

ULORIC[®] (febuxostat) Tablets

Arthritis Advisory Committee Meeting

November 24, 2008

Introduction

Nancy Joseph-Ridge, MD
President
**Takeda Global Research &
Development Center, Inc (US)**

Agenda for Today

Introduction	Nancy Joseph-Ridge, MD <i>President</i> <i>Takeda Global Research & Development</i>
Medical Need	Michael A. Becker, MD <i>Professor of Medicine Emeritus</i> <i>University of Chicago</i>
Efficacy and Safety	Nancy Joseph-Ridge, MD <i>President</i> <i>Takeda Global Research & Development</i>
Cardiovascular Safety	William B. White, MD <i>Professor of Medicine, Cardiology Center</i> <i>University of Connecticut School of Medicine</i>
Risk/Benefit	Nancy Joseph-Ridge, MD <i>President</i> <i>Takeda Global Research & Development</i>

Febuxostat

- ