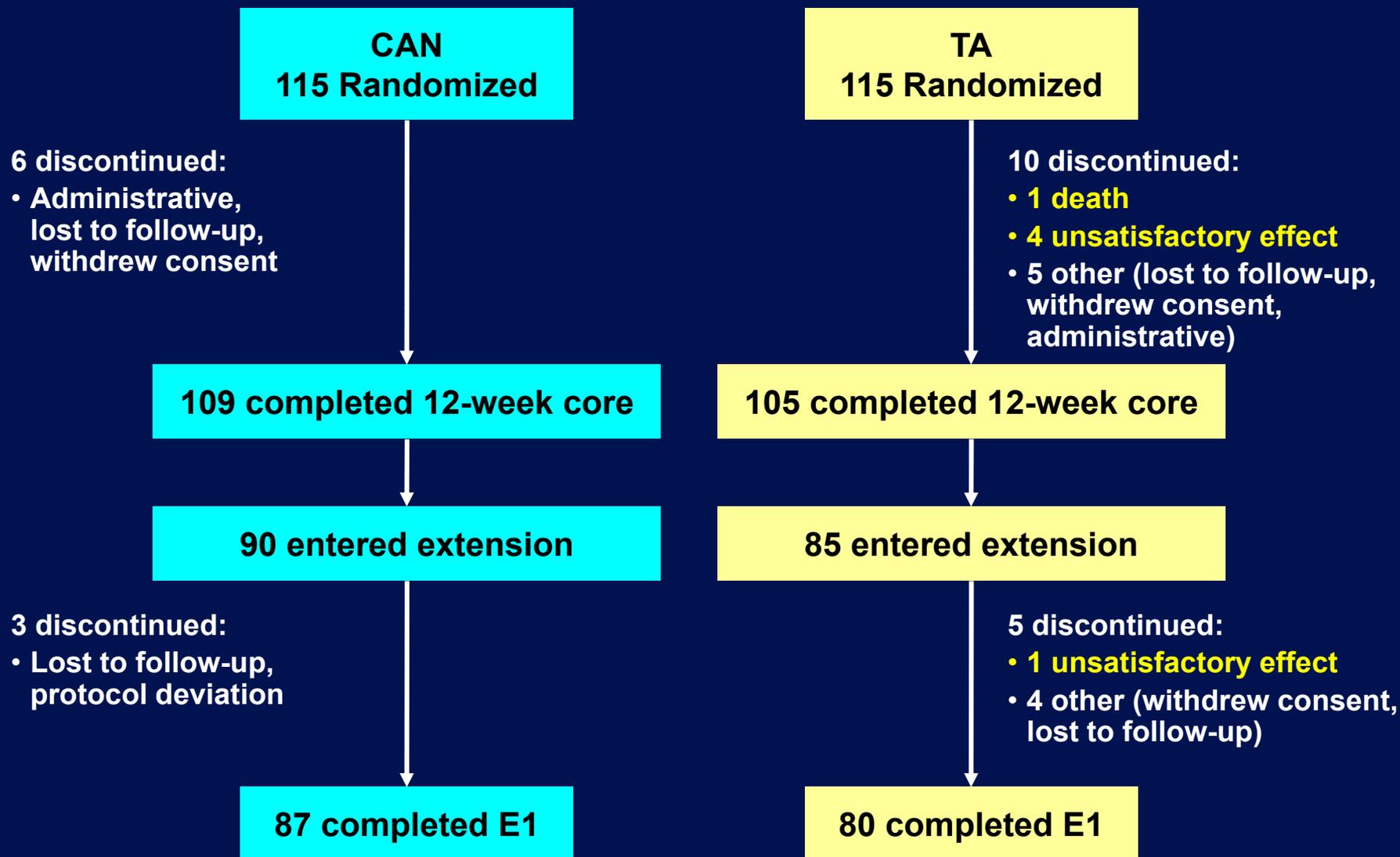
# Selection of Canakinumab 150 mg Dose Supported by Safety Profile in H2255

*Safety and tolerability data*

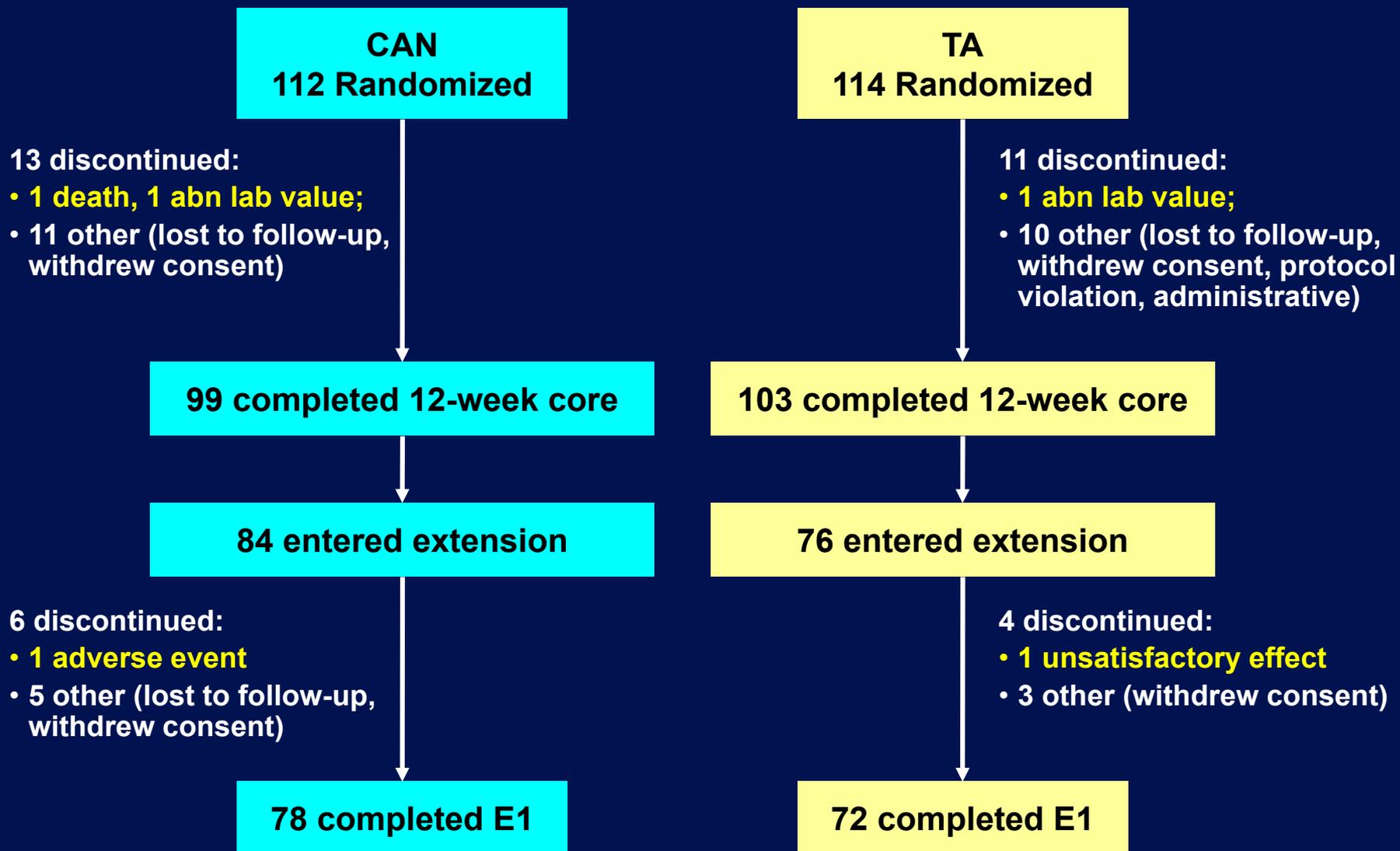
	CAN					TA
	10 mg N=28	25 mg N=29	50 mg N=28	90 mg N=29	150 mg N=27	40 mg N=57
<b>SAEs</b>	0	2 (6.9)	2 (6.9)	0	0	1 (1.8)
<b>Overall AEs</b>	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
<b>D/Cs due to AEs</b>	0	0	0	0	0	0
<b>Infectious AEs</b>	0	3 (10.3)	3 (10.3)	2 (6.9)	2 (7.1)	4 (7.0)

# Phase III Results

# Patient Disposition: H2356



# Patient Disposition: H2357



# Patient Demographics

	H2356		H2357	
	CAN 150 mg	TA 40 mg	CAN 150 mg	TA 40 mg
Male sex, (%)	89.4	93.9	89.3	92.1
Mean (SD) age (years)	54.0 (11)	54.6 (11)	50.6 (12.1)	52.6 (12.3)
BMI (kg/m <sup>2</sup> ), mean	31.8	31.6	32.1	31.5
Race, (%)				
Caucasian	82.3	83.5	66.1	70.2
Black	0.0	0.0	23.2	21.1
Asian	2.7	2.6	8.9	7.9
Other	14.2	13.0	1.8	0.9

# Patient Characteristics Reveal Population with Frequent Attacks and Tophi

	H2356		H2357	
	CAN 150 mg	TA 40 mg	CAN 150 mg	TA 40 mg
<b>                     Joints affected, (%)                 </b>				
<b>                     1                 </b>	<b>50.4</b>	<b>51.3</b>	<b>63.4</b>	<b>64.0</b>
<b>                     2                 </b>	<b>20.4</b>	<b>22.6</b>	<b>17.0</b>	<b>20.2</b>
<b>                     ≥3                 </b>	<b>29.2</b>	<b>26.0</b>	<b>19.6</b>	<b>15.8</b>
<b>                     Serum urate level (mg/dL)                 </b>	<b>8.2</b>	<b>8.5</b>	<b>8.2</b>	<b>8.2</b>
<b>                     On ULT, (%)                 </b>	<b>50.4</b>	<b>54.8</b>	<b>28.6</b>	<b>35.1</b>
<b>                     With visible tophi, (%)                 </b>	<b>38.9</b>	<b>39.1</b>	<b>17.9</b>	<b>20.2</b>
<b>                     Mean number of attacks in the previous year (min, max)                 </b>	<b>6.5 (3, 36)</b>	<b>7.0 (3, 30)</b>	<b>6.5 (3, 50)</b>	<b>5.9 (3, 25)</b>
<b>                     Mean (SD) VAS score                 </b>	<b>73.3 (11.4)</b>	<b>74.8 (12.7)</b>	<b>74.9 (13.3)</b>	<b>73.6 (12.6)</b>

# Percentage of Patients with Contraindication\*, Intolerance, or Lack of Efficacy to NSAIDs or Colchicine

	<b>CAN</b> <b>N=225</b> <b>n (%)</b>	<b>TA</b> <b>N=229</b> <b>n (%)</b>
<b>NSAIDs</b>	<b>204 (90.7)</b>	<b>209 (91.3)</b>
<b>Colchicine</b>	<b>94 (41.8)</b>	<b>98 (42.8)</b>
<b>NSAIDs and colchicine</b>	<b>76 (33.8)</b>	<b>84 (36.7)</b>

\*Absolute or relative contraindication

All defined by the investigator based on patient history

# Majority of Patients Presented with Comorbidities (Phase III Pooled)

<b>n (%)</b>	<b>CAN 150 mg N=225</b>	<b>TA 40 mg N=229</b>
<b>Total patients with any comorbidity/ CV risk factor at baseline</b>	<b>190 (84.4)</b>	<b>198 (86.5)</b>
<b>Hypertension</b>	<b>131 (58.2)</b>	<b>139 (60.7)</b>
<b>Obesity</b>	<b>117 (52.0)</b>	<b>123 (53.7)</b>
<b>Dyslipidemia*</b>	<b>86 (38.2)</b>	<b>103 (45.0)</b>
<b>Metabolic syndrome</b>	<b>80 (35.6)</b>	<b>66 (28.8)</b>
<b>Diabetes mellitus</b>	<b>34 (15.1)</b>	<b>32 (14.0)</b>
<b>Chronic kidney disease</b>	<b>33 (14.7)</b>	<b>22 (9.6)</b>
<b>Cardiac arrhythmia</b>	<b>26 (11.6)</b>	<b>22 (9.6)</b>
<b>Coronary artery disease**</b>	<b>25 (11.1)</b>	<b>30 (13.1)</b>
<b>Cerebrovascular disease</b>	<b>10 (4.4)</b>	<b>6 (2.6)</b>
<b>Current or prior symptoms of heart failure</b>	<b>8 (3.6)</b>	<b>5 (2.2)</b>

\* Includes terms “hypercholesterolemia “ and “on stable lipid lowering medications”

\*\* Includes term “ischemic heart disease”

# Co-Primary Endpoints

# Canakinumab is Superior to TA on Attack Pain and Risk of Subsequent Attacks

	VAS Pain at 72 h		Delay Time to Next Attack over 12 Wks	
	Delta vs. TA	P-value	Risk Reduction	P-value
H2356	-11.4	.0005	55%	.0014
H2357	-9.8	.0018	68%	<.0001

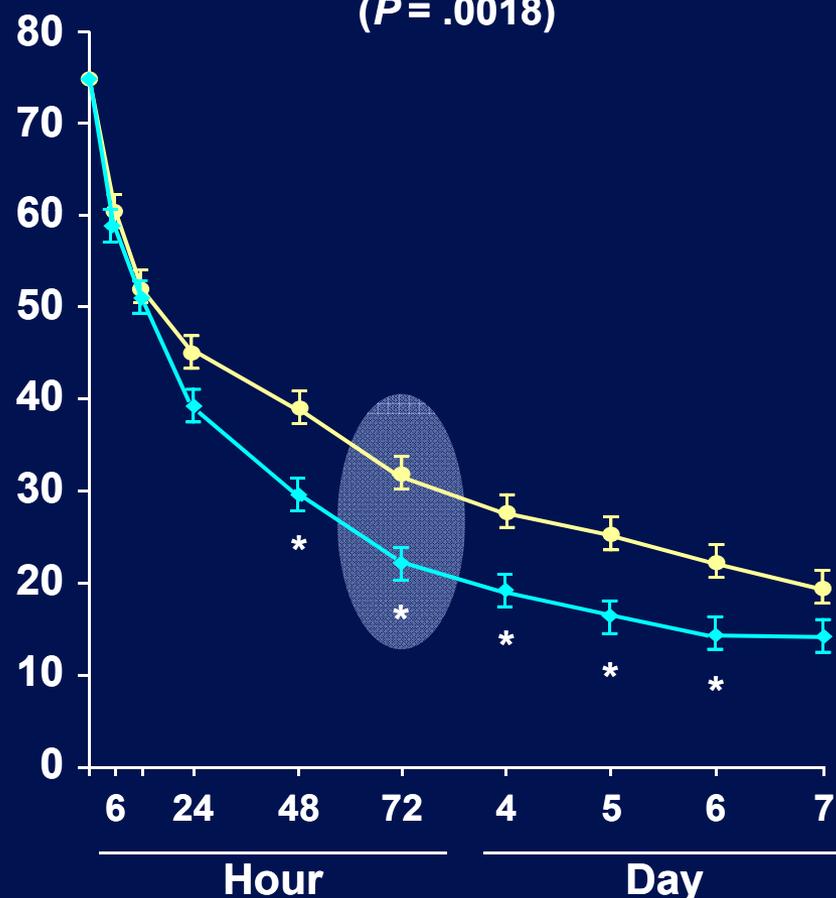
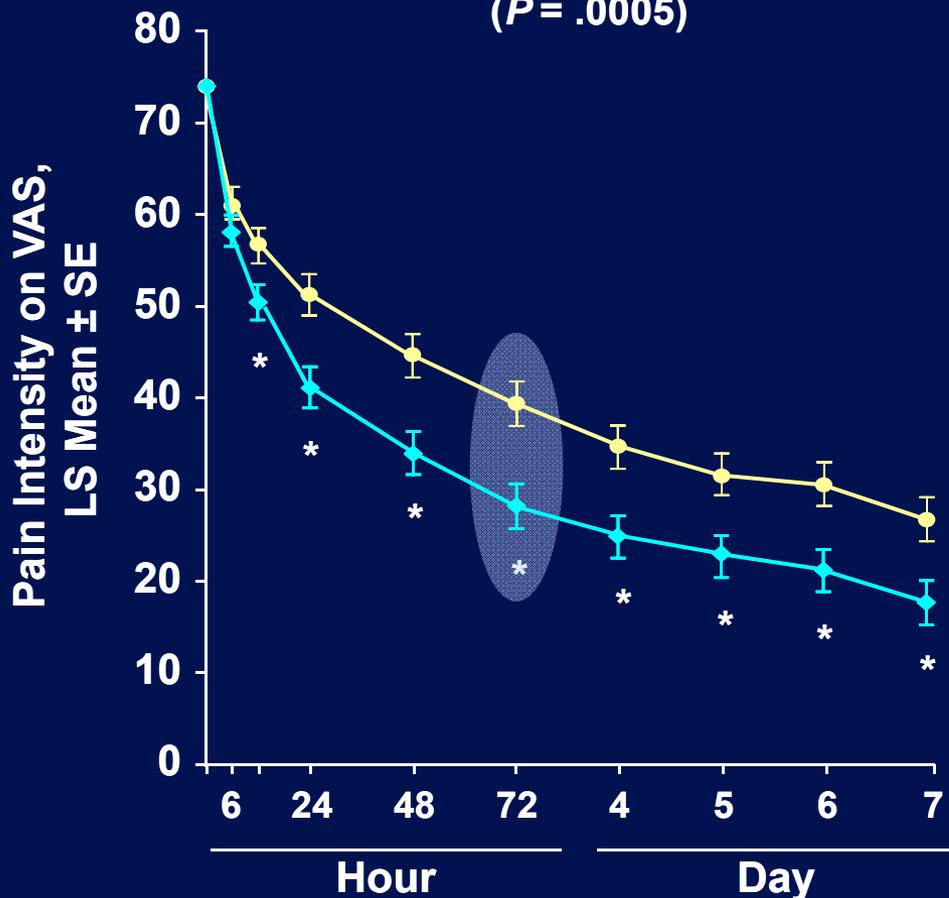
# Canakinumab Provided Superior Pain Relief vs. TA in Both Studies

**H2356**

Mean VAS diff vs. TA at 72 hours: -11.4 mm  
( $P = .0005$ )

**H2357**

Mean VAS diff vs. TA at 72 hours: -9.8 mm  
( $P = .0018$ )

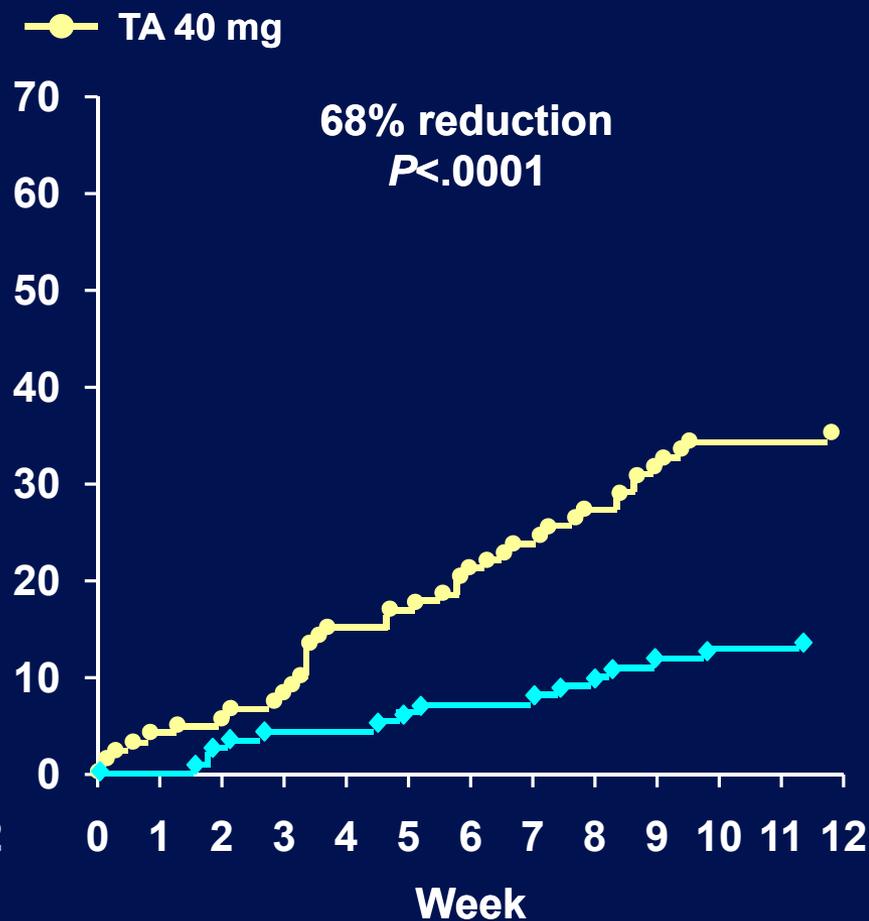
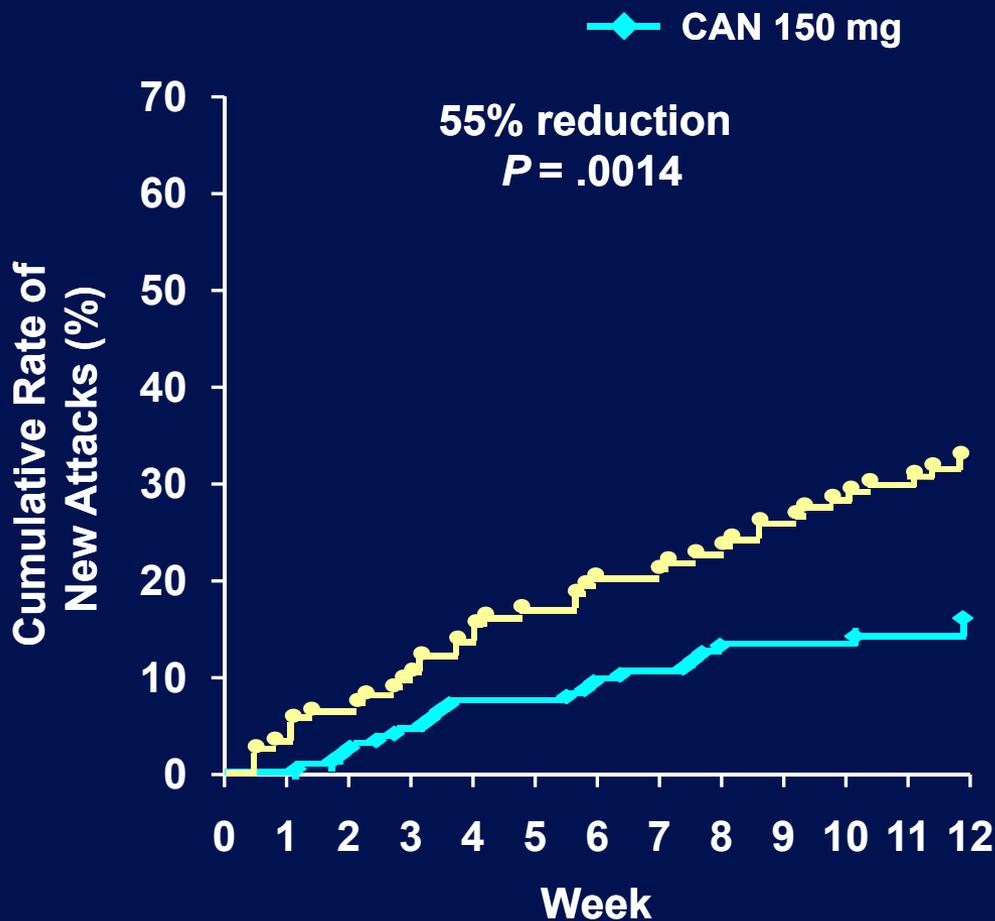


● TA 40 mg (n=111, H2356; n=109, H2357) ◆ CAN 150 mg (n=112, H2356; n=111, H2357)

# Canakinumab Significantly Delayed the Time to First New Attack vs. TA

H2356

H2357

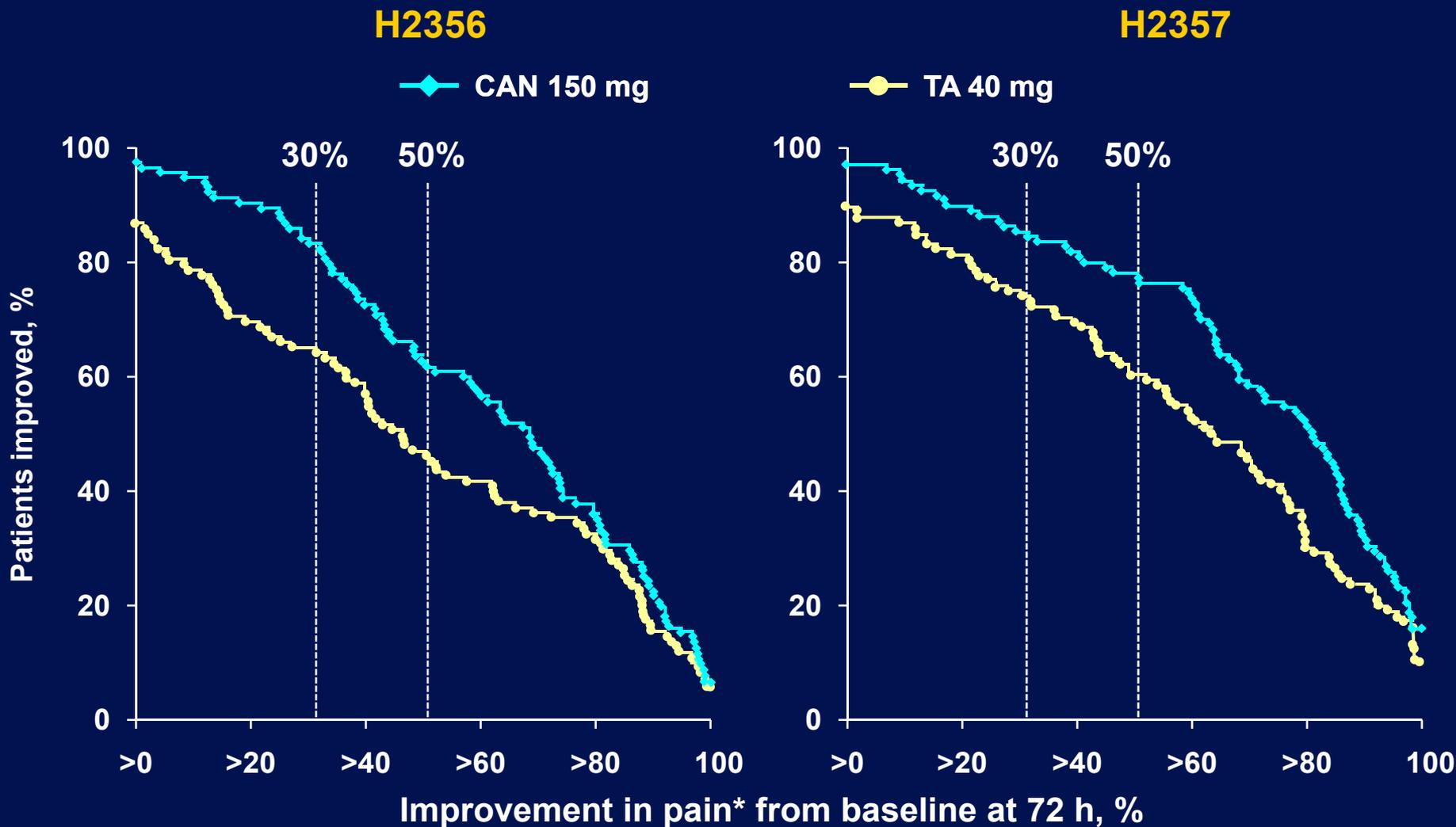


HR = 0.45 (95% CI: 0.26, 0.76)

HR = 0.32 (95% CI: 0.18, 0.58)

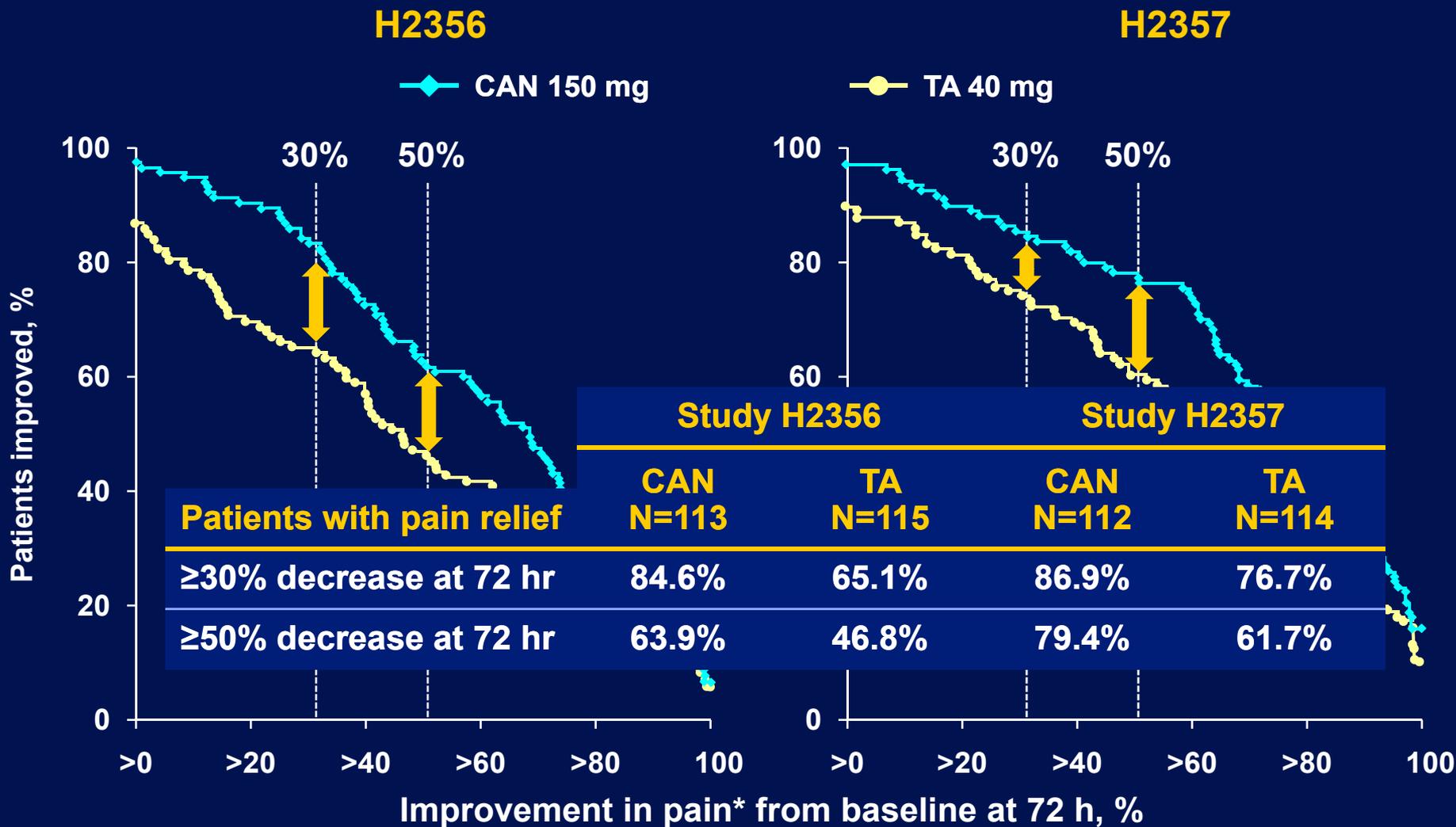
# Secondary Analyses

# More Canakinumab vs. TA Patients Achieved Successful Pain Response at 72 Hours



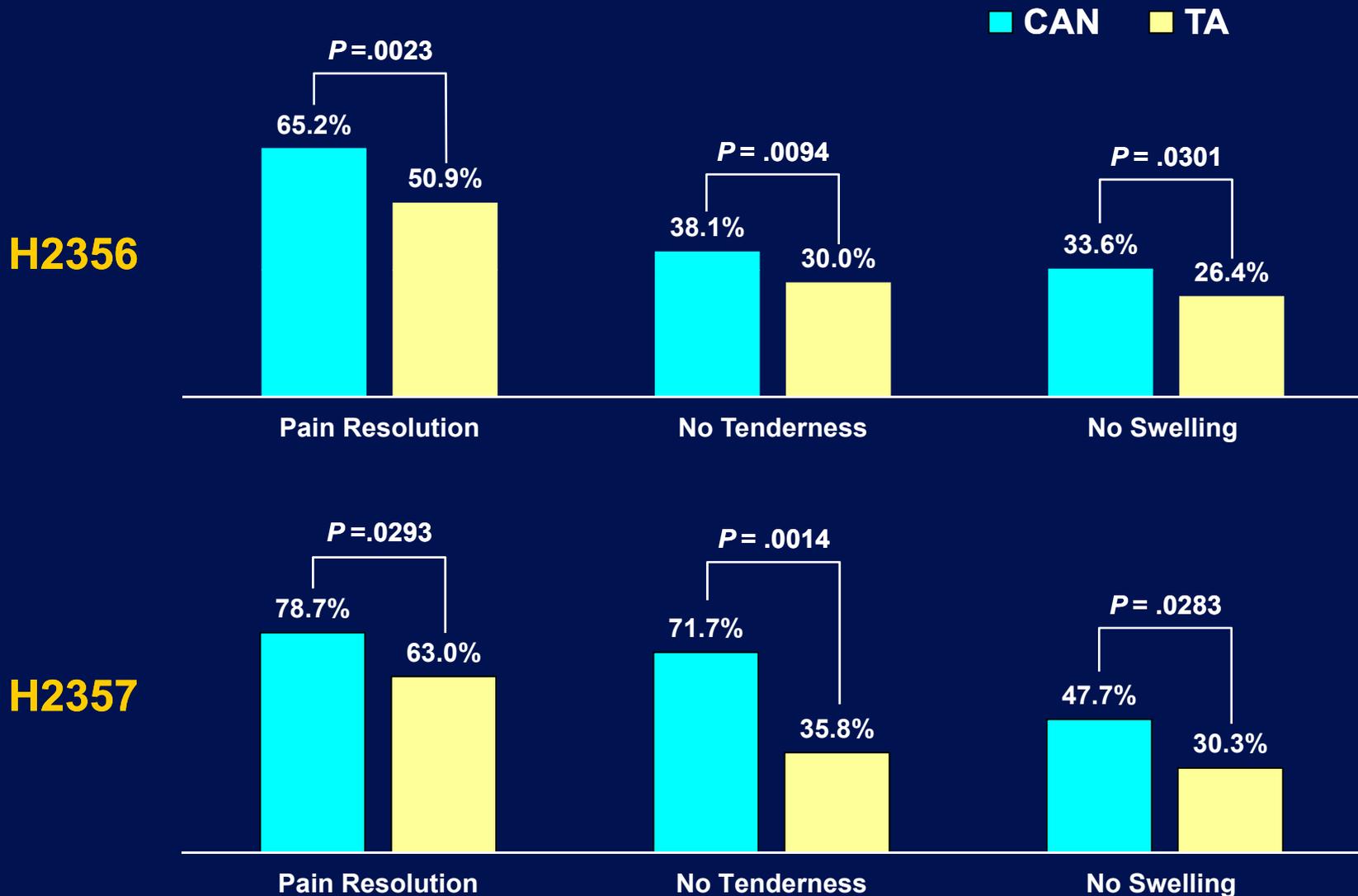
\*VAS 0-100 mm

# More Canakinumab vs. TA Patients Achieved Successful Pain Response at 72 Hours



\*VAS 0-100 mm

# More Canakinumab Patients Had Pain Resolution, No Tenderness or Swelling at 72 Hours



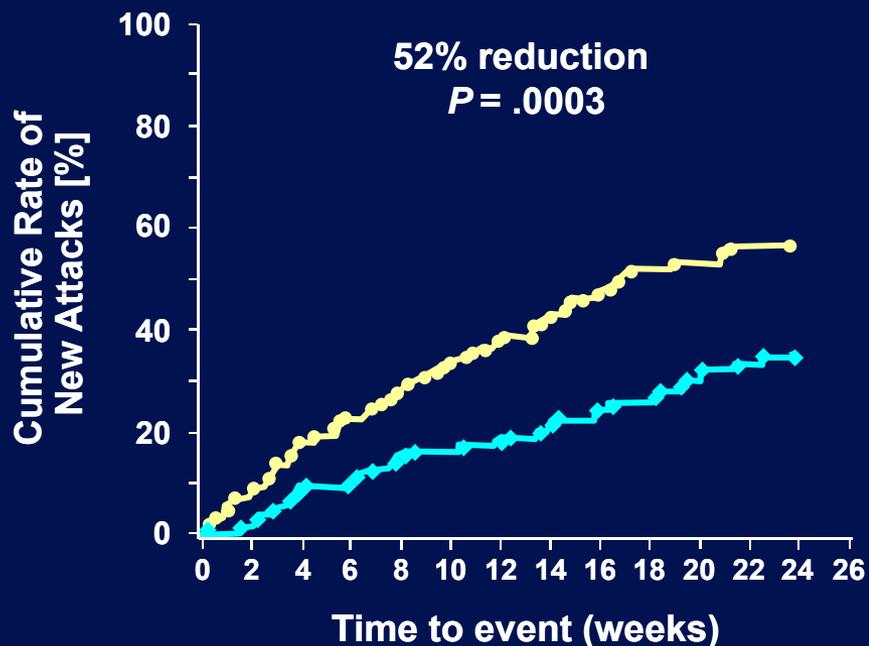
# Rescue Medication Use Was Greater in the Triamcinolone Acetonide Groups than in the Canakinumab Groups Across Both Studies

	H2356		H2357	
	CAN 150 mg n=113	TA 40 mg n=115	CAN 150 mg n=112	TA 40 mg n=114
Patients using rescue medication, %	31.0	52.2	43.8	57.0
Estimated odds ratio (P value)	0.42 (P = .0022)		0.52 (P = .0214)	
Type of rescue medication				
<b>Prednisolone/ prednisone, %</b>	<b>9.7</b>	<b>27.0</b>	<b>12.5</b>	<b>20.2</b>
Acetaminophen/ paracetamol, %	28.3	45.2	36.6	50.0
Codeine, %	4.4	14.8	18.8	23.7

# **Efficacy in Delaying Subsequent Attacks Through 24 Weeks**

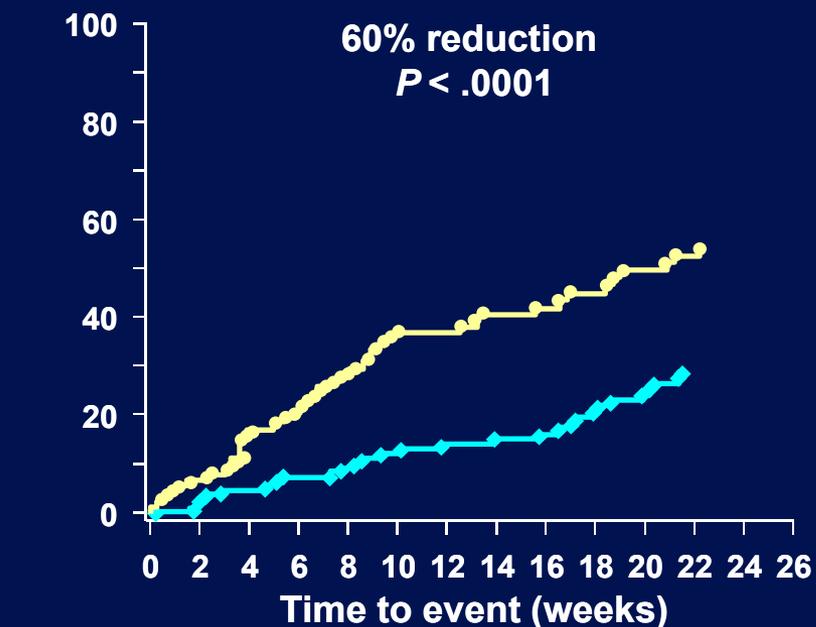
# Canakinumab Reduces the Risk of a New Attack vs. TA Through 24 Weeks

H2356-E1



HR=0.48 ( 95% CI:0.32-0.73)

H2357-E1



HR=0.40 (95% CI: 0.25-0.64)

# Efficacy in Reducing Risk of New Attacks Maintained Through 24 Weeks

	H2356-E1		H2357-E1	
	CAN 150 mg n=113	TA 40 mg n=115	CAN 150 mg n=112	TA 40 mg n=114
<b>No. of attacks/patient</b>				
Mean	0.40	0.87	0.35	0.80
Est rate ratio	0.45		0.42	
95% CI	(0.31, 0.67)		(0.27, 0.64)	
<i>P</i> value (two-sided)	.0001		.0001	
<b>% of pts w/ new attacks</b>				
None	68.1	48.7	75.0	51.1
1	23.9	29.6	17.9	24.6
2	8.0	12.2	4.5	14.0
3	0	6.1	2.7	7.0
≥4	0	3.5	0	0.9

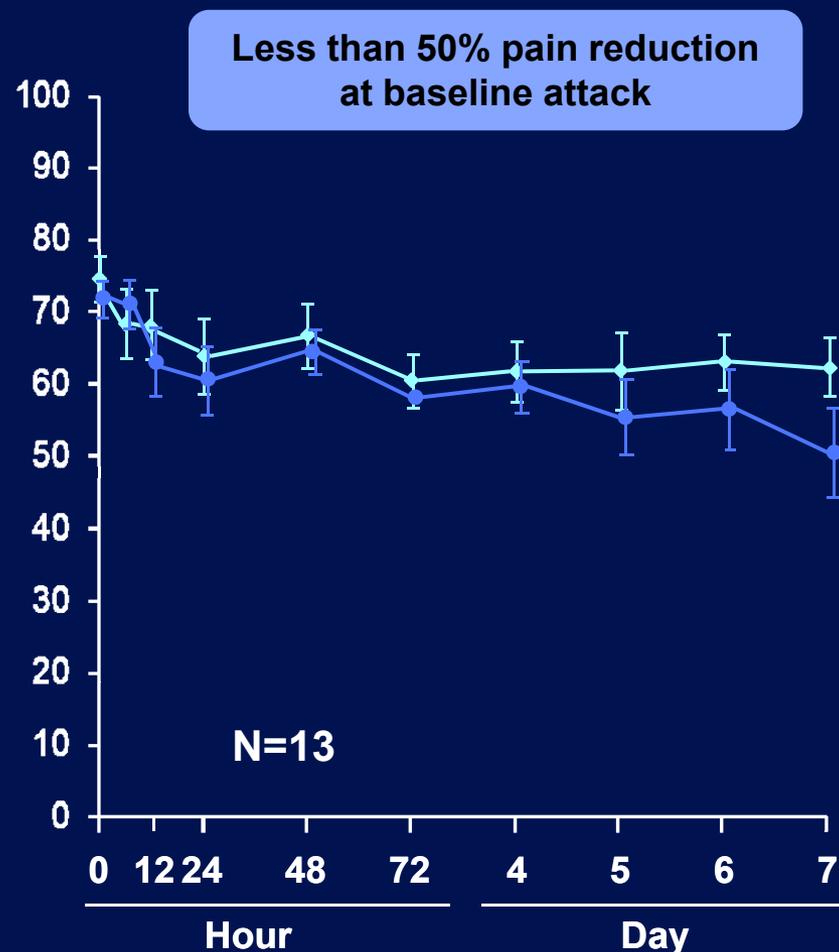
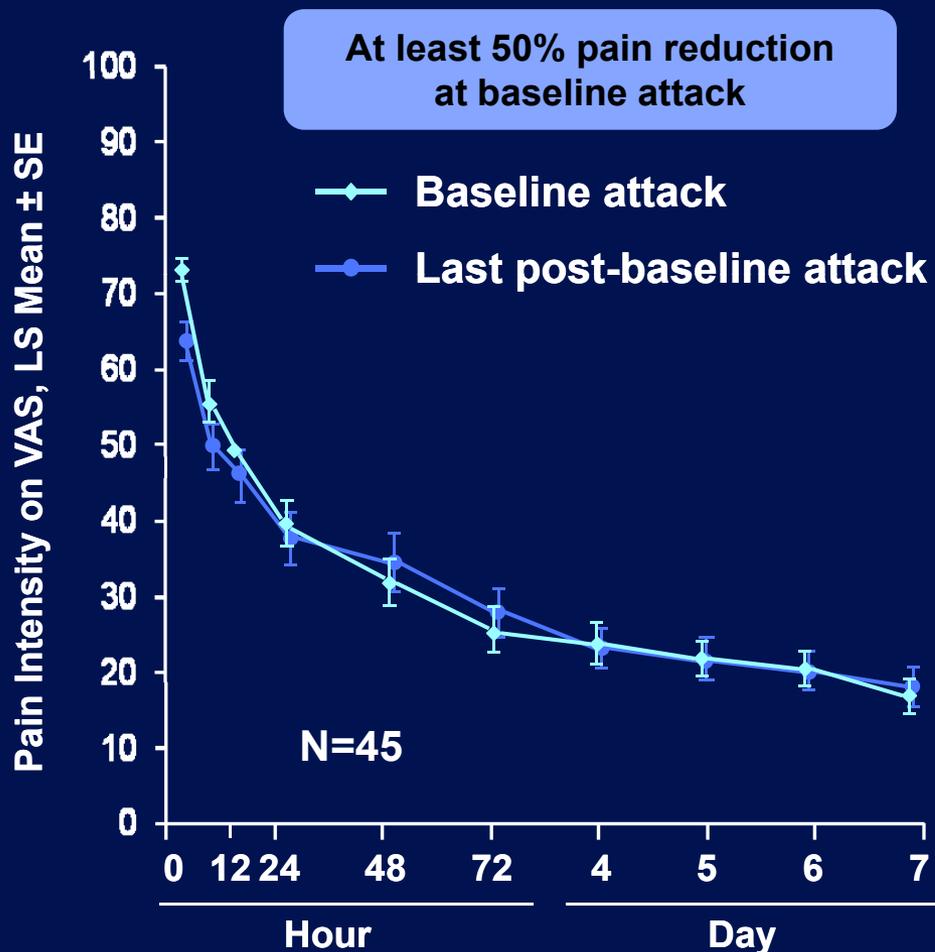
# **Efficacy in Re-Treatment**

# Canakinumab Patients with New Attacks Were Those With More Tophi and More Attacks in the Last Year Compared to TA

<b>Variable</b>	<b>CAN 150 mg n=60</b>	<b>TA 40 mg n=89</b>
<b>Classification of acute gout, (%)</b>		
Acute monoarticular	35.0	51.7
Acute oligoarticular	33.3	34.8
Acute polyarticular	31.7	13.5
<b>Number of attacks in the last year</b>		
Mean	8.1	6.3
>6 attacks in the last year, (%)	43.3	29.2
<b>Patient contraindicated, (%)</b>		
NSAIDs	40.0	20.2
Colchicine	3.3	7.9
Both NSAIDs and colchicine	0.0	3.4
<b>Known presence of tophi, (%)</b>		
Yes	46.7	33.7
No	53.3	66.3

# Pain Response During First Attack Predicts Response During New Attack With Canakinumab

*Pooled Extension H2356E1, H2357E1*



VAS: 0-100 mm.

VAS = visual analog scale; LS = least-squares; SE = standard error

# >80% of Patients on Canakinumab Can Expect a Benefit

Pooled Data	12 Weeks		24 Weeks	
	CAN 150 mg	TA 40 mg	CAN 150 mg	TA 40 mg
Patients with dual benefit	77%	49%	65%	39%
Patients with repeated benefit	6%	17%	17%	25%
Patients with weak/varying benefit*	10%	25%	11%	26%
Patients with no benefit	4%	2%	4%	3%

\* Uncertain benefits were defined as: weak pain relief, no new flare; inconsistent pain relief for baseline (BL) and new flare; and new flare occurring within 2 weeks of dosing/no re-treatment

# Superiority of Canakinumab vs. Triamcinolone Demonstrated by Multiple Endpoints

- **Canakinumab 150 mg demonstrated superior efficacy compared with triamcinolone 40 mg, providing more rapid, sustained pain relief during an acute attack**
  - 2/3 of canakinumab patients did not require rescue medication
- **Canakinumab significantly delayed a new attack compared with triamcinolone**
  - 72% of patients were attack free for 6 months
- **Canakinumab is as efficacious treating the last attack as the baseline attack**
  - Pain response during first attack predicts response during subsequent attacks

# Integrated Safety Review

**Michael Shetzline, MD, PhD**

*Global Program Head  
Novartis Pharmaceuticals Corp*

# Overview

- **Safety Populations**
  - Exposure
  - Patient Disposition, Characteristics and Comorbidities
- **Safety Profile**
  - AEs
  - SAEs and Deaths
  - Serious Infections
  - Serious Cardiovascular Events
  - Malignancies
- **Safety Areas of Special Interest**
  - Immunogenicity and Hypersensitivity
  - Hypertension
  - Renal Function
  - Neutrophils
  - Other Lab Abnormalities: Hyperlipidemia, LFTs and Uric Acid
  - Safety on retreatment
- **Summary and Safety Recommendations**

# Safety Populations

	Duration	Rationale
<b>Gouty Arthritis Dataset</b>		
Phase III (2)/II (2) active controlled trials and extensions (2 x E1)	24 weeks	Target population with active control
Open label long term extension trials Phase III/II (3)	48 weeks 72 weeks	long Term safety, Retreatment Safety
<b>Rheumatoid Arthritis Dataset</b>		
Placebo-controlled RA Phase II (4)	26 weeks	Placebo controlled
Open label studies, long term extensions (4)	144 weeks	Long Term Safety
<b>Approved Indication</b>		
CAPS (Clinical trials, post-approval) (150 mg every 8 weeks)	Up to 5 yrs	Post marketing

# All Gouty Arthritis Phase II/III and RA – Exposure and Observation Duration

	Gouty Arthritis					RA	
	≤100 mg N=278	CAN 150 mg N=253	≥200 mg N=107	TA N=286	Colchicine N=108	CAN 150-300 mg* N=441	Placebo N=121
Patient-years controlled (open label)	66.3	96.5 (151.5)	32.2	97.3 (124.6)	31.5	116.1 (461.2)	40.6
<b>Duration – n</b>							
>12 weeks	153	211	101	209	100	411	105
> 24 weeks	–	140	1	129	–	332	30
>36 weeks		129		81		301	
>48 weeks		74		30		255	
>72 weeks		–		–		150	
>96 weeks		–		–		38	

\* 150 to 300 mg every 2-4 weeks

# All Gouty Arthritis Phase III – Patient Characteristics

	<b>CAN 150 mg N=225</b>	<b>TA 40 mg N=229</b>
<b>Male sex, n (%)</b>	<b>201 (89)</b>	<b>213 (93)</b>
<b>Mean (SD) age, y</b>	<b>52.3</b>	<b>53.6</b>
<b>BMI (kg/m<sup>2</sup>), mean</b>	<b>31.9</b>	<b>31.6</b>
<b>Joints affected, n (%)</b>		
<b>1</b>	<b>128 (57)</b>	<b>132 (58)</b>
<b>2</b>	<b>42 (19)</b>	<b>49 (21)</b>
<b>≥3</b>	<b>55 (24)</b>	<b>48 (21)</b>
<b>Serum urate level (mg/dl)</b>	<b>8.1</b>	<b>8.2</b>
<b>On ULT, n (%)</b>	<b>89 (40)</b>	<b>103 (45)</b>
<b>With visible tophi, n (%)</b>	<b>64 (28)</b>	<b>68 (30)</b>
<b>Mean no. of flares in previous year (min, max)</b>	<b>6.5 (3-50)</b>	<b>6.5 (3-30)</b>
<b>Mean VAS score</b>	<b>74.4</b>	<b>74.2</b>
<b>Contraindication to NSAIDs, n (%)</b>	<b>78 (35)</b>	<b>69 (30)</b>
<b>Contraindication to colchicine, n (%)</b>	<b>22 (10)</b>	<b>14 (6)</b>
<b>Contraindication to both NSAIDs and colchicine, n (%)</b>	<b>12 (5)</b>	<b>9 (3.9)</b>

# Gouty Arthritis Phase III – Comorbidities at Baseline

n (%)	CAN 150 mg, n=225	TA 40 mg, n=229
Total patients with any comorbidity	190 (84)	198 (87)
Hypertension	131 (58)	139 (61)
Obesity	117 (52)	123 (54)
Dyslipidemia*	86 (38)	103 (45)
Metabolic syndrome	80 (36)	66 (29)
Diabetes mellitus	34 (15)	32 (14)
Chronic kidney disease	33 (15)	22 (10)
Cardiac arrhythmia	26 (12)	22 (10)
Coronary artery disease**	25 (11)	30 (13)
Cerebrovascular disease	10 (4)	6 (3)
Current or prior symptoms of heart failure	8 (4)	5 (2)

\*Including “hypercholesterolemia “ and “on stable lipid lowering medications”

\*\*Including “ischemic heart disease”

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# Gouty Arthritis Phase II/III – AEs ≥2% of Patients

%	CAN			TA	Colchicine
	≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
<b><i>Infections</i></b>					
Nasopharyngitis	4.7	2.4	0.0	2.4	0.9
URI	2.2	2.0	3.7	1.4	3.7
Sinusitis	0.0	2.0	0.0	0.7	0.0
<b><i>Musculoskeletal</i></b>					
Arthralgia	5.4	4.0	4.7	3.8	2.8
Pain in extremity	2.5	1.2	1.9	3.8	0.0
Back pain	3.2	5.1	2.8	0.7	3.7
OA	0.4	2.8	0.9	0.7	2.8
Gout	0.4	0.4	0.0	3.1	0.0
Muscle spasm	0.4	1.2	0.0	2.4	0.9
Hypertension	3.6	4.7	8.4	4.5	0.9
Headache	5.4	4.7	7.5	4.2	5.6
Dizziness	1.1	2.0	2.8	0.3	0.0
Hypertriglyceridemia	0.7	3.6	2.8	0.7	0.0
Hypercholesterolemia	0.4	2.4	0.0	0.0	0.0
CPK increased	1.8	0.4	0.9	2.1	0.0
GGT increased	1.4	3.2	0.9	1.7	1.9
Diarrhea	2.9	2.0	3.7	2.1	1.9
Fatigue	0.4	2.0	0.9	0.7	0.9

# Gouty Arthritis Phase II/III – Deaths, SAEs and AEs

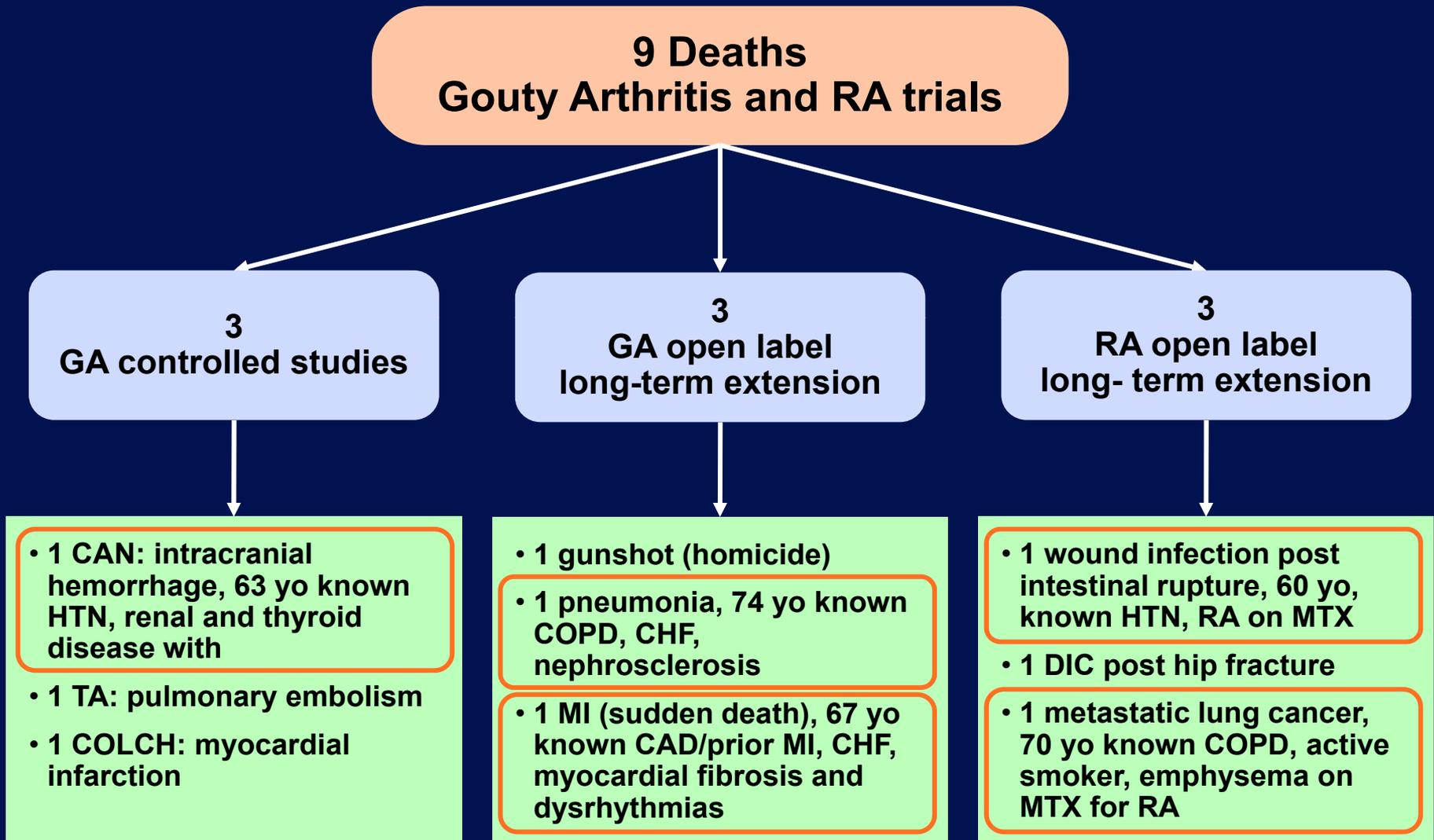
	CAN				TA	Colchicine
	≤100 mg N=278	Split 150 mg N=53	150 mg N=253	≥200 mg N=107	N=286	N=108
Exposure/ observation (pt-yrs)	66.3	16.5	96.5	32.2	97.3	31.5
<b>% Patients with event</b>						
At least one SAE	4.0	1.9	7.1	5.6	3.1	5.6
• Deaths	0.0	0	0.4	0.0	0.3	0.9
• Infectious SAEs	1.4	1.9	1.6	1.9	0	0
At least one AE	49.3	58.5	62.5	53.3	50.7	53.7
• D/C due to AE	1.4	0	0.8	4.7	0.0	1.9
• Infectious AEs	15.1	18.9	19.4	17.8	12.9	12.0

# Rheumatoid Arthritis – SAEs and AEs

*Higher drug exposure compared to GA program*

	CAN			Placebo
	<150 mg N=12 n (%)	150 mg N=69 n (%)	>150 mg N=263 n (%)	N=121 n (%)
Exposure/observation (pt-yrs)	3.8	15.8	96.5	40.6
At least one SAE	3 (25.0)	1 (1.4)	12 (4.6)	9 (7.4)
• Deaths	0	0	0	0
• Infectious SAEs	2 (16.7)	0	7 (2.7)	0
At least one AE	12 (100)	32 (46.4)	165 (62.7)	82 (67.8)
• D/C due to AE	0	1 (1.4)	10 (3.8)	3 (2.5)
• Infectious AEs	6 (50%)	11 (15.9)	82 (31.2)	43 (35.5)

# All Deaths (Gouty Arthritis Phase II/III and RA)



# Gouty Arthritis Phase II/III – Leading Non-Fatal SAEs per Patient

<b>System Organ Class</b>	<b>CAN 150 mg N=253</b>	<b>TA N=286</b>	<b>Colchicine N=108</b>
<b>Cardiac disorders</b>	<b>3</b>	<b>1</b>	<b>1</b>
<b>Eye disorders</b>	<b>2</b>	<b>–</b>	<b>–</b>
<b>Gastrointestinal disorders</b>	<b>2</b>	<b>1</b>	<b>1</b>
<b>Infections and Infestations</b>	<b>3</b>	<b>–</b>	<b>–</b>
<b>Injury, poisoning and procedural complications</b>	<b>–</b>	<b>–</b>	<b>1</b>
<b>Investigations</b>	<b>1</b>	<b>–</b>	<b>–</b>
<b>Metabolism and nutrition disorders</b>	<b>1</b>	<b>2</b>	<b>–</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>3</b>	<b>1</b>	<b>1</b>
<b>Neoplasm</b>	<b>–</b>	<b>–</b>	<b>1</b>
<b>Nervous system disorders</b>	<b>1</b>	<b>3</b>	<b>–</b>

# All Gouty Arthritis Phase II/III – Infectious SAEs

*CAN All Doses*

11 subjects with infectious SAEs

## Skin infections

- Erysypelas
- Abscess jaw
- Abscess forearm

## Respiratory tract infections

- Bronchitis
- Pneumonia and ear infection
- Pneumonia (fatal event in E2)
- Tonsillitis

## Gastrointestinal infections

- 2 appendicitis
- Gastroenteritis

- Toe gangrene in 59 yo diabetic with prior toe gangrene and amputation and septicemia

**No confirmed opportunistic infections (including TB)**

# Gouty Arthritis Phase II/III – Cardiovascular Events

N (%)	CAN			TA	Colch
	≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
Other Cardiac SAEs	0	4 (1.6)	1 (0.9)	1 (0.3)	2 (0.9)
Angina pectoris	–	1 (0.4)	–	–	1 (0.9)
Myocardial ischemia	–	1 (0.4)	–	–	–
Arrhythmia	–	1 (0.4)	–	–	–
Atrial fibrillation	–	1 (0.4)	–	–	–
Cardiomyopathy, AS	–	–	–	1 (0.3)	–
MI / Acute MI	–	–	1 (0.9)	–	1 (0.9)

N (%)	CAN			TA	Colch
	≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
MACE	1 (0.4)	2 (0.8)	1 (0.9)	2 (0.6)	2 (1.9)
CV death	–	–	–	–	1 (0.9)
Stroke or TIA	1 (0.4)	2 (0.8)	–	2 (0.6)	–
MI / acute MI	–	–	1 (0.9)	–	1 (0.9)

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# Gouty Arthritis Phase II/III and RA – Malignancies

GA Dataset, n (%)	CAN			TA	Colchicine
	≤100 mg N=27	150 mg N=253	≥200 mg N=107	N=286	N=108
Prostate cancer	0	0	1 (0.9)	0	0
Renal cancer	0	0	0	0	1 (0.9)

Long-term RA (open label), n (%)	CAN					
	Overall N=441	0-24 weeks N=441	>24-48 weeks N=357	>48-72 weeks N=276	>72-96 weeks N=173	>96-144 weeks N=65
Malignancies	8 (1.8)	2 (0.5)	4 (1.1)	2 (0.7)	0	0

# Summary – SAEs and Infectious SAEs (SIEs)

- **Fatal events were balanced across treatments and consistent with underlying comorbidities**
- **SAEs and SIEs reported with canakinumab are consistent with the mechanism of action**
  - **SIEs respond to standard of care**
  - **One exception, complicated patient with multiple comorbidities**
- **MACE events are balanced across treatment groups**
- **Low and balanced incidence of malignancies**

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# Immunogenicity and Hypersensitivity

- **Gouty arthritis**
  - No subject with confirmed anaphylaxis (Sampson et al, 2005 & 2006)
  - No severe injection site reactions as AEs (1 moderate, 2 mild AE) in CAN 150 mg
  - One subject demonstrated PK changes in the setting of loss of efficacy, however did not develop anti-canakinumab antibodies
  - **Anti-canakinumab antibodies**
    - 8/691 patients (1.1%) positive at study end, low titers only in Phase II RCTs
    - No PK abnormalities or immunogenicity-related AEs reported
- **All RA**
  - No subject with confirmed anaphylaxis (Sampson et al, 2005 & 2006)
    - No patient identified with anti-canakinumab antibodies
- **CAPS**
  - No immunogenicity or anaphylactic reactions reported

**Low rate of immunogenicity to date –  
continued observation warranted**

# Gouty Arthritis Phase II/III – Blood Pressure

<b>Parameter, n (%)</b>	<b>CAN 150 mg N=253</b>	<b>TA 40 mg N= 286</b>
<b>Systolic blood pressure</b>		
≥140 mmHg (at least 1 measurement post baseline)	<b>65 (25.8)</b>	<b>80 (28.3)</b>
<b>Systolic blood pressure, change from baseline, mmHg</b>		
Mean (SD)	-2.8 (15.6)	-2.9 (15.4)
Median	-2.0	-2.0
<b>Diastolic blood pressure</b>		
≥90 mmHg (at least 1 measurement post baseline)	<b>76 (30.2)</b>	<b>75 (26.5)</b>
<b>Diastolic blood pressure, change from baseline, mmHg</b>		
Mean (SD)	-0.9 (10.4)	-0.6 (9.8)
Median	0	0

- **In addition, no worsening of hypertension in patients with baseline hypertension**

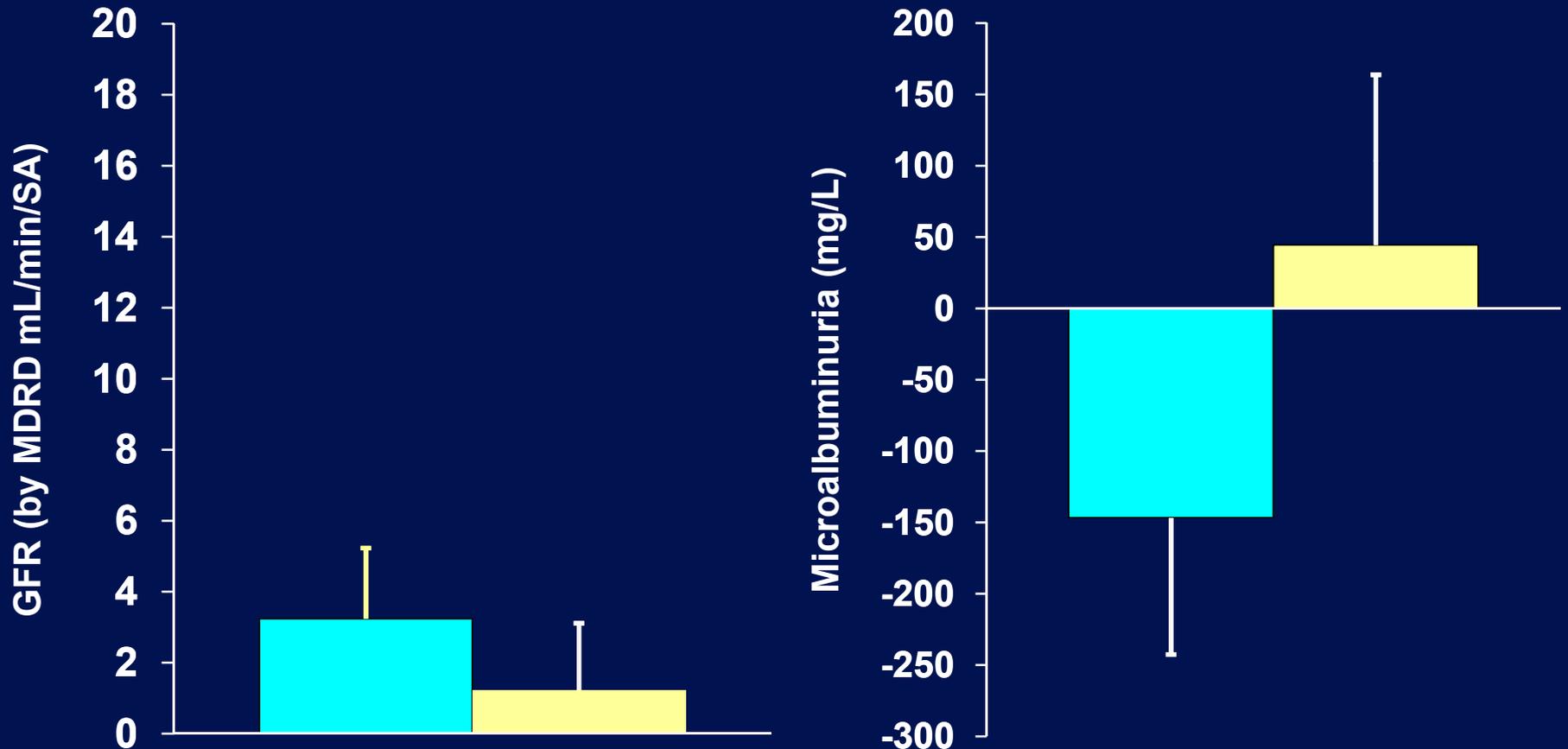
# Gouty Arthritis Phase II/III – Renal Function

Lab test	Criterion	CAN			TA	Colchicine
		≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
<b>ANY change post baseline %</b>						
Cr Cl (Cockcroft –Gault)	↓ ≥25% (baseline)	7.7	10.7	8.4	8.7	3.7
<b>SUSTAINED change post baseline n(%)</b>						
Cr >1.5 ULN* or GFR < 25% (MDRD)	At all post baseline visits		4 (1.6)		3 (1.1)	

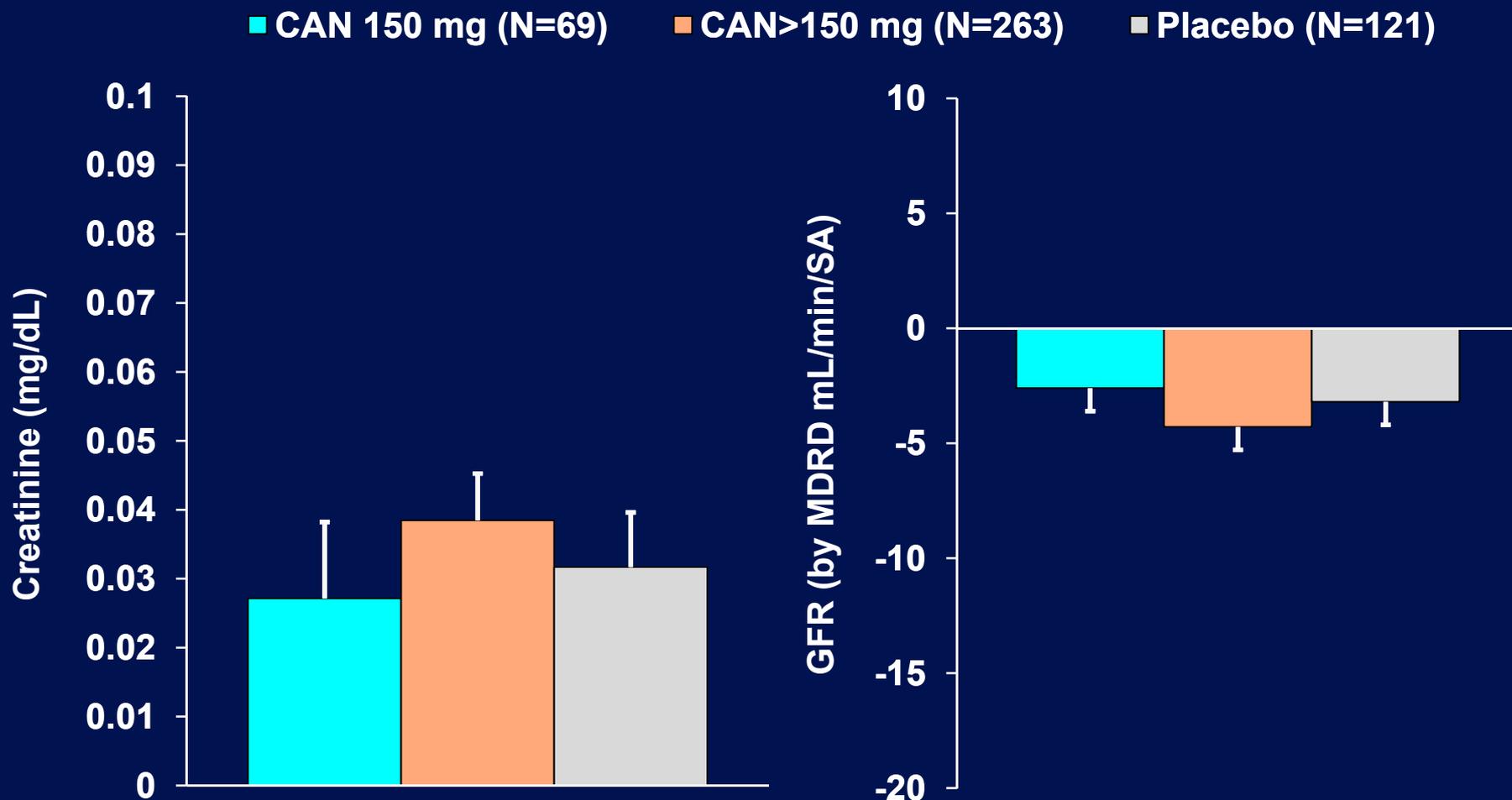
\* LLN 90 ml/min/SA ; Creatinine ULN = 1.2 mg/dl

# Gouty Arthritis Phase III: Renal Function (Change from Baseline) in Patients with CKD at Baseline

■ CAN 150 mg (N=33)    ■ TA 40 mg (N=21)



# Rheumatoid Arthritis (Placebo Controlled): Renal Function (Change from Baseline)



# Rheumatoid Arthritis Long Term – Renal Function

*Higher drug exposure compared to GA program*

	<b>Overall N=441 n (%)</b>	<b>0-24 weeks N=441 n (%)</b>	<b>&gt;24-48 weeks N=332 n (%)</b>	<b>&gt;48-72 weeks N=255 n (%)</b>	<b>&gt;72-96 weeks N=149 n (%)</b>	<b>&gt;96-144 weeks N=37 n (%)</b>
<b>CreatinineTotal</b>	<b>440</b>	<b>439</b>	<b>329</b>	<b>254</b>	<b>149</b>	<b>37</b>
<b>≥1.5 x ULN</b>	<b>5 (1.1)</b>	<b>4 (0.9)</b>	<b>2 (0.6)</b>	<b>1 (0.4)</b>	<b>0</b>	<b>0</b>
<b>≥3 x ULN</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

# Gouty Arthritis – Reported Renal ‘Failure’

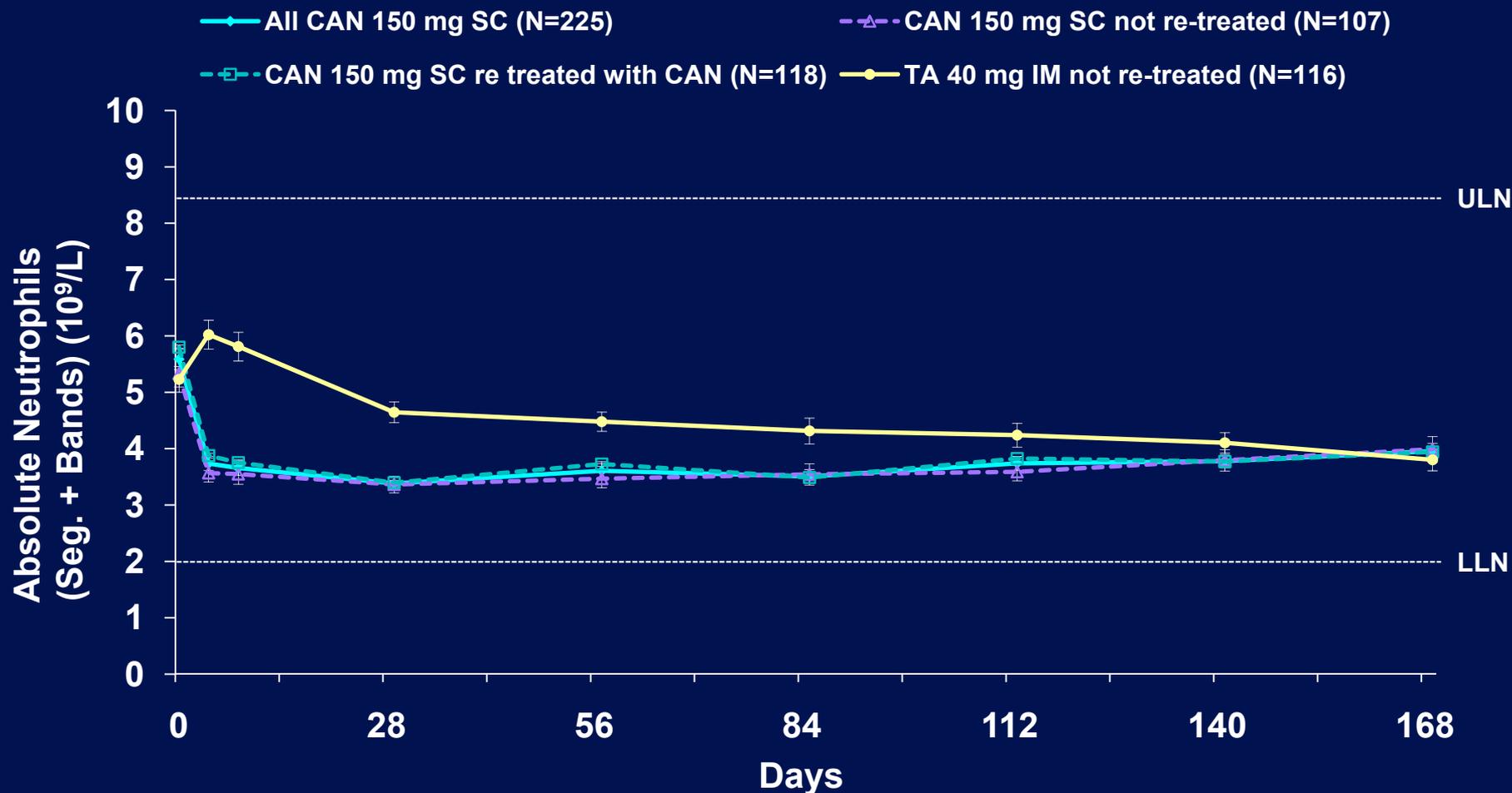
<b>CAN</b>	<b>Patient description</b>	<b>Outcome</b>
150 mg	<u>Worsening of chronic renal failure</u> 73 yo female with history of renal insufficiency, HTN, hospitalized with gastritis, vomiting with UTI day 47. Treated with rehydration and ciprofloxacin	Recovered to baseline
200 mg	<u>Worsening acute renal insufficiency</u> 44 yo male with known renal impairment /failure, untreated at study entry, hematuria, nephrotic syndrome and hyperlipidemia initiating allopurinol in Phase II improved when started on steroids for nephrotic syndrome present prior to enrollment.	Recovered to baseline
200 mg	<u>Renal insufficiency</u> 60 yo male initiated allopurinol (200 mg q d) with abnormal renal function tests at baseline, known renal insufficiency, angina, OA, hypercholesterolemia and HTN, completed the study as planned.	Recovered to baseline

# Gouty Arthritis Phase II/III – CTC Grade for Neutropenia (PMN)

Neutrophils CTC grade / n (%)	CAN			TA	Colchicine
	≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
<b>Total N</b>	<b>273</b>	<b>252</b>	<b>106</b>	<b>284</b>	<b>108</b>
<b>Grade 1</b> PMN < LLN – 1.5 10 <sup>9</sup> /L	26 (9.5)	52 (20.6)	17 (16.0)	15 (5.3)	7 (6.5)
<b>Grade 2</b> PMN < 1.5 – 1.0 10 <sup>9</sup> /L	7 (2.6)	20 (7.9)	3 (2.8)	2 (0.7)	3 (2.8)
<b>Grade 3</b> PMN < 1.0 – 0.5 10 <sup>9</sup> /L	1 (0.4)	5 (2.0)	0	0	0
<b>Grade 4</b> PMN < 0.5 10 <sup>9</sup> /L	0	0	2 (1.9)*	0	0

\* Both drawn from same investigational site on same day and both normal on repeated sampling

# Gouty Arthritis Phase III – Neutrophils



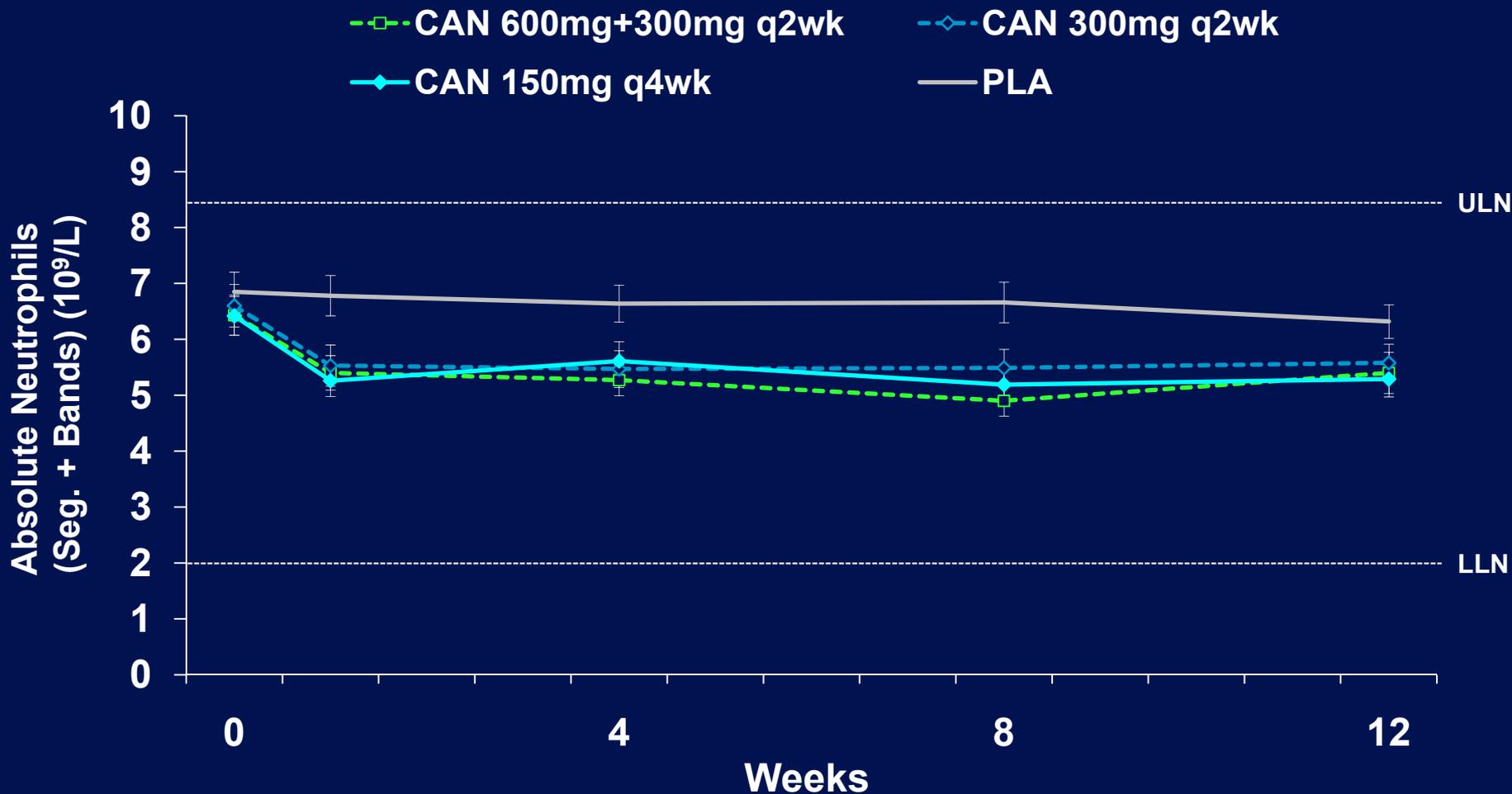
# Rheumatoid Arthritis Long Term – CTC Grade for Neutropenia (PMN)

*Higher drug exposure compared to GA program*

		CAN					
Neutrophils CTC grade / n (%)	Overall	0-24	>24-48	>48-72	>72-96	>96-144	
	N=441 n (%)	weeks N=441 n (%)	weeks N=332 n (%)	weeks N=255 n (%)	weeks N=149 n (%)	weeks N=37 n (%)	
Total N	402	397	328	254	148	37	
Grade 1 PMN < LLN – 1.5 10 <sup>9</sup> /L	8.2	5.5	4.6	4.3	4.7	5.4	
Grade 2 PMN < 1.5 – 1.0 10 <sup>9</sup> /L	3.0	1.8	0	1.2	2.0	0	
Grade 3 PMN < 1.0 – 0.5 10 <sup>9</sup> /L	0.7	0.3	0	0.4	0.7	0	
Grade 4 PMN < 0.5 10 <sup>9</sup> /L	0	0	0	0	0	0	

# Rheumatoid Arthritis Phase II – Neutrophils

*Higher drug exposure compared to GA program*



# Gouty Arthritis Phase II/III – Neutropenia and Infections

PID	CAN	Patient Description	Outcome																					
H2251-75-2	200 mg	58 yo male. Normal WBC at baseline, low ANC and WBC day 29, and low WBC at day 85. Normal after day 113. <u>Respiratory tract infection</u> on day 131 reported as mild. Improved with antibiotics, blood counts normalized. Completed study as planned.	Recovered																					
		<table border="1"> <thead> <tr> <th>Day</th> <th>ANC (2.03-8.36 10<sup>9</sup>/L)</th> <th>WBC (4.1-12.3 10<sup>9</sup>/L)</th> </tr> </thead> <tbody> <tr> <td>29</td> <td>1.96</td> <td>4.0</td> </tr> <tr> <td>57</td> <td>3.53</td> <td>5.1</td> </tr> <tr> <td>85</td> <td>2.54</td> <td>3.7</td> </tr> <tr> <td>113</td> <td>3.09</td> <td>4.6</td> </tr> </tbody> </table>	Day	ANC (2.03-8.36 10 <sup>9</sup> /L)	WBC (4.1-12.3 10 <sup>9</sup> /L)	29	1.96	4.0	57	3.53	5.1	85	2.54	3.7	113	3.09	4.6							
Day	ANC (2.03-8.36 10 <sup>9</sup> /L)	WBC (4.1-12.3 10 <sup>9</sup> /L)																						
29	1.96	4.0																						
57	3.53	5.1																						
85	2.54	3.7																						
113	3.09	4.6																						
H2356-121-1	150 mg	52 yo male with low WBC day 2 and low neutrophils day 4 and 58. <u>Jaw abscess</u> on day 29, improved with antibiotics, I&D and resolved by day 86.	Recovered																					
		<table border="1"> <thead> <tr> <th>Day</th> <th>ANC (2.03-8.36 10<sup>9</sup>/L)</th> <th>WBC (4.1-12.3 10<sup>9</sup>/L)</th> </tr> </thead> <tbody> <tr> <td>2</td> <td>–</td> <td>4.0</td> </tr> <tr> <td>4</td> <td>1.90</td> <td>5.0</td> </tr> <tr> <td>8</td> <td>3.68</td> <td>5.7</td> </tr> <tr> <td>28</td> <td>3.13</td> <td>6.2</td> </tr> <tr> <td>58</td> <td>1.50</td> <td>4.4</td> </tr> <tr> <td>86</td> <td>2.57</td> <td>5.0</td> </tr> </tbody> </table>	Day	ANC (2.03-8.36 10 <sup>9</sup> /L)	WBC (4.1-12.3 10 <sup>9</sup> /L)	2	–	4.0	4	1.90	5.0	8	3.68	5.7	28	3.13	6.2	58	1.50	4.4	86	2.57	5.0	
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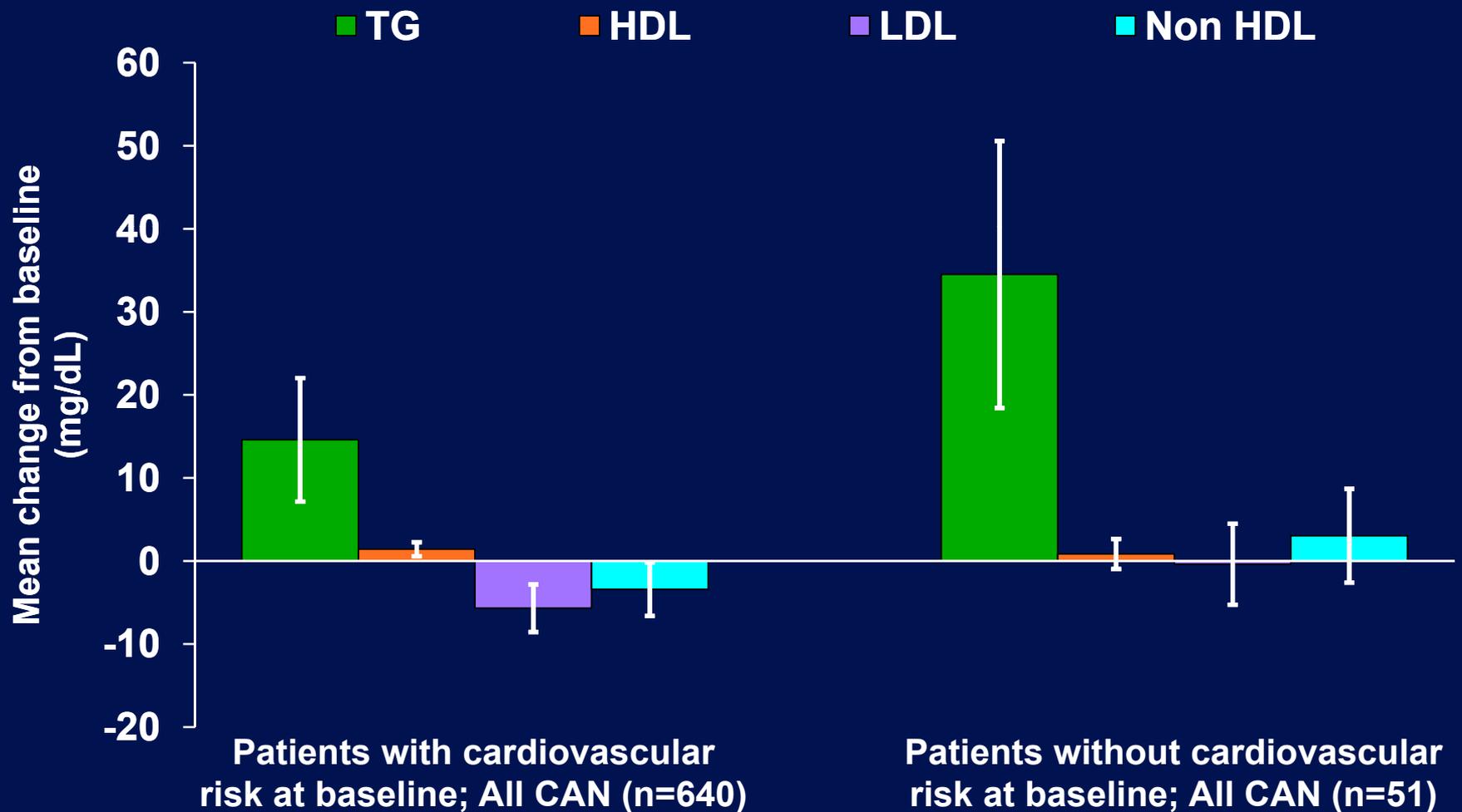
# Overview

- **Safety Populations**
  - Exposure
  - Patient Disposition, Characteristics and Comorbidities
- **Safety Profile**
  - AEs
  - SAEs and Deaths
  - Serious Infections
  - Serious Cardiovascular Events
  - Malignancies
- **Safety Areas of Special Interest**
  - Immunogenicity and Hypersensitivity
  - Hypertension
  - Renal Function
  - Neutrophils
  - **Other Lab Abnormalities: Hyperlipidemia, LFTs and Uric Acid**
  - Safety on retreatment
- **Summary and Safety Recommendations**

# Gouty Arthritis Phase II/III – Lipid Profile

Notable Value n (%)		CAN			TA	Colchicine
		≤100 mg N=278	150 mg N=253	≥200 mg N=107	N=286	N=108
<b>Total cholesterol</b>	<b>Total</b>	273	252	106	284	108
	> ULN	63 (23.1)	57 (22.6)	22 (20.8)	57 (20.1)	24 (22.2)
<b>HDL</b>	<b>Total</b>	273	211	NA	284	NA
	< LLN	NA	25 (11.8)	NA	13 (6.0)	NA
<b>LDL</b>	<b>Total</b>	NA	211	NA	218	NA
	> ULN	NA	19 (9.0)	NA	20 (9.2)	NA
<b>Triglycerides</b>	<b>Total</b>	273	252	106	284	108
	≥ 2.5x ULN	24 (8.8)	26 (10.3)	8 (7.5)	9 (3.2)	8 (7.4)
	≥ 5x ULN	9 (3.3)	6 (2.4)	1 (0.9)	2 (0.7)	6 (5.6)

# Gouty Arthritis Phase II/III – Lipids and Triglycerides (Change from Baseline)



# Rheumatoid Arthritis – Placebo-controlled

*Higher drug exposure compare to GA program*

Laboratory Test	Criterion	CAN 300 mg/2 wks N=128		Placebo N=51	
		n	%	n	%
<i>Triglycerides</i>	>ULN	40	31.3	17	33.3
	≥1.5 x ULN	17	13.3	8	15.7
	≥2.5 x ULN	3	2.3	0	0.0
	≥5 x ULN	0	0.0	0	0.0
	≥10 x ULN	0	0.0	0	0.0

# Gouty Arthritis Phase II/III – Liver Function

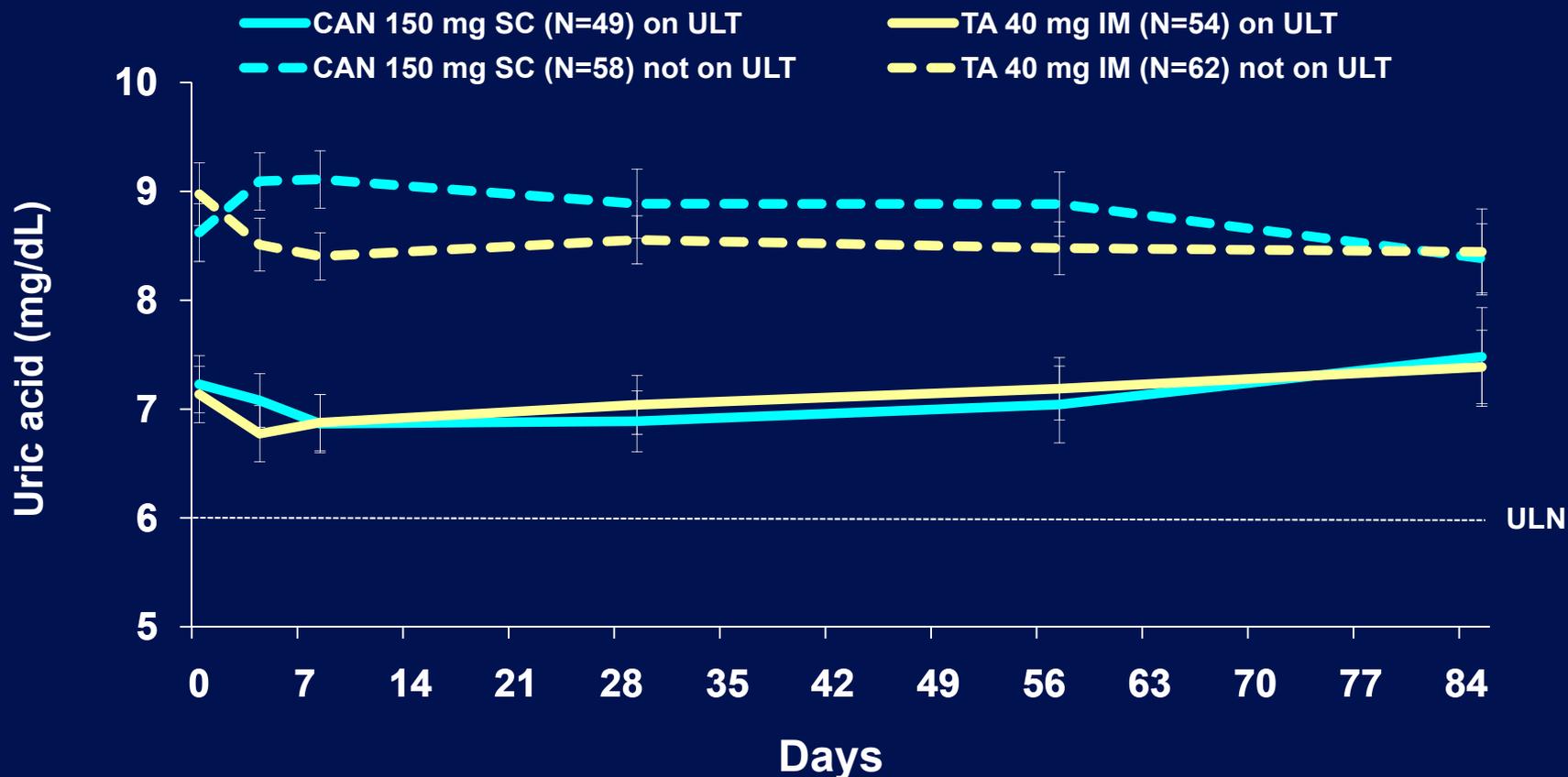
ALT/ AST	CAN			TA	Colchicine
	≤100 mg N=278 n (%)	150 mg N=253 n (%)	≥200 mg N=107 n (%)	N=286 n (%)	N=108 n (%)
<b>Total</b>	<b>273</b>	<b>252</b>	<b>106</b>	<b>284</b>	<b>108</b>
≥ 3x ULN	7 (2.6) / 5 (1.8)	4 (1.6) / 2 (0.8)	5 (4.7) / 2 (1.9)	7 (2.5) / 7 (2.5)	2 (1.9) / 1 (0.9)
≥ 5x ULN	3 (1.1) / 1 (0.4)	–	1 (0.9) / 0	0 / 2 (0.7)	–
≥ 10 x ULN	1 (0.4) / 1 (0.4)	–	–	0 / 1 (0.4)	–
ALT/AST ≥ 3x ULN, bilirubin ≥1.5 x ULN	1 (0.4)*	1 (0.4)**	–	–	–

\* One patient, LFT abnormal at baseline and comparable at end of study

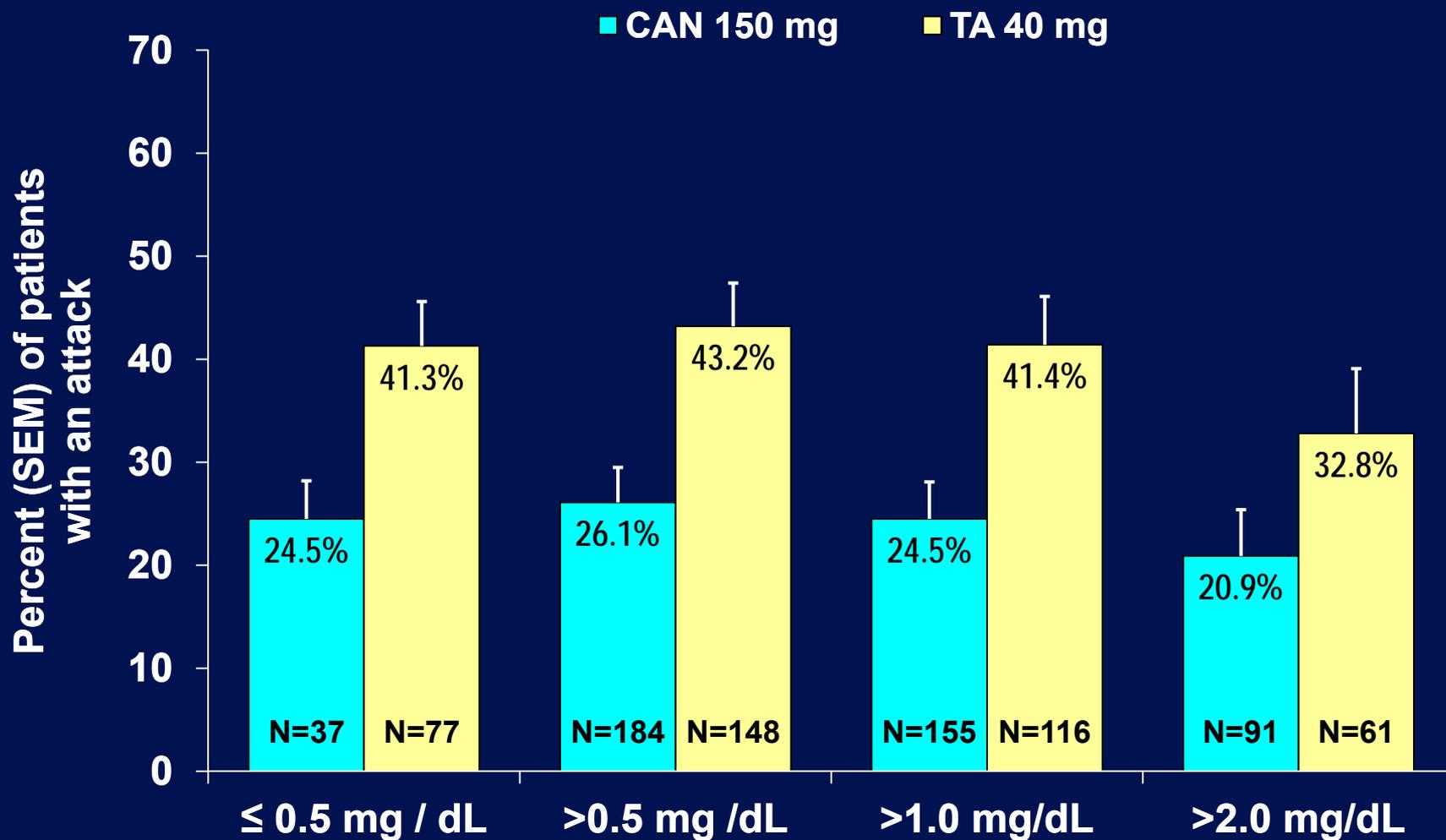
\*\* h/o hepatic steatosis, similar LFT elevations baseline

# Gouty Arthritis Phase III – Uric Acid

*Uric acid in patients treated single dose TA or CAN by ULT*



# Gouty Arthritis Phase III – Number of Patients with New Attacks AFTER Uric Acid Increases



# Overview

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# Gouty Arthritis Phase III – Retreatment Exposure with Canakinumab

	Original submission SCS (incl E1)	120-Day Safety update (incl E2 i.a.)
<b>Number of Injections, n</b>		
1	193	107
2	47	75
3	11	25
4	2	15
≥ 5	0	3
<b>Number of patients, n</b>		
≥ one retreatment	60	118
≥ two retreatments	13	43

- CAPS program provides significant retreatment experience (5 yrs of continuous retreatment; 314 pt-yrs exposure)

# Gouty Arthritis Phase III – Exposure Adjusted (per 100 Pt-Yrs) Incidence of AEs and SAEs

Frequency >10 (per 100 pt-yrs) Primary System Organ Class	Subjects Treated at Least 3x (2 Retreatment) (n=43)		
	Before (1) N=43	After (1) N=43	After (2) N=43
<b>SAEs</b> (per 100 pt-yrs)	<b>24</b>	<b>7.6</b>	<b>0</b>
<b>AEs</b> (per 100 pt-yrs)	<b>547</b>	<b>376</b>	<b>338</b>
<b>Infections</b>	<b>97</b>	<b>76</b>	<b>89</b>
<b>Nervous system</b>	<b>32</b>	<b>34</b>	<b>40</b>
<b>General disorders</b>	<b>24</b>	<b>27</b>	<b>32</b>
<b>Musculoskeletal</b>	<b>16</b>	<b>68</b>	<b>32</b>
<b>Vascular</b>	<b>24</b>	<b>27</b>	<b>24</b>
<b>Skin</b>	<b>56</b>	<b>15</b>	<b>16</b>
<b>Metabolism</b>	<b>56</b>	<b>27</b>	<b>16</b>
<b>GI</b>	<b>32</b>	<b>19</b>	<b>16</b>
<b>Neoplasm</b>	<b>0</b>	<b>8</b>	<b>16</b>

**Retreatment does not lead to an increase in AEs or SAEs**

# Gouty Arthritis Phase III – Exposure Adjusted (per 100 Pt-Yrs) Incidence of AEs

Preferred Terms	Re-treated (n=43)		
	Before (1) N=43	After (1) N=43	After (2) N=43
<b>AEs</b>	<b>547</b>	<b>376</b>	<b>338</b>
Fatigue	0	19	24
Hypertension/BP fluctuation	24	23	24
Influenza	0	11	16
Rhinitis	0	11	16
Upper respiratory tract infection	24	11	16
Acrochordon	0	8	16
Carpal tunnel syndrome	0	8	16
Abdominal pain upper	0	8	8
Asthenia	16	8	8
Dizziness	8	8	8
Headache	8	8	8
Food allergy	0	8	8
Arthropod bite	0	8	8
Oropharyngeal pain	0	8	8

AEs reported by >1 patient after retreatment

# Overview

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  - Other Lab Abnormalities: Hyperlipidemia, LFTs and Uric Acid
- **Summary and Safety Recommendations**

# Summary *(1 of 2)*

- Overall safety profile consistent with postmarketing experience in CAPS and the mechanism of action for this anti-inflammatory therapy
- In this population with a high incidence of co-morbidities, reported deaths were consistent with underlying medical conditions
- MACE reports were balanced across treatment groups and BP changes were not clinically significant
- Lipid metabolism
  - No significant changes in cholesterol (HDL-C, LDL-C)
  - Triglyceride changes were not linked to adverse clinical outcomes (pancreatitis)
- No confirmed cases of treatment related renal failure
  - Changes in renal function were transient and reversible
  - Long term exposure (>10 fold estimated in GA) no effect on renal function

## Summary (2 of 2)

- **Uric Acid**
  - UA levels increase acutely and return to baseline after single dose
  - UA levels decrease with concomitant ULT
  - The increase in UA levels is more evident in patients not on ULT but does not result in occurrence of gouty arthritis attacks
- **Anti-canakinumab antibodies were found in approximately 1% of treated subjects and no immunogenicity AEs were reported in this limited dataset**
- **Neutrophil decreases were transient and reversible; none were  $<500$  ( $\times 10^9/L$ ) in the 150 mg group**
- **Canakinumab is associated with an increased risk of infection**
  - Serious infections temporally related to a decrease in neutrophils have been reported and responded to standard of care
  - No opportunistic infections were observed

# Ensuring Patient Safety Post-Approval

- **Labeling**
  - **Appropriate patient population**
  - **Actual and potential risks**
- **Pharmacovigilance**
  - **Routine Pharmacovigilance, including cumulative safety evaluations**
  - **Targeted follow-up of serious clinical trial and post marketing cases**
    - **Targeted questionnaires/checklist in key areas of actual and potential risk: infection, malignancy, hypersensitivity**
    - **Adjudication of all clinical trial cases**
- **Proposed Registry**
  - **Further evaluation of relative risk long term**
  - **Expected to include up to 3,000 patients for at least 1 year**
  - **In addition, a CV placebo-controlled clinical trial is ongoing in over 7000 patients**

# **Benefit-Risk: Clinical Perspective**

**Robert L. Wortmann, MD, FACP, MACR**

*Professor of Medicine*

*Dartmouth Medical School and  
Dartmouth-Hitchcock Medical Center*

# There is an Unmet Need for Treating Gout Patients

- **Example –**
  - 78 year old woman with gout averaging 1 attack per month for last year
  - Hypertension, CHF, insulin requiring diabetes, chronic renal failure
  - Cannot take NSAIDs, colchicine or corticosteroids

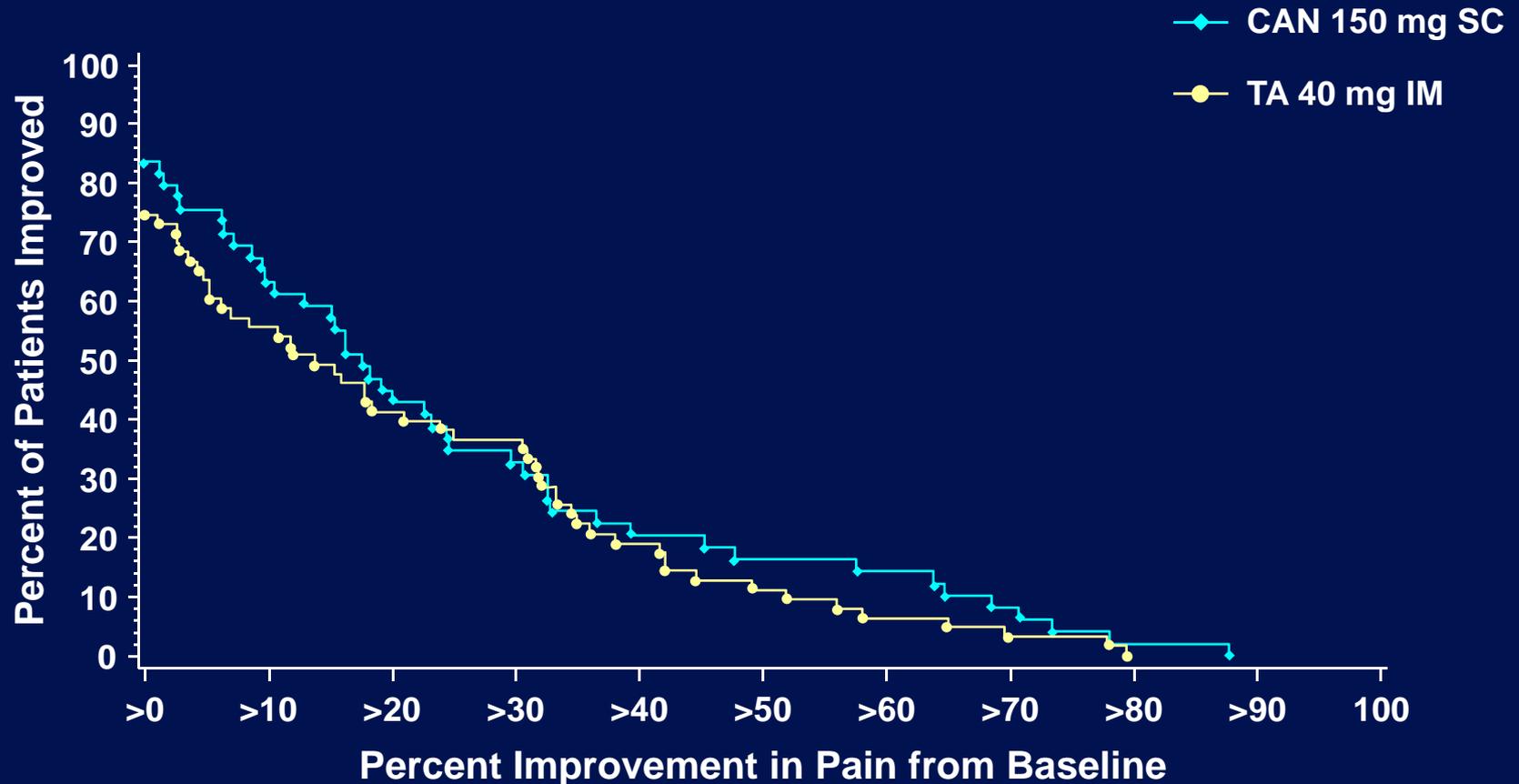


## **Unmet Need**

- **We need a therapy for gout patients in whom existing therapies are:**
  - **Ineffective**
  - **Cannot be tolerated**
  - **Contraindicated**
- **Only a relatively small subset of the diagnosed patients are likely candidates**

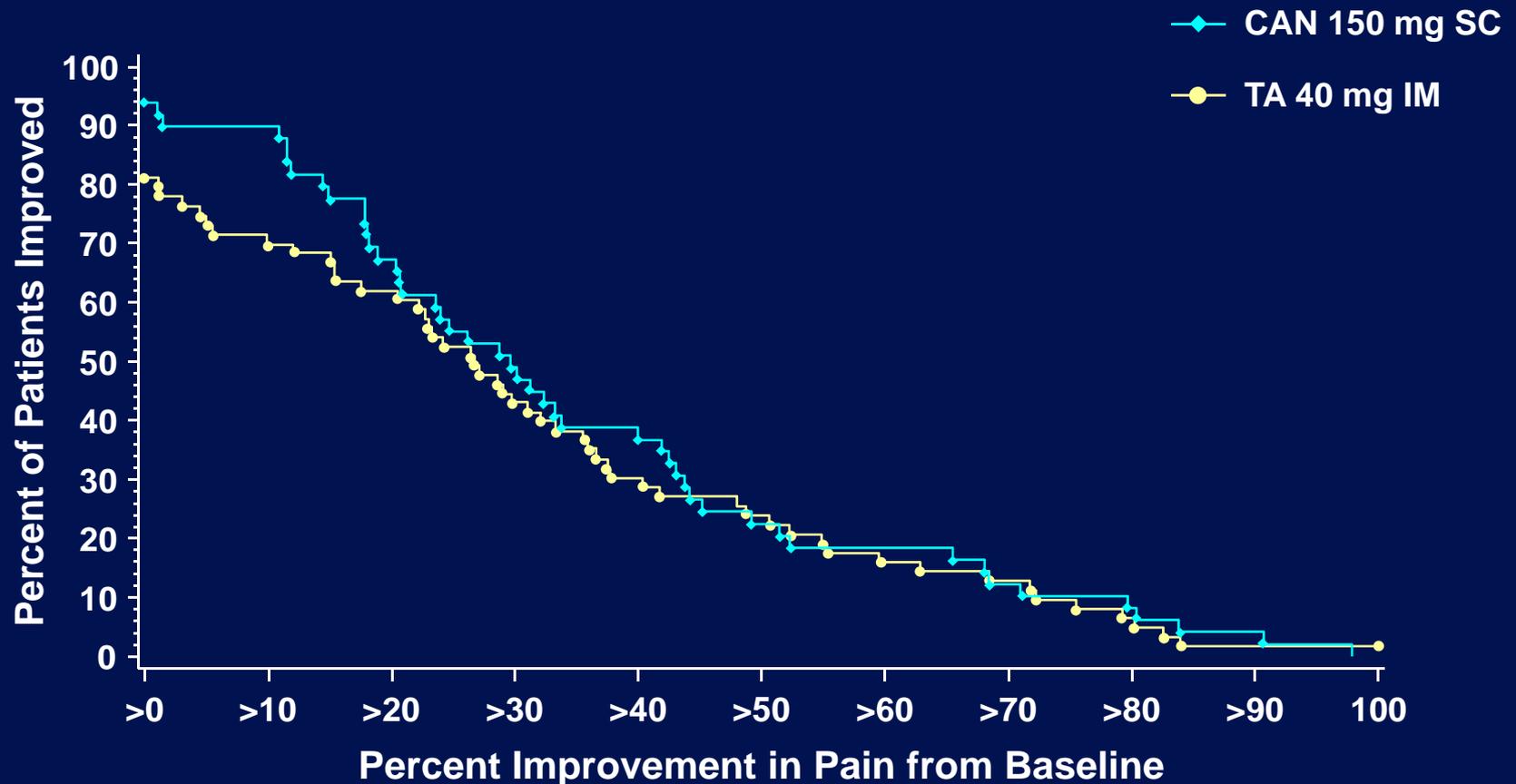
# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time

6 Hours



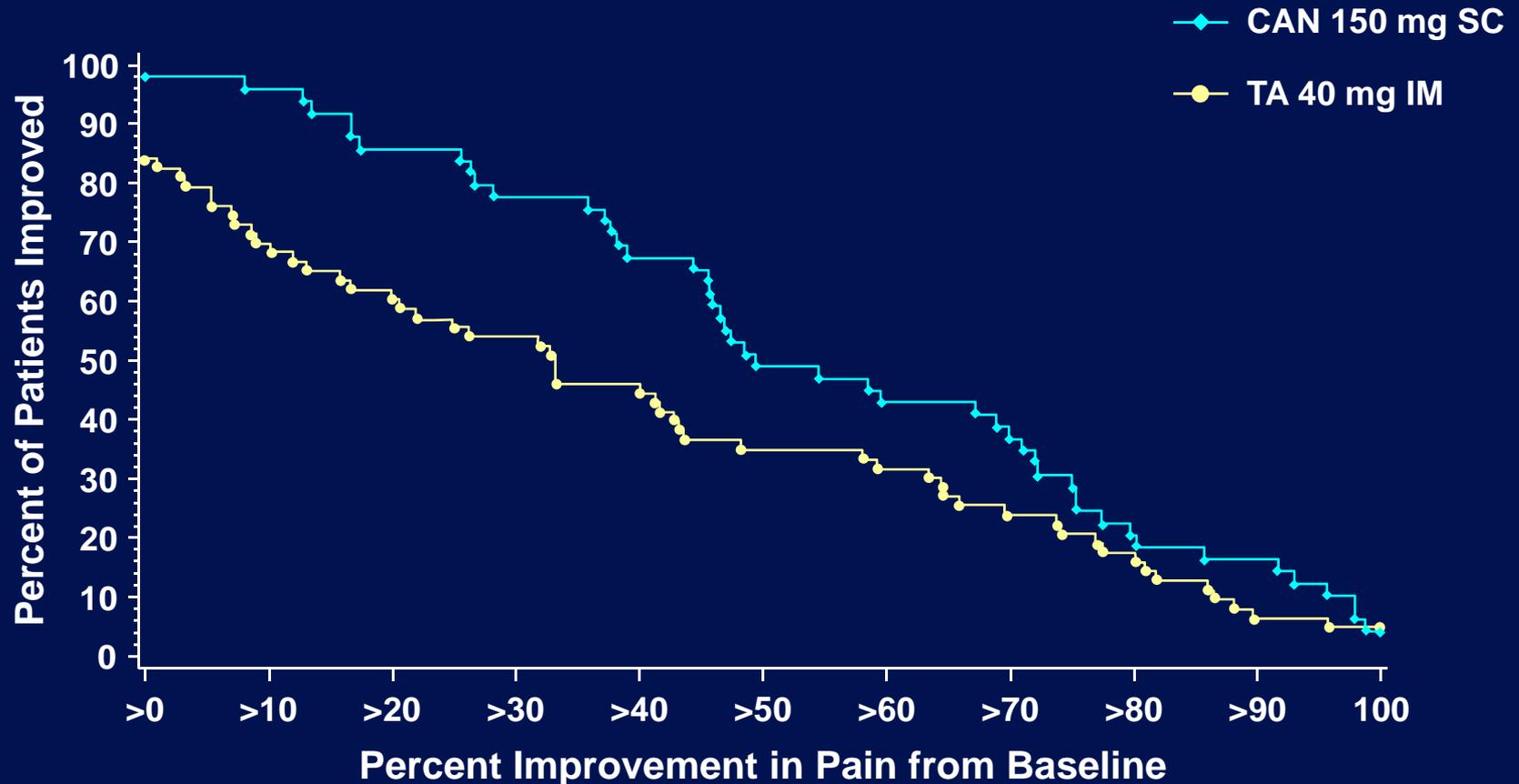
# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time

12 Hours



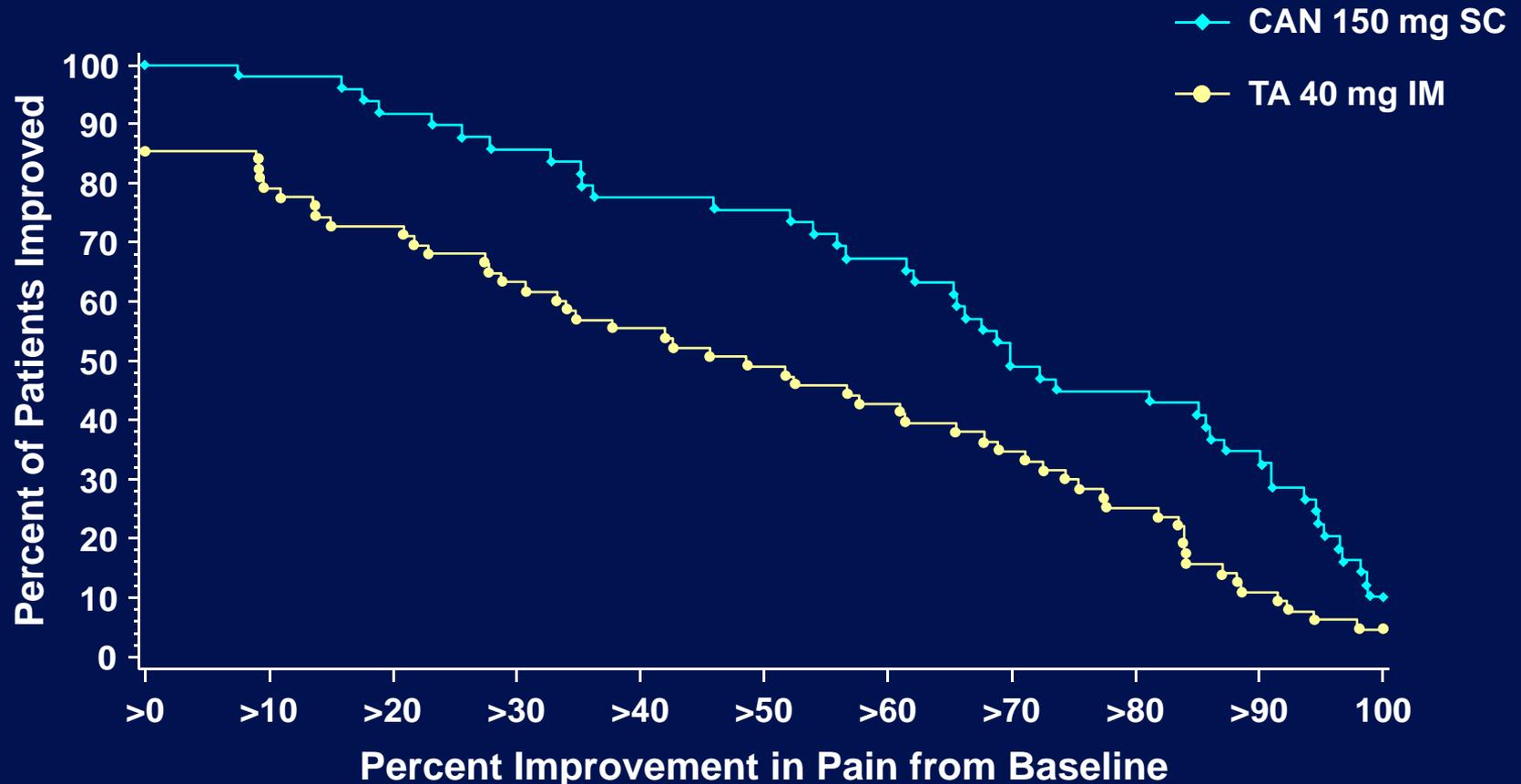
# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time

24 Hours



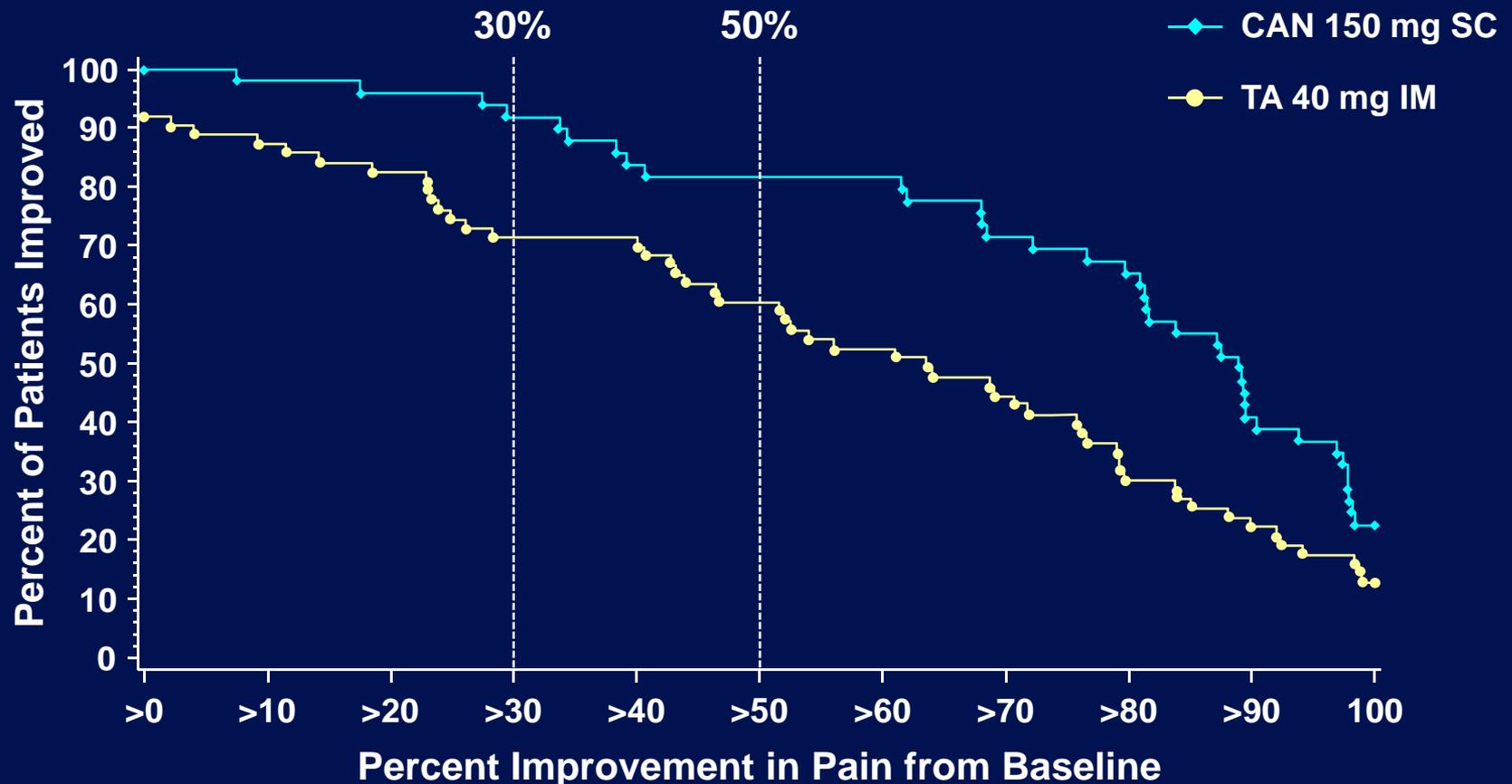
# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time

48 Hours

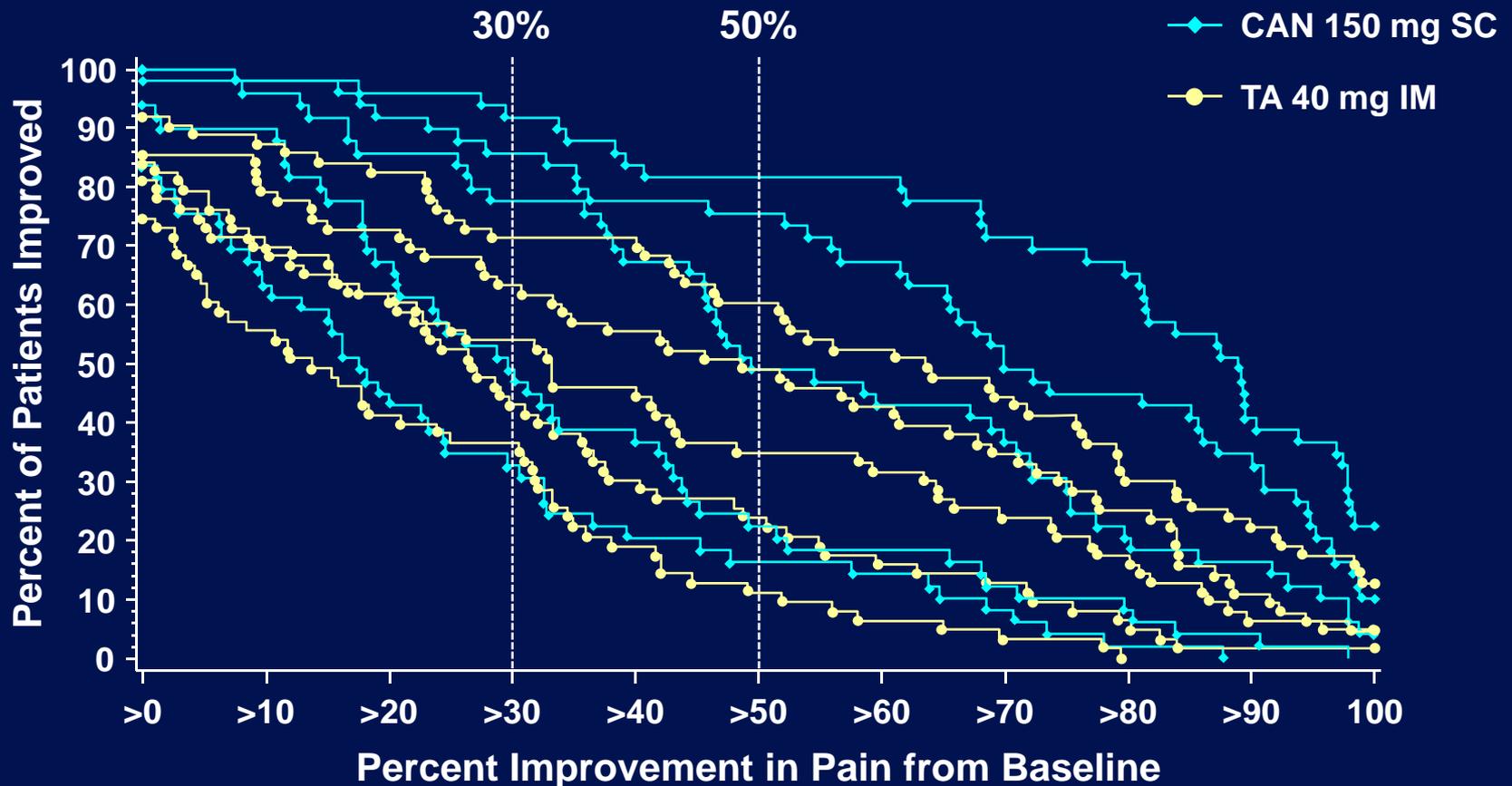


# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time

72 Hours

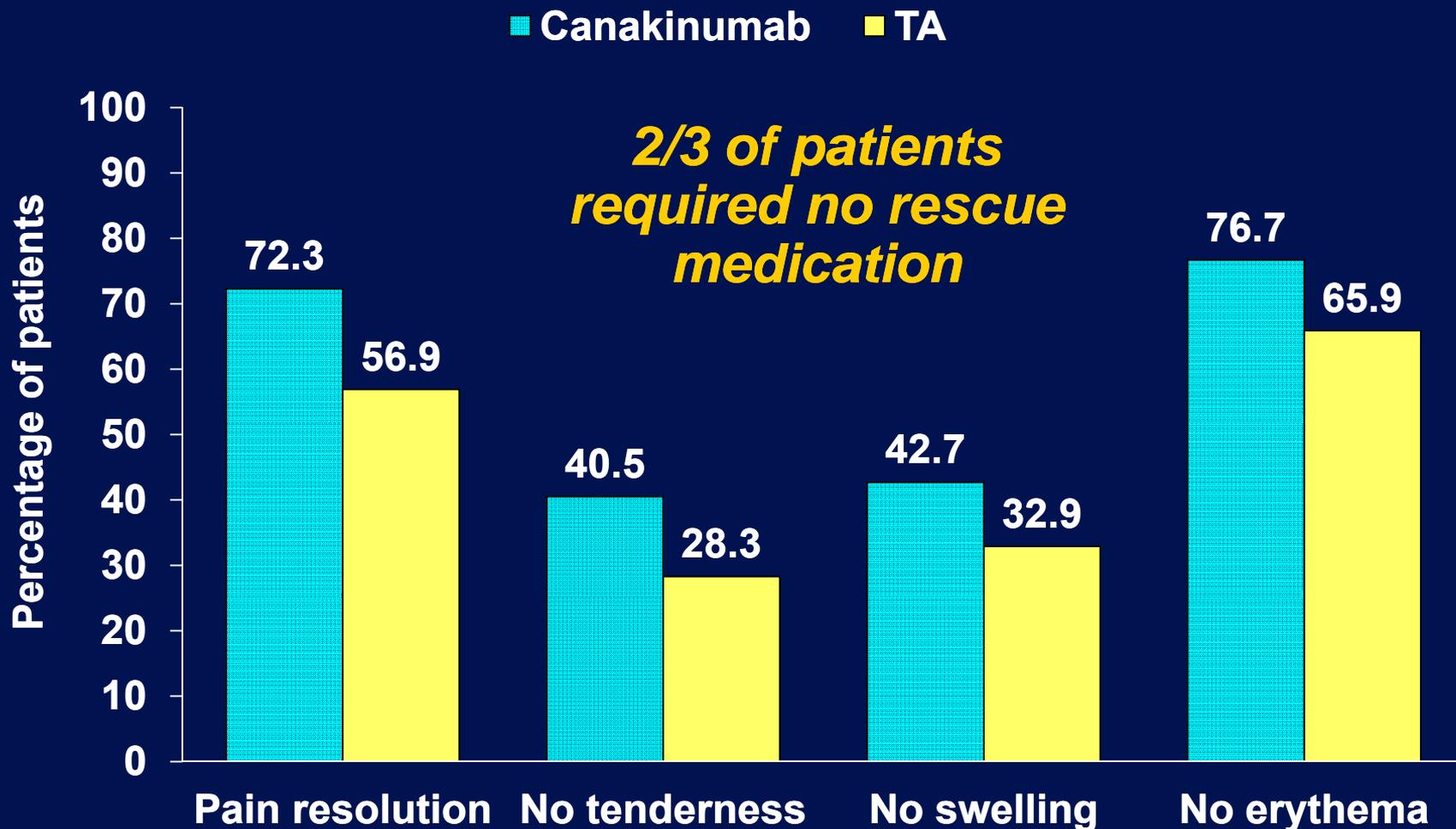


# Patients Treated Early (0-1 Day from Attack Onset) Achieve More Substantial Pain Relief over Time (6, 12, 24, 48, 72 Hours)



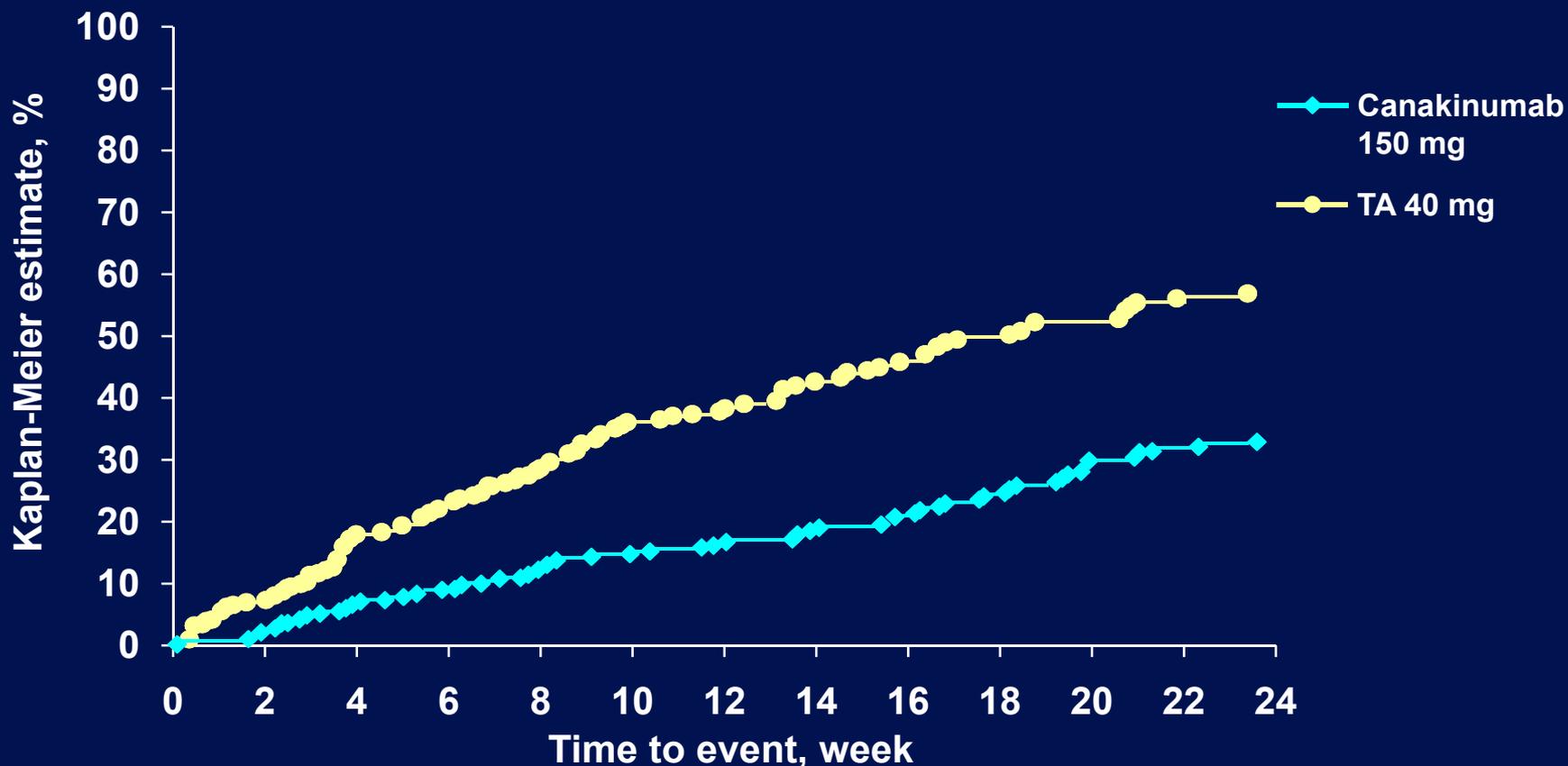
# Resolution of Inflammation

*Pooled data at 72 hrs*



# Durable Response: Delay in Time to Subsequent Attacks

- 72% of patients remained attack free for 6 months



# Over 80% of Patients Can Expect Major Clinical Benefit

<b>Pooled Data</b>	<b>12 Weeks</b>	<b>24 Weeks</b>
<b>Dual benefit:</b> <ul style="list-style-type: none"><li>• Major pain relief</li><li>• No new attack</li></ul>	<b>77%</b>	<b>65%</b>
<b>Consistent benefit:</b> <ul style="list-style-type: none"><li>• Major pain relief for baseline and subsequent attack</li></ul>	<b>6%</b>	<b>17%</b>
<b>Total patients with major benefit</b>	<b>83%</b>	<b>82%</b>

# Increased Risk of Infections and Serious Infections

	<b>Canakinumab</b>	<b>TA</b>
<b>Infections</b>	<b>19.4%</b>	<b>12.9%</b>
<b>SIEs</b>	<b>1.6%</b>	<b>0</b>

- Consistent with inhibition of inflammatory cascade
- Risk can be managed with standard of care
- **Decreased neutrophils**
  - Most within normal limits
  - Not correlated with infections

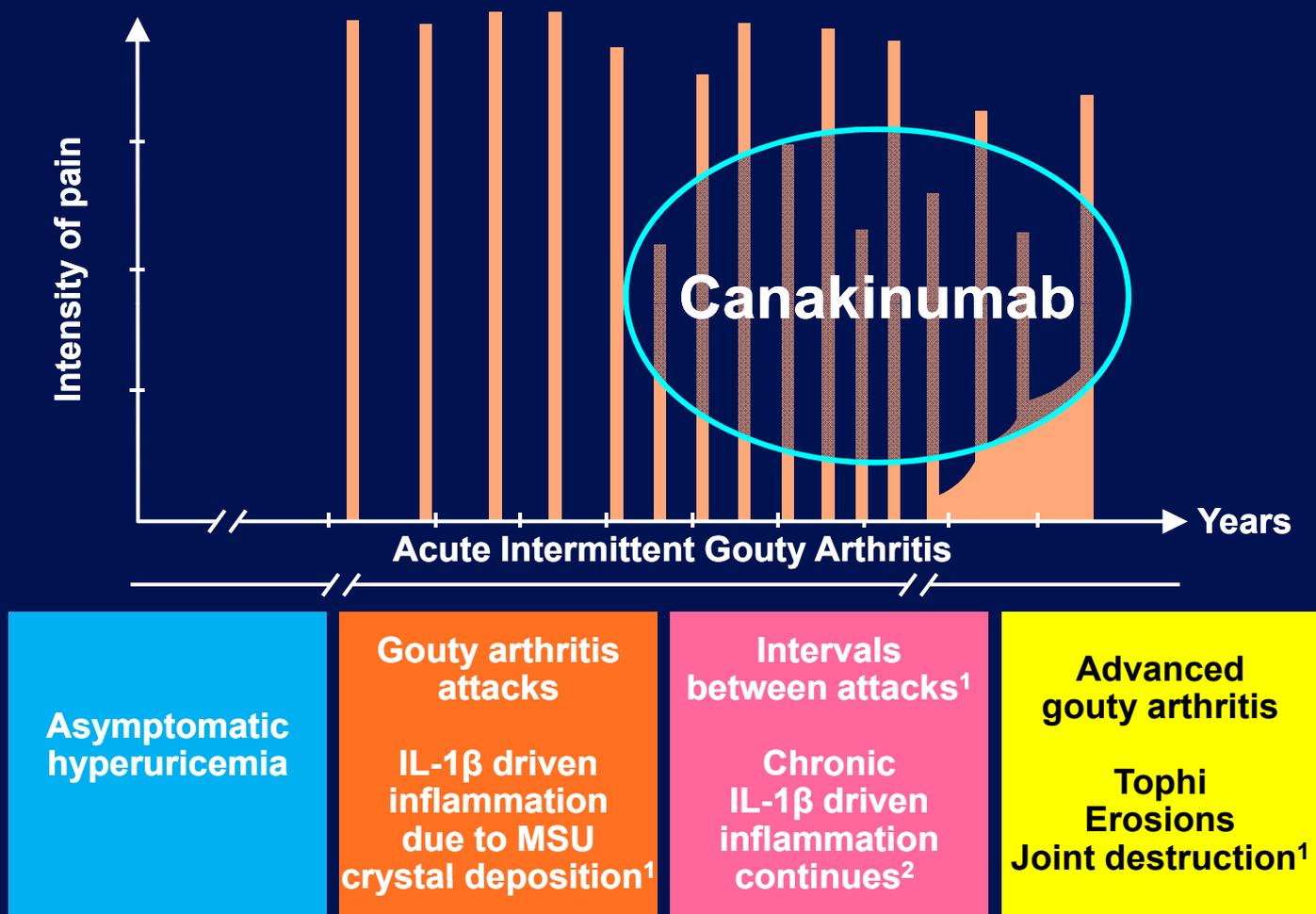
# Laboratory Changes Can be Monitored and are Reversible

- **↑ Triglycerides**
  - Increases were small
  - No evidence that increases are harmful
  - No evidence that lowering TGs is helpful
- **↑ Uric acid**
  - Mean changes were minimal (+0.5 mg/dl)
  - Increases are predictable after attacks resolve
    - IL-6 is uricosuric
  - Observed increases were not associated with increased risk of attack

# Canakinumab – Clinical Perspective

- **Canakinumab is the first and only targeted anti-inflammatory agent for the treatment of gouty arthritis**
- **The PK profile render it as an effective agent for rapid relief and durable response**
- **Canakinumab provides a very effective option for appropriate subset of gout patients**
- **Canakinumab has a manageable safety profile for this generally sick and complicated patient population**

# Gouty Arthritis Is a Chronic Progressive Disease Characterized by Acute Inflammation



1. Edwards NL. Gout; clinical features. Also Choi HK. Gout; epidemiology, pathology, and pathogenesis. In: Klippel JH et al, eds. *Primer on the Rheumatic Diseases*. 13th ed. 2008:241-257. 2. Pascual E. *Arthritis Rheum*. 1991;34:141-145.

# There is an Unmet Need for Treating Gout Patients

- **Example –**
  - 78 year old woman with gout averaging 1 attack per month for last year
  - Hypertension, CHF, insulin requiring diabetes, chronic renal failure
  - Cannot take NSAIDs, colchicine or corticosteroids



# Q&A Slides Presented

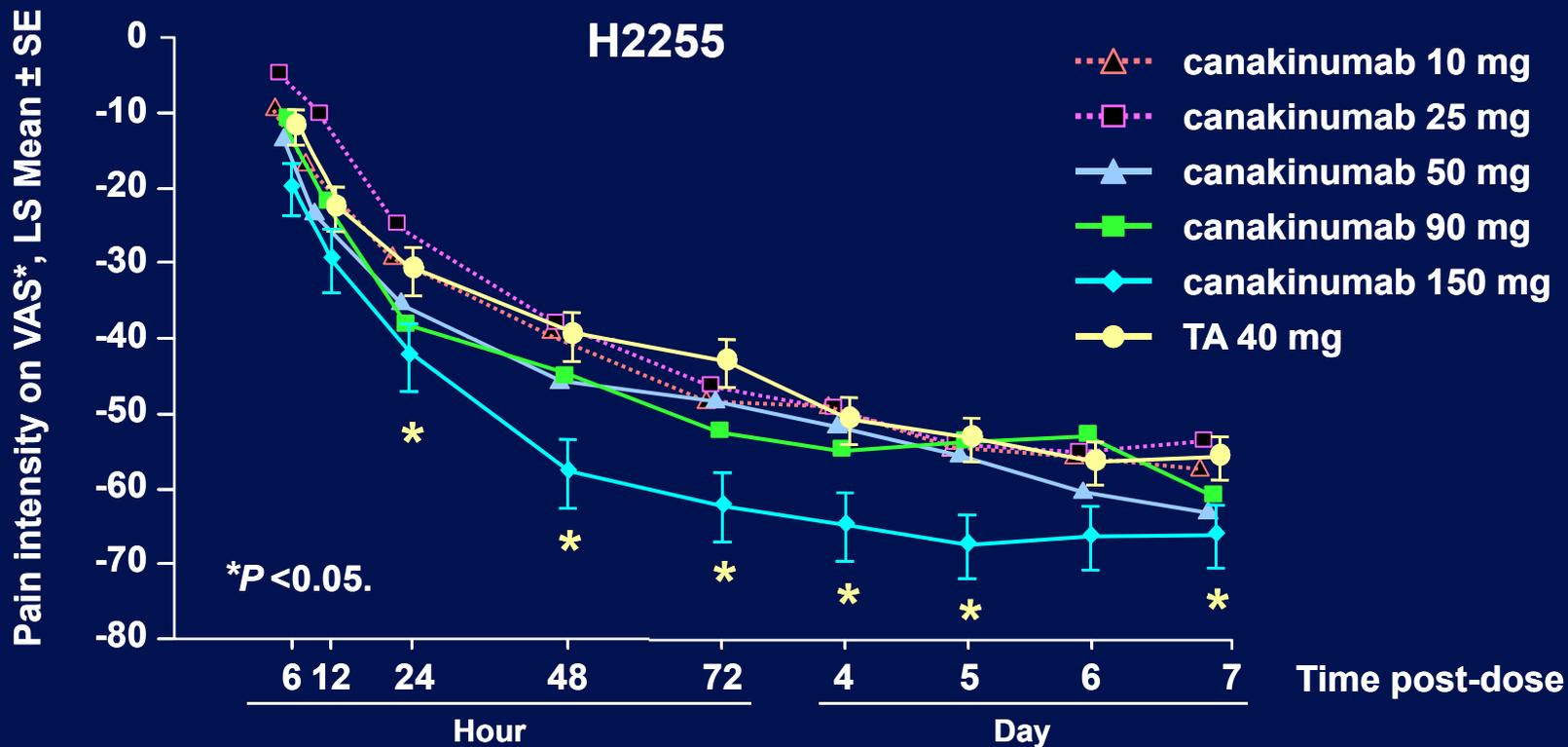
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**FDA CDER**

***Arthritis Drugs  
Advisory Committee***

***June 21, 2011***

# Canakinumab 150 mg Provided Superior Pain Relief vs. Triamcinolone Acetonide 40 mg



Time	24 h	48 h	72 h	4 d	5 d	6 d	7 d
canakinumab 150 mg vs TA 40 mg: mean difference, mm	-11.5	-18.2	-19.2	-14.1	-14.2	-9.9	-10.5
P value	0.039	0.002	<0.001	0.012	0.007	0.055	0.042

\*VAS 0–100 mm.

LS, least-squares; SE, standard error; VAS, visual analog scale.

So A, et al. *Arthritis Rheum.* 2010;62:3064-76.

# Study H2255: Dose Response Data for Efficacy and Safety

	Canakinumab					Triamcinolone Acetonide
	10 mg N = 28	25 mg N = 29	50 mg N = 28	90 mg N = 29	150 mg N = 27	40 mg N = 57
<b>Response to treatment</b>						
Good/excellent (patient assessment), n (%)	18 (64.3)	18 (62.1)	20 (71.4)	19 (65.5)	24 (88.8)	30 (53.6)
Good/very good (physician assessment), n (%)	21 (75.0)	18 (62.1)	22 (78.6)	22 (75.9)	25 (92.6)	34 (60.7)
Absence of tenderness, n (%)	10 (35.7)	7 (24.1)	9 (32.1)	9 (31.0)	14 (51.9)	16 (28.6)
<b>Patient use of rescue medication up to day 7</b>						
Total, n (%)	13 (46.4)	16 (55.2)	16 (57.1)	14 (48.3)	6 (22.2)	31 (55.4)
<i>P</i> value (relative to triamcinolone acetonide)	.39	.93	1.00	.53	.01*	–
Prednisone/prednisolone	5 (17.9)	9 (31.0)	8 (28.6)	6 (20.7)	2 (7.4)	16 (28.6)
Codeine	4 (14.3)	6 (20.7)	4 (14.3)	4 (13.8)	1 (3.7)	9 (16.1)
Acetaminophen	9 (32.1)	12 (41.4)	15 (53.6)	12 (41.4)	5 (18.5)	23 (41.1)
<b>Safety and tolerability data</b>						
Overall rate of AEs	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
Infectious AEs	0	3 (10.3)	3 (10.3)	2 (6.9)	2 (7.1)	4 (7.0)
Serious adverse events <sup>a</sup>	0	2 (6.9)	2 (6.9)	0	0	1 (1.8)
Safety/tolerability discontinuations	0	0	0	0	0	0

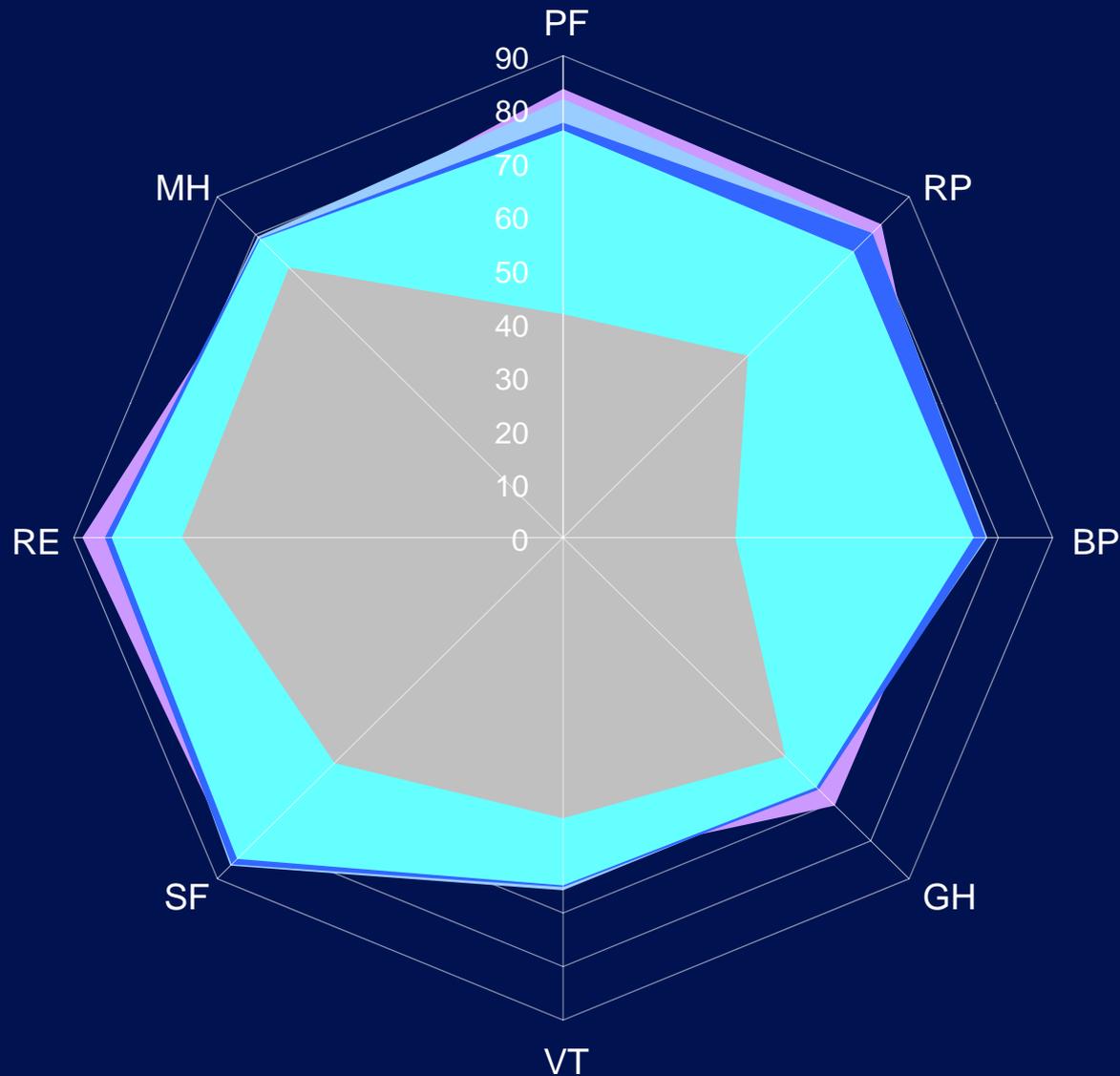
\*Indicates statistical significance.

<sup>a</sup> All serious adverse events were rated as unrelated to study drug by the investigator. AEs, adverse events.

Source: [Study H2255-Table 14.2-2.5] (pain reduction), [Study H2255-Table 14.2-5.2] (median time), [Study H2255-Table 14.2-3.5] (pain intensity), [Study H2255-Table 14.2-4.1] (patient's assessment), [Study H2255-Table 14.2-4.3] (physician's assessment), [Study H2255-Table 14.2-4.5] (tenderness assessment), [Study H2255-Table 14.2-7.1, 14.2-7.2] (rescue medication), [Study H2255-Table 14.3.1-1.1, Table 14.3.1-1.2]

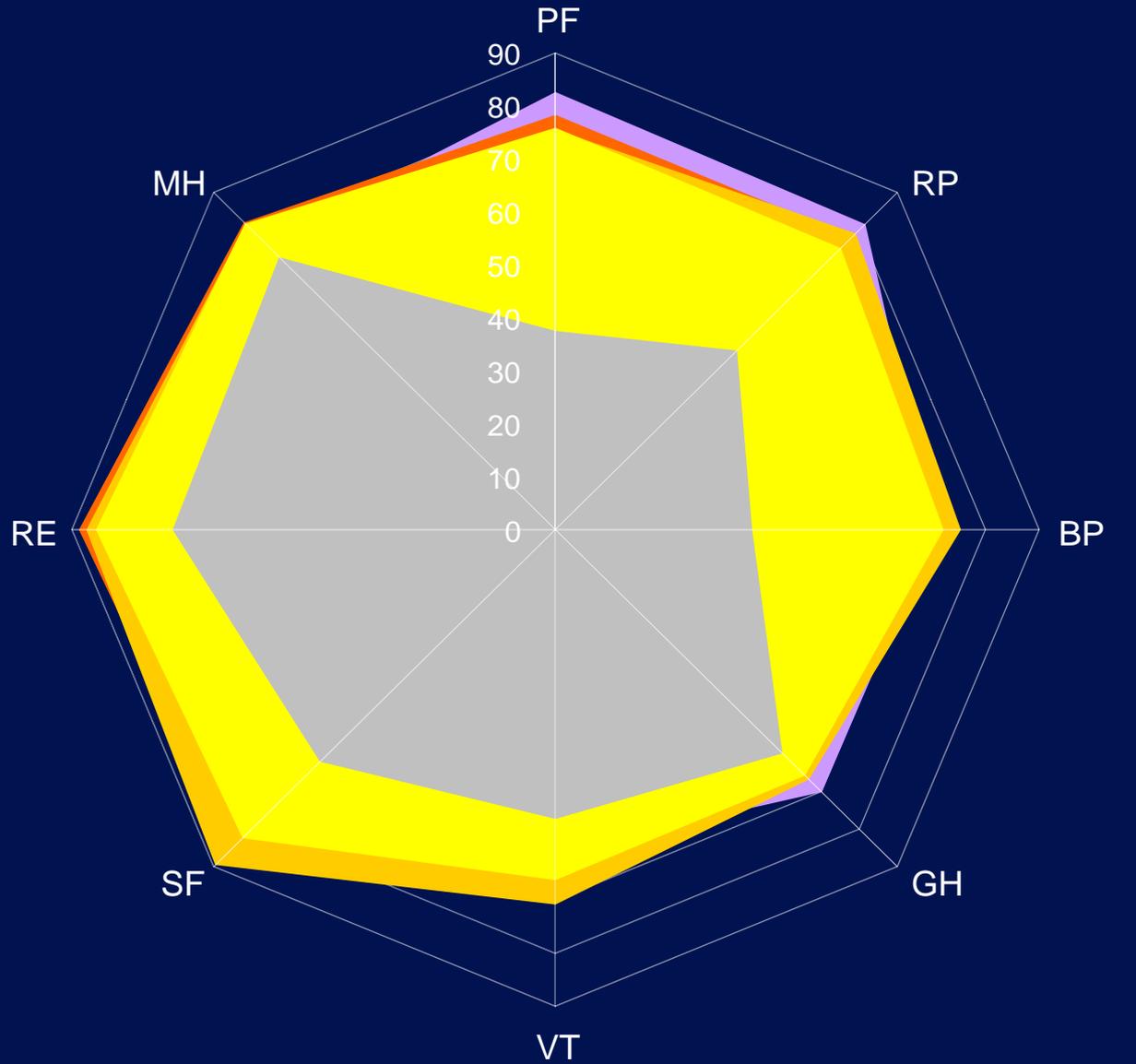
(AEs, infectious AEs), Study H2255-Table 14.3.1-1.11] (SAEs), Study H2255-Table 14.1-1.1] (discontinuations) E-14

# 2357-SF-36 Domain Scores: CAN: BL to 12 weeks



■ CAN - BL: n=102-103 ■ AG Norms ■ CAN - 4wks: n=88-92 ■ CAN - 8wks: n=84-88 ■ CAN - 12wks: n=83-88

# 2357-SF-36 Domain Scores: TA: BL to 12 weeks

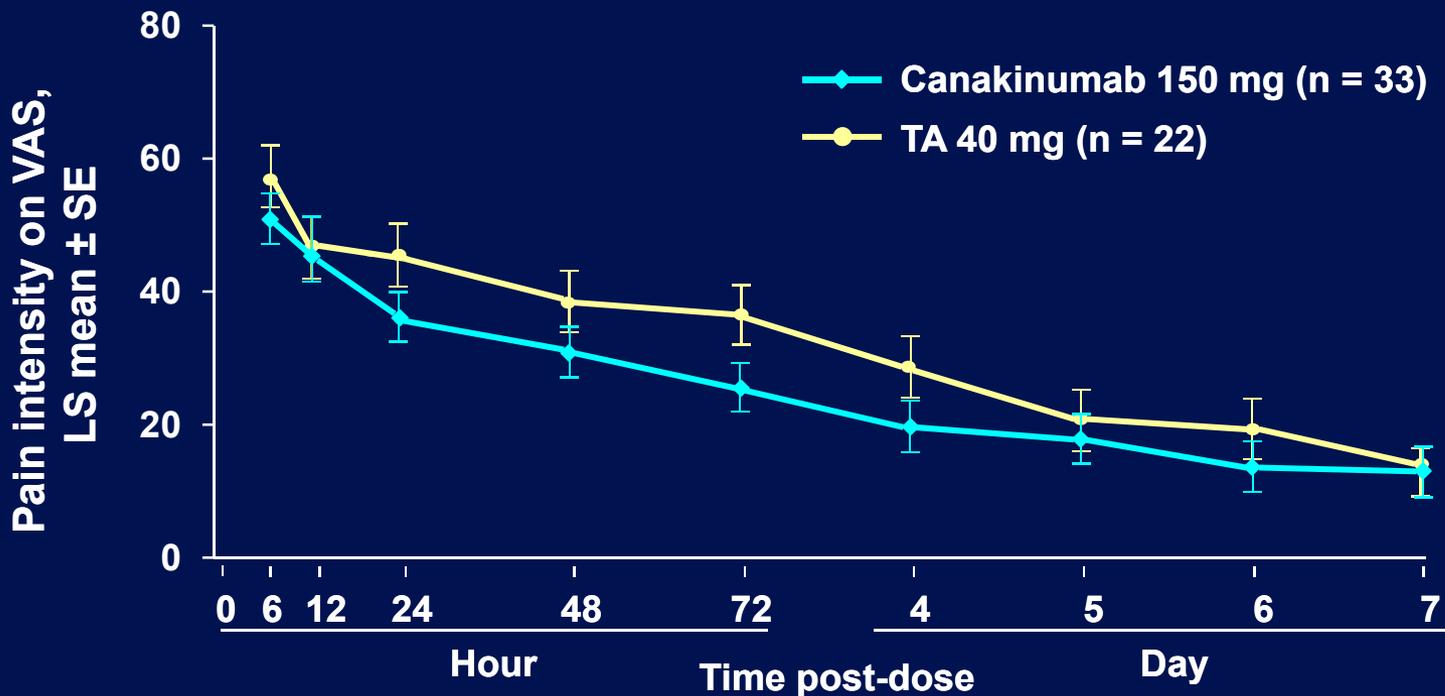


■ TA - BL: n=95-98 ■ AG Norms ■ TA - 4wks: n=83-86 ■ TA - 8wks: n=79-84 ■ TA - 12wks: n=79-82

# Renal Function Is Impaired in Gouty Arthritis

	<b>Canakinumab 150 mg</b> <b>N=253</b> <b>n (%)</b>	<b>TA</b> <b>N=286</b> <b>n (%)</b>
<b>CKD as reported under co-morbidities</b>	<b>33 (14.7)</b>	<b>22 (9.6)</b>
<b>Baseline GFR (by MDRD ml/min/SA) – at study entry</b>	<b>N (%)</b>	<b>N (%)</b>
<b>Total</b>	<b>221</b>	<b>212</b>
<b>≥90</b>	<b>33 (15)</b>	<b>20 (9)</b>
<b>≥60 GFR &lt;90</b>	<b>123 (56)</b>	<b>143 (67)</b>
<b>≥30 GFR &lt;60</b>	<b>59 (27)</b>	<b>46 (22)</b>
<b>&lt;30</b>	<b>6 (3)</b>	<b>3 (1)</b>

# Efficacy Pattern of Canakinumab in CKD Patients Was Similar to the Overall Population

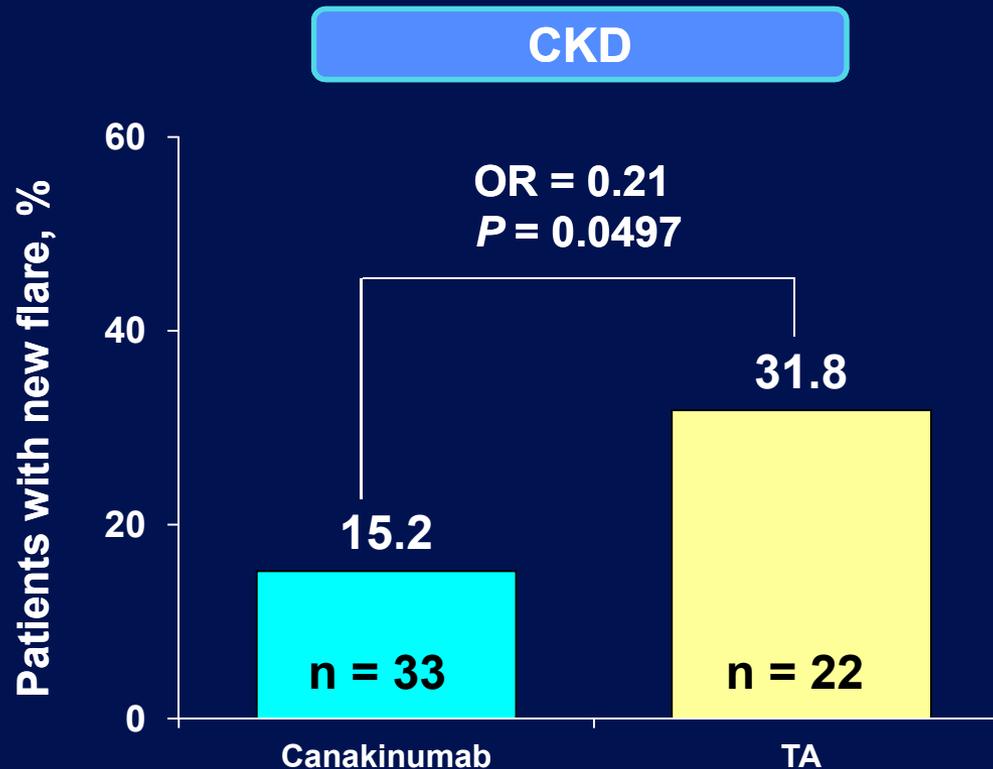


Time	6 h	12 h	24 h	48 h	72 h	4 d	5 d	6 d	7 d
Canakinumab 150 mg, mean	53.8	48.5	39.7	33.1	29.8	23.6	21.6	19.2	15.4
TA 40 mg, mean	55.9	45.6	44.5	38.0	36.1	28.5	20.0	19.2	13.8
P value	0.2906	0.8474	0.1249	0.2120	0.0712	0.1437	0.6304	0.3678	0.8784

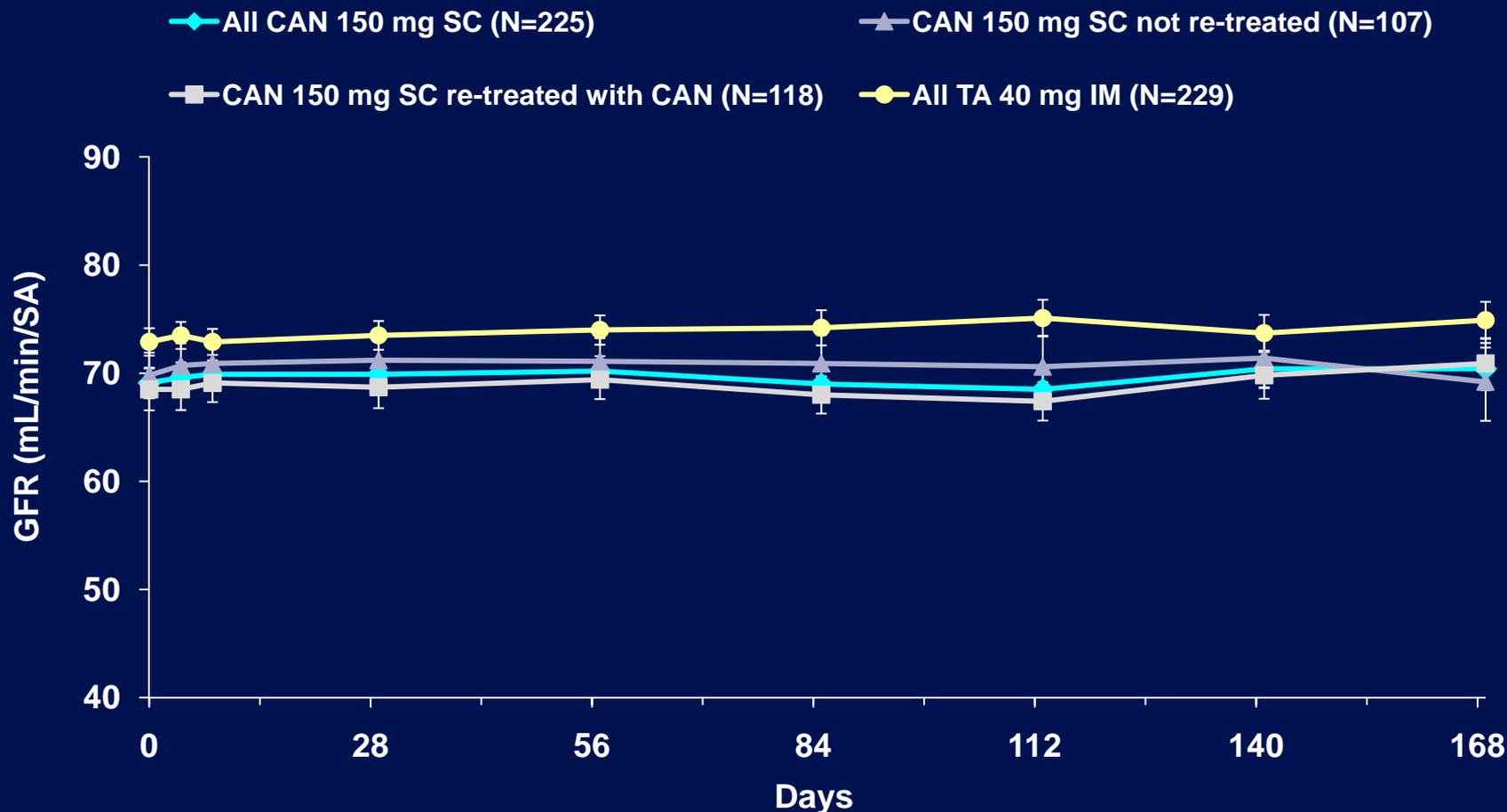
VAS 0–100 mm.

P values not significant at all time points.

# Canakinumab Significantly Reduced Risk of New Attack in Patients with CKD



# Renal Function, GFR over Time, GA Phase III E2 (Day 0-169)



CAN = canakinumab; TA = triamcinolone acetonide; SC = subcutaneous; IM = intramuscular; GFR = glomerular filtration rate.

# AEs and SAEs Incidence by GFR – All GA

		CAN 150 mg N=278	TA N=286
<b>GFR ≥ 90 ml/min/SA</b>	<b>Total</b>	<b>33</b>	<b>35</b>
Total AEs - N (%)		22 (66.7)	20 (57.1)
Total SAEs – n (%)		3 (9.1)	2 (5.7)
<b>60 ≤ GFR &lt; 90 ml/min/SA</b>	<b>Total</b>	<b>123</b>	<b>143</b>
Total AES- N(%)		77 (62.6)	75 (52.4)
Total SAEs – N (%)		8 (6.5)	6 (4.2)
<b>30 ≤ GFR &lt; 60 ml/min/SA</b>	<b>Total</b>	<b>59</b>	<b>46</b>
Total AEs		43 (72.9)	24 (52.2)
Total SAEs		5 (8.5)	0 (0.0)

# Creatinine, GFR (by MDRD), Cholesterol, and Triglycerides: Mean Change From BL to EoS (All RA) 1/2

Parameter		Baseline	Post-baseline	Change From Baseline	
Period	n	Mean (SD)	Mean (SD)	Mean (SD)	Median
<b>Creatinine (mg/dL)</b>					
Week 24 (N=441)	438	0.7930 (0.1697)	0.8224 (0.1891)	0.0294 (0.1072)	0.00
Week 48 (N=332)	328	0.7839 (0.1736)	0.8247 (0.1837)	0.0407 (0.1079)	0.01
Week 72 (N=255)	253	0.7817 (0.1753)	0.8450 (0.2115)	0.0633 (0.1382)	0.06
Week 96 (N=149)	148	0.7986 (0.1829)	0.8586 (0.1960)	0.0600 (0.1201)	0.07
Week 144 (N=37)	37	0.8314 (0.1724)	0.8993 (0.1491)	0.0690 (0.1410)	0.10
End of study (N=441)	439	0.7930 (0.1701)	0.8462 (0.2018)	0.0532 (0.1302)	0.01
<b>GFR (by MDRD mL/min/SA)</b>					
Week 24 (N=441)	438	84.79 (23.258)	81.53 (22.495)	-3.25 (12.270)	-0.30
Week 48 (N=332)	328	86.11 (23.718)	81.13 (22.467)	-4.97 (13.031)	-2.80
Week 72 (N=255)	253	85.66 (22.406)	78.93 (22.449)	-6.73 (14.069)	-6.10
Week 96 (N=149)	148	82.49 (20.804)	75.68 (20.040)	-6.81 (13.537)	-7.85
Week 144 (N=37)	37	79.90 (17.798)	71.30 (13.484)	-8.61 (13.833)	-8.10
End of study (N=441)	439	84.71 (23.290)	79.18 (23.316)	-5.53 (13.379)	-1.70

Studies A2101, A2201, A2204, A2207, A2206, A2201E1, A2201E2, and A2211.

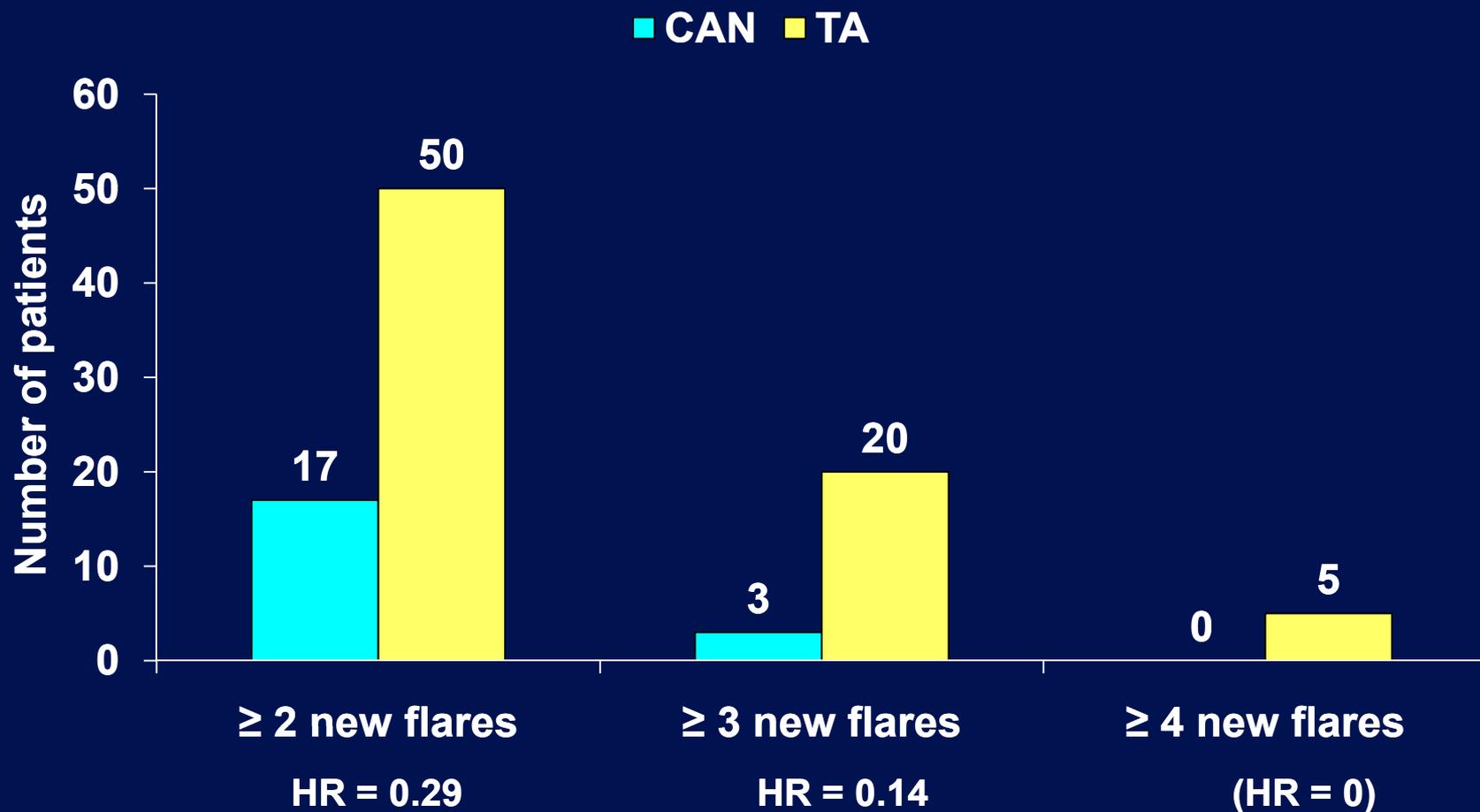
Only patients with a value at both baseline and the post-baseline period are included in the summaries. The by period value is defined as the last value that is measured closest to the period cut-off.

GFR (by MDRD), glomerular filtration rate by modification of diet in renal disease study formula; SA, surface area.

Source: [SCS Appendix 1-Table 3.4-1C].

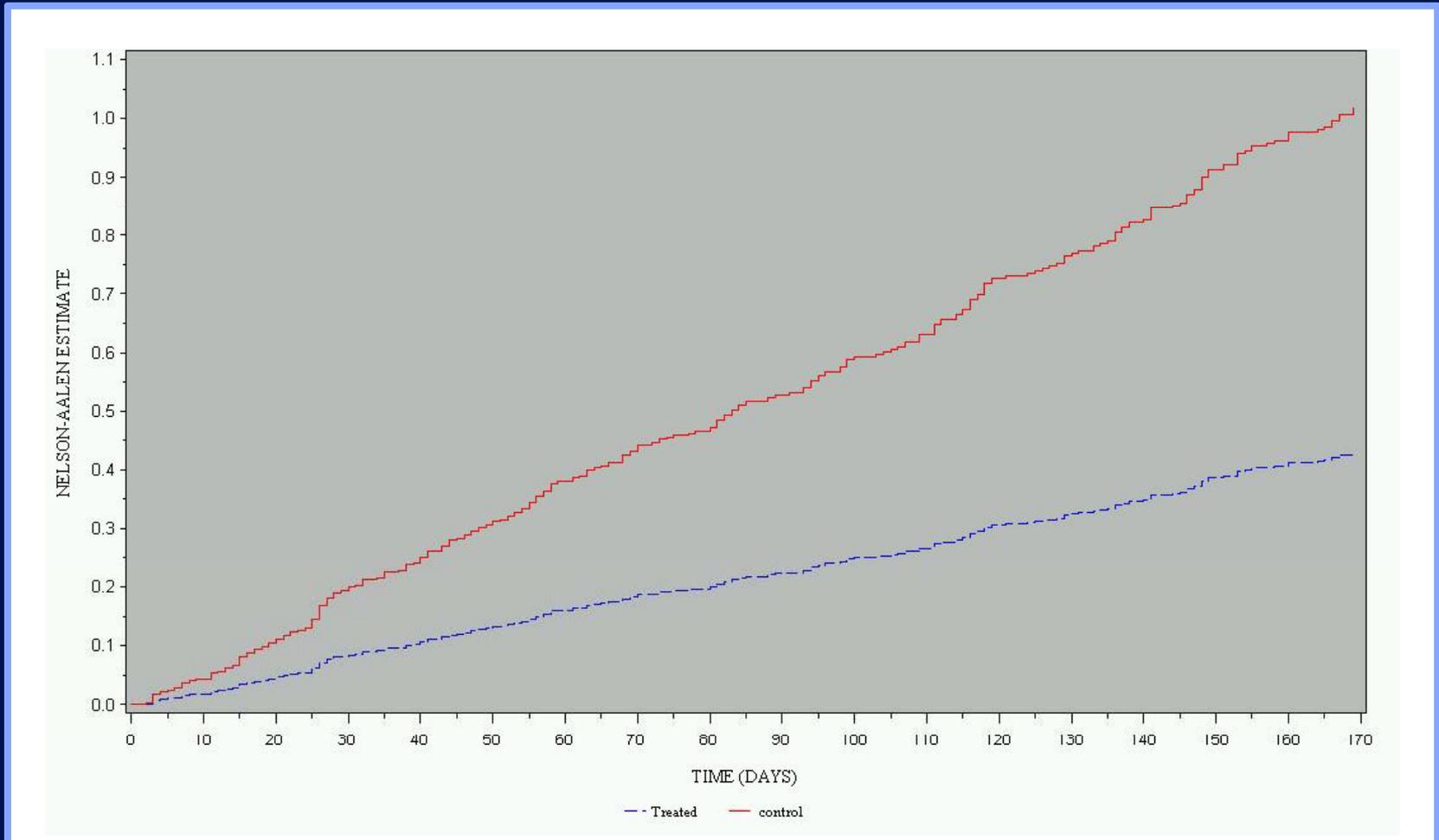
# Canakinumab Shows Reduced Incidence of Multiple Re-flares during 6 Months

*Studies H2356, H2357 combined; CAN: N=225, TA: N=229*



# Time to Multiple Gout Attacks, 24 Weeks Pooled Studies H2356, H2357

Cumulative intensity plot; HR = 0.42



# SAEs by Primary SOC (All RA) 1/2

Primary SOC	Canakinumab					
	Overall N=441 n (%)	0-24 weeks N=441 n (%)	>24-48 weeks N=357 n (%)	>48-72 weeks N=276 n (%)	>72-96 weeks N=173 n (%)	>96-144 weeks N=65 n (%)
<b>Total number (%) of patients with any SAE</b>	<b>67 (15.2)</b>	<b>29 (6.6)</b>	<b>17 (4.8)</b>	<b>18 (6.5)</b>	<b>10 (5.8)</b>	<b>2 (3.1)</b>
Infections and infestations	21 (4.8)	11 (2.5)	3 (0.8)	3 (1.1)	4 (2.3)	1 (1.5)
Musculoskeletal and connective tissue disorders	17 (3.9)	3 (0.7)	5 (1.4)	5 (1.8)	5 (2.9)	0
Gastrointestinal disorders	13 (2.9)	6 (1.4)	2 (0.6)	3 (1.1)	2 (1.2)	0
Injury, poisoning, and procedural complications	10 (2.3)	5 (1.1)	2 (0.6)	2 (0.7)	1 (0.6)	0
Vascular disorders	7 (1.6)	2 (0.5)	3 (0.8)	2 (0.7)	0	0
Respiratory, thoracic, and mediastinal disorders	4 (0.9)	2 (0.5)	2 (0.6)	0	0	0
Nervous system disorders	4 (0.9)	1 (0.2)	2 (0.6)	1 (0.4)	0	0

Studies A2101, A2201, A2204, A2207, A2206, A2201E1, A2201E2, and A2211.

Primary SOC's are sorted in descending order of frequency in the ACZ885 overall group.

SOC, system organ class; SAE, severe adverse event.

Source: [SCS Appendix 1-Table 2.1-3C].

# Pivotal Trials: Mean VAS Pain at Time Points After Starting Treatment

	Study H2356		Study H2357	
	CAN N = 113	TA N = 115	CAN N = 112	TA N = 114
VAS pain reduction (mean change from baseline in mm)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
At 6 hours	-16.1 (18.58)	-13.1 (18.64)	-16.6 (20.66)	-13.8 (21.25)
At 12 hours	-23.4 (19.33)	-17.5 (21.02)	-23.9 (22.81)	-22.1 (22.80)
At 24 hours	-33.3 (23.05)	-23.2 (22.58)	-36.1 (23.80)	-29.0 (26.63)
At 48 hours	-41.3 (24.43)	-30.4 (24.99)	-46.3 (25.19)	-35.5 (27.60)
At 72 hours	-45.9 (23.08)	-35.4 (28.79)	-53.4 (23.54)	-42.5 (27.28)
At 7 days	-57.4 (21.48)	-48.6 (27.73)	-61.3 (22.34)	-55.0 (26.16)

VAS, visual analog scale; SD, standard deviation.

Source: [Study H2356-Table 14.2-3.2], [Study H2357-Table 14.2-3.2]

# SAEs by Primary SOC (All RA) 1/2

Primary SOC	Canakinumab					
	Overall N=441 n (%)	0-24 weeks N=441 n (%)	>24-48 weeks N=357 n (%)	>48-72 weeks N=276 n (%)	>72-96 weeks N=173 n (%)	>96-144 weeks N=65 n (%)
<b>Total number (%) of patients with any SAE</b>	<b>67 (15.2)</b>	<b>29 (6.6)</b>	<b>17 (4.8)</b>	<b>18 (6.5)</b>	<b>10 (5.8)</b>	<b>2 (3.1)</b>
Infections and infestations	21 (4.8)	11 (2.5)	3 (0.8)	3 (1.1)	4 (2.3)	1 (1.5)
Musculoskeletal and connective tissue disorders	17 (3.9)	3 (0.7)	5 (1.4)	5 (1.8)	5 (2.9)	0
Gastrointestinal disorders	13 (2.9)	6 (1.4)	2 (0.6)	3 (1.1)	2 (1.2)	0
Injury, poisoning, and procedural complications	10 (2.3)	5 (1.1)	2 (0.6)	2 (0.7)	1 (0.6)	0
Vascular disorders	7 (1.6)	2 (0.5)	3 (0.8)	2 (0.7)	0	0
Respiratory, thoracic, and mediastinal disorders	4 (0.9)	2 (0.5)	2 (0.6)	0	0	0
Nervous system disorders	4 (0.9)	1 (0.2)	2 (0.6)	1 (0.4)	0	0

Studies A2101, A2201, A2204, A2207, A2206, A2201E1, A2201E2, and A2211.

Primary SOC's are sorted in descending order of frequency in the ACZ885 overall group.

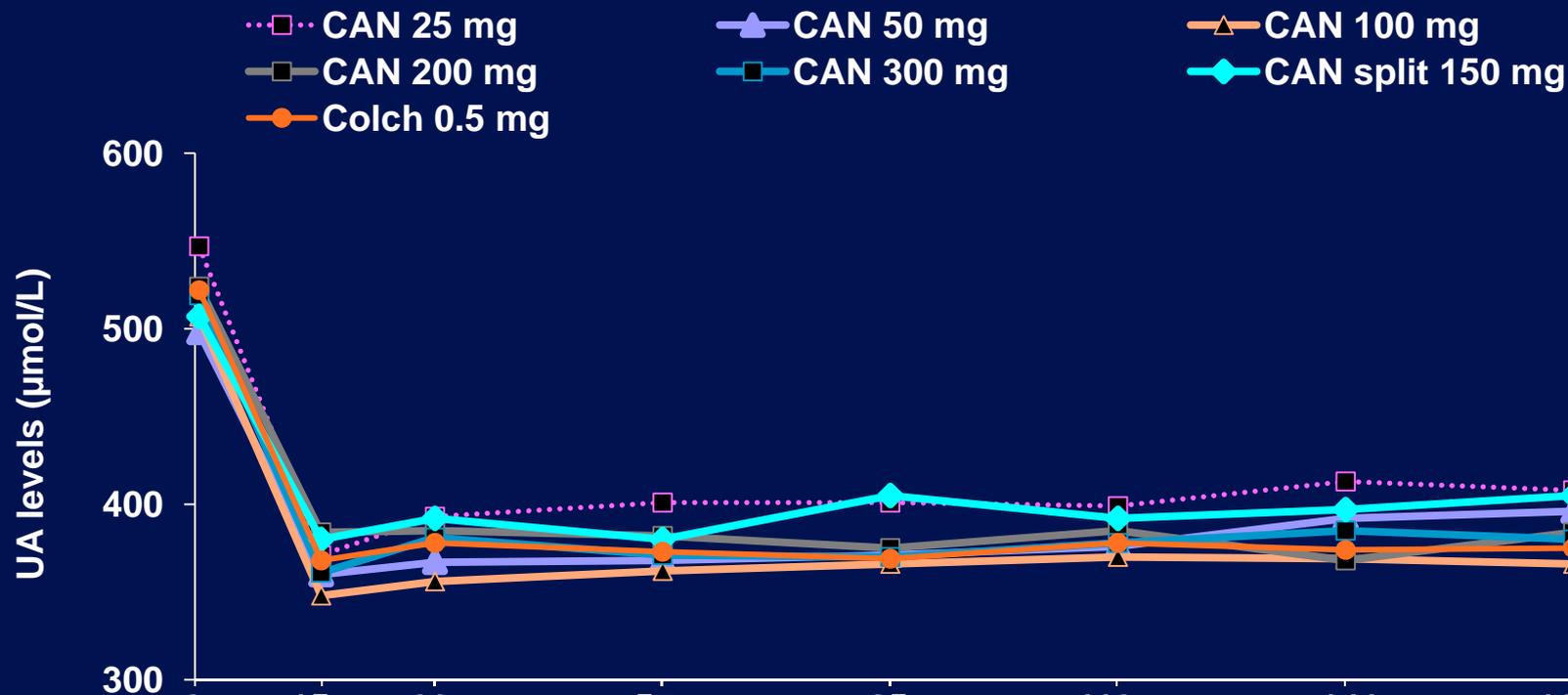
SOC, system organ class; SAE, severe adverse event.

Source: [SCS Appendix 1-Table 2.1-3C].

# Frequency Distribution of Canakinumab Re-treated Patients



# Urate Levels in Patients Starting UALT H2251



	0	15	29	57	85	113	141	169
CAN 25 mg	547	371	393	401	401	399	413	408
CAN 50 mg	498	360	367	368	371	376	392	396
CAN 100 mg	507	348	356	362	366	370	369	366
CAN 200 mg	524	384	385	382	375	385	368	384
CAN 300 mg	519	361	381	371	370	378	385	380
CAN split 150 mg	507	380	392	380	405	392	397	405
Colch 0.5 mg	522	368	378	373	369	378	374	375

# VAS Pain Response According to Time of Treatment after Start of Flare

	Canakinumab (Pooled)				Triamcinolone Acetonide (Pooled)			
	Baseline	1d	3d	7d	Baseline	1d	3d	7d
Time Since Start of Flare	Mean (SD) VAS Pain (mm)				Mean (SD) VAS Pain (mm)			
0-1 day	73.8 (12.9) n = 49	33.5 (22.0) n = 49	16.0 (19.5) n = 47	9.7 (16.7) n = 46	73.5 (12.4) n = 63	47.6 (28.1) n = 64	30.3 (25.6) n = 62	15.4 (23.6) n = 59
2 days	74.2 (11.7) n = 67	41.7 (23.3) n = 64	24.6 (20.6) n = 65	13.1 (16.7) n = 63	75.7 (12.3) n = 63	49.3 (27.7) n = 71	34.9 (27.8) n = 72	22.4 (25.2) n = 64
3 days	74.8 (12.2) n = 65	40.7 (24.8) n = 64	29.3 (24.3) n = 65	21.1 (23.6) n = 63	73.2 (13.2) n = 63	47.9 (24.8) n = 50	37.5 (30.8) n = 51	27.2 (30.3) n = 46
≥4 days	73.1 (13.4) n = 42	40.8 (23.1) n = 43	24.3 (20.3) n = 43	12.8 (18.4) n = 41	73.9 (13.3) n = 42	46.8 (26.9) n = 40	40.1 (29.7) n = 40	27.8 (27.1) n = 39

Resolved: percentage of patients with full resolution of pain at 7 days.

SD, standard deviation; VAS, visual analog scale.

Source: [SCE Appendix 1-Table 3.3-4f1, Table 3.3-2f1]

# Study H2255: Dose Response Data for Efficacy and Safety

	Canakinumab					Triamcinolone Acetonide
	10 mg N = 28	25 mg N = 29	50 mg N = 28	90 mg N = 29	150 mg N = 27	40 mg N = 57
<b>Speed of pain relief</b>						
6-hour pain reduction (VAS in mm)	-9.6	-5.1	-13.8	-11.1	-20.2	-11.9
<i>P</i> value (relative to triamcinolone acetonide)	.5860	.1053	.6489	.8359	.0505*	–
Days to 50% pain reduction	2.9	2.9	1.0	1.0	1.0	2.0
<i>P</i> value (relative to triamcinolone acetonide)	.798	.962	.379	.297	.0006*	–
<b>Extent of pain relief at 72 hours</b>						
72-hour pain reduction (VAS in mm)	-48.6	-46.6	-48.6	-52.7	-62.5	-43.3
<i>P</i> value (relative to triamcinolone acetonide)	.3311	.5516	.3401	.0815	.0007*	–
72-hour pain decrease (Likert scale)	-1.7	-1.5	-1.5	-1.7	-2.1	-1.4
<i>P</i> value (relative to triamcinolone acetonide)	.1395	.9696	.7320	.1792	.0005*	–

\*Indicates statistical significance. VAS, visual analog scale.

Source: [Study H2255-Table 14.2-2.5] (pain reduction), [Study H2255-Table 14.2-5.2] (median time), [Study H2255-Table 14.2-3.5] (pain intensity), [Study H2255-Table 14.2-4.1] (patient's assessment), [Study H2255-Table 14.2-4.3] (physician's assessment), [Study H2255-Table 14.2-4.5] (tenderness assessment), [Study H2255-Table 14.2-7.1, 14.2-7.2] (rescue medication), [Study H2255-Table 14.3.1-1.1, Table 14.3.1-1.2] (AEs, infectious AEs), Study H2255-Table 14.3.1-1.11] (SAEs), Study H2255-Table 14.1-1.1] (discontinuations)

# Study H2255: Dose Response Data for Efficacy and Safety

	Canakinumab					Triamcinolone Acetonide
	10 mg N = 28	25 mg N = 29	50 mg N = 28	90 mg N = 29	150 mg N = 27	40 mg N = 57
<b>Response to treatment</b>						
Good/excellent (patient assessment), n (%)	18 (64.3)	18 (62.1)	20 (71.4)	19 (65.5)	24 (88.8)	30 (53.6)
Good/very good (physician assessment), n (%)	21 (75.0)	18 (62.1)	22 (78.6)	22 (75.9)	25 (92.6)	34 (60.7)
Absence of tenderness, n (%)	10 (35.7)	7 (24.1)	9 (32.1)	9 (31.0)	14 (51.9)	16 (28.6)
<b>Patient use of rescue medication up to day 7</b>						
Total, n (%)	13 (46.4)	16 (55.2)	16 (57.1)	14 (48.3)	6 (22.2)	31 (55.4)
<i>P</i> value (relative to triamcinolone acetonide)	.39	.93	1.00	.53	.01*	–
Prednisone/prednisolone	5 (17.9)	9 (31.0)	8 (28.6)	6 (20.7)	2 (7.4)	16 (28.6)
Codeine	4 (14.3)	6 (20.7)	4 (14.3)	4 (13.8)	1 (3.7)	9 (16.1)
Acetaminophen	9 (32.1)	12 (41.4)	15 (53.6)	12 (41.4)	5 (18.5)	23 (41.1)
<b>Safety and tolerability data</b>						
Overall rate of AEs	10 (35.7)	13 (44.8)	15 (51.7)	12 (41.4)	9 (32.1)	24 (42.1)
Infectious AEs	0	3 (10.3)	3 (10.3)	2 (6.9)	2 (7.1)	4 (7.0)
Serious adverse events <sup>a</sup>	0	2 (6.9)	2 (6.9)	0	0	1 (1.8)
Safety/tolerability discontinuations	0	0	0	0	0	0

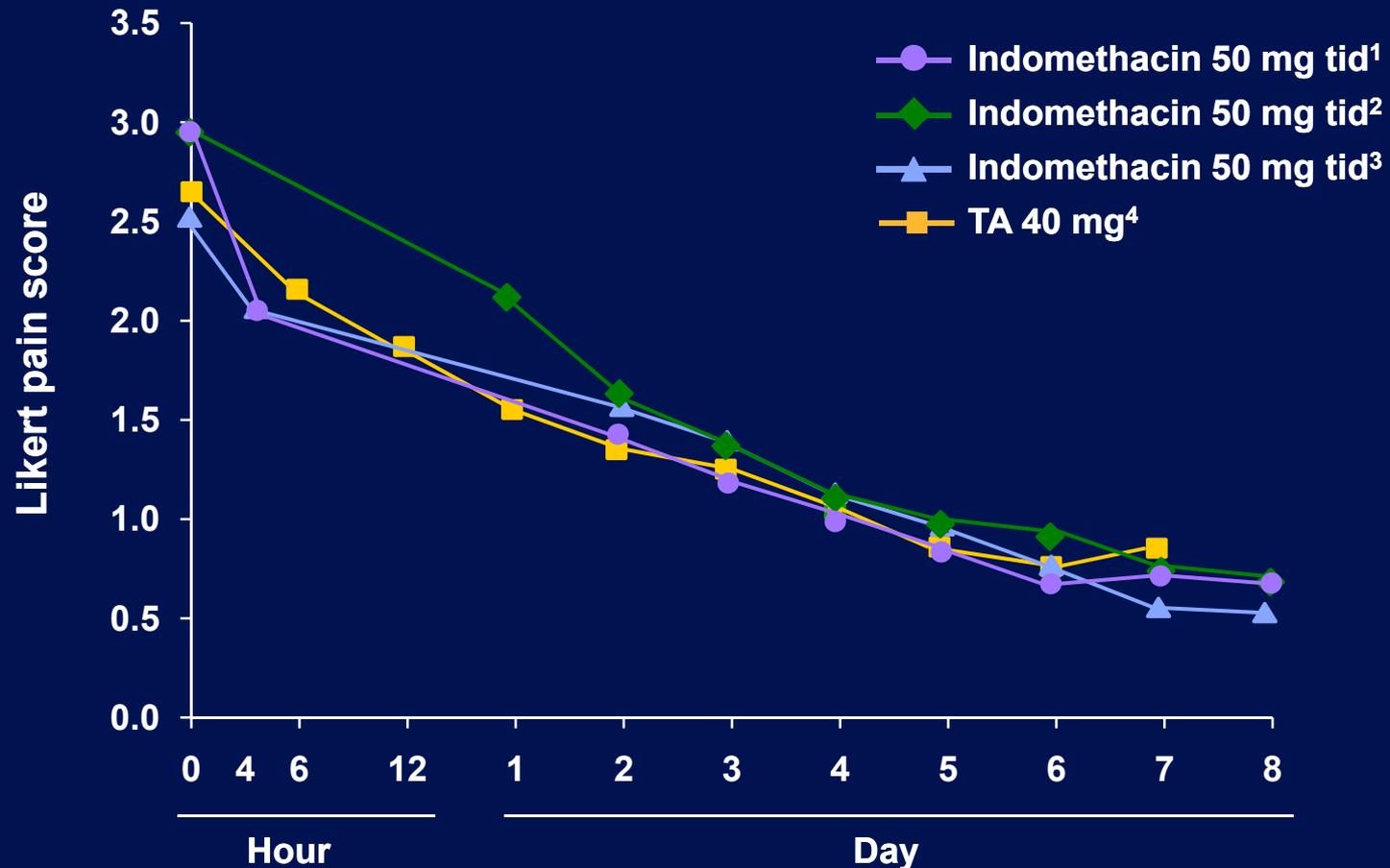
\*Indicates statistical significance.

<sup>a</sup> All serious adverse events were rated as unrelated to study drug by the investigator. AEs, adverse events.

Source: [Study H2255-Table 14.2-2.5] (pain reduction), [Study H2255-Table 14.2-5.2] (median time), [Study H2255-Table 14.2-3.5] (pain intensity), [Study H2255-Table 14.2-4.1] (patient's assessment), [Study H2255-Table 14.2-4.3] (physician's assessment), [Study H2255-Table 14.2-4.5] (tenderness assessment), [Study H2255-Table 14.2-7.1, 14.2-7.2] (rescue medication), [Study H2255-Table 14.3.1-1.1, Table 14.3.1-1.2]

(AEs, infectious AEs), Study H2255-Table 14.3.1-1.11] (SAEs), Study H2255-Table 14.1-1.1] (discontinuations) E-14

# TA Is as Efficacious as Indomethacin in Reducing Pain, According to Data from Three Studies



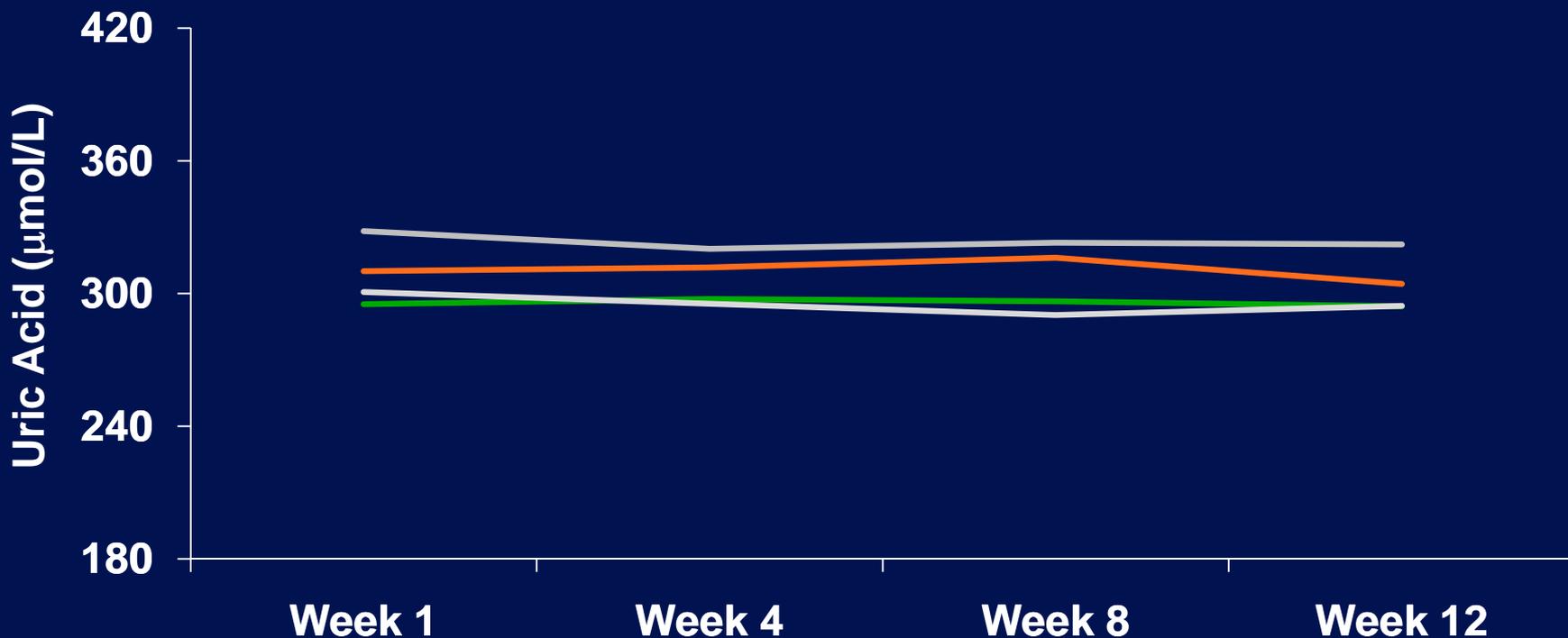
Cross study comparison.

1 Schumacher HR, et al. *BMJ*. 2002;324:1488-92. 2 Rubin BR, et al. *Arthritis Rheum*. 2004;50:598-606.

3 Willburger RE, et al. *Rheumatology*. 2007;46:1126-32. 4 So A, et al. *Arthritis Rheum* 2010;62:3064-76.

# Rheumatoid Arthritis Long Term – Uric Acid

- CAN 600mg iv + 300mg sc q2wk (N=71)
- CAN 300mg sc q2wk (N=64)
- CAN 150mg sc q4wk (N=69)
- Placebo (N=70)



# Frequency Distribution of Canakinumab Re-treated Patients



# Protocol Specifications on Rescue Medication Use

- Acetaminophen/paracetamol 500 mg to a maximum of 1g/dose or 3g/day
- Codeine 30 mg to a maximum of 30 mg/dose or 180 mg/day
- Oral prednisone 30 mg/day for 2 days followed by up to 20 mg/day for subsequent 3 days

# Gouty Arthritis – Injection Site Reactions in CAN Treated Patients, with Severity

Study/PID	Pain	Swelling	Induration /knot s.c.	Redness	Itching	Hemorrhage	Other
<b>2251</b>							
55/2				mild			
516/9			mild				
519/5						mild	
<b>2255</b>							
43/2	mild						
519/6			mild	mild			
123/901						mild	
537/12			mild				
<b>2357 + E1</b>							
540/3	mod.	mod.	mod.	mod.	mod.	mod.	mod.
540/5	mild	mild	mild	mild	mild	mild	mild

# Serum Clearance of Canakinumab Is Similar Between Elderly Gout Patients (>65 years) and Adult Gout Patients (<65 years)

<b>BMI Category</b>	<b>Clearance (L/d)</b>	
	<b>N</b>	<b>Geometric mean (95% CI)</b>
<b>Age &lt;65</b>	<b>608</b>	<b>0.229 (0.221,0.236)</b>
<b>Age ≥65</b>	<b>111</b>	<b>0.206 (0.192,0.22)</b>

# Malignancies - All RA

Any malignancy or Unspecified Tumors (SMQ narrow)	CAN Overall N=441 n (%)	CAN 0-24 weeks N=441 n (%)	CAN >24-48 weeks N=357 n (%)	CAN >48-72 weeks N=276 n (%)	CAN >72-96 weeks N=173 n (%)	CAN >96-144 weeks N=65 n (%)
any malignant or unspecified tumor	8 (1.8)	2 (0.5)	4 (1.1)	2 (0.7)	0	0
<b>Preferred terms:</b>						
Basal cell carcinoma	2 (0.5)	0	2 (0.6)	0	0	0
Gammopathy	1 (0.2)	1 (0.2)	0	0	0	0
Neoplasm skin	1 (0.2)	1 (0.2)	0	0	0	0
Thyroid neoplasm	1 (0.2)	0	1 (0.3)	0	0	0
Lung adenocarcinoma	1 (0.2)	0	1 (0.3)	0	0	0
Lung adenocarcinoma metastatic	1 (0.2)	0	0	1 (0.4)	0	0
Non-Hodgkin's lymphoma <sup>a</sup>	1 (0.2)	0	0	1 (0.4)	0	0
Squamous cell carcinoma of skin <sup>a</sup>	1 (0.2)	0	0	1 (0.4)	0	0

<sup>a</sup> Same patient.

Studies A2101, A2201, A2204, A2207, A2206, A2201E1, A2201E2, and A2211.

AEs with start dates in the follow-up periods after the patients completed or discontinued from the studies are included; therefore, N per time period for AEs is greater than N per time period in the exposure Table 1-10.

Source: [SCS Appendix 1-Table 2.5-9C].

# Number Needed to Treat (NNT)

*CAN vs TA, Pooled Studies H2356, H2357*

<b>Outcome</b>	<b>NNT</b>
<b>50% pain reduction at 72 hours</b>	<b>5.7</b>
<b>Major clinical benefit, 12 weeks (50% VAS improvement 72 hrs, no new flare)</b>	<b>3.6</b>
<b>Major clinical benefit, 24 weeks (50% VAS improvement 72 hrs, no new flare)</b>	<b>3.8</b>
<b>New attack, 12 weeks (prevent 1 attack)</b>	<b>3.1</b>
<b>New attack, 24 weeks (prevent 1 attack)</b>	<b>2.2</b>

# Number Needed to Harm (NNH)

*CAN vs TA, Gouty Arthritis Database*

<b>Outcome</b>	<b>NNH</b>
<b>All SAEs</b>	<b>25</b>
<b>Infection SAEs</b>	<b>62.5</b>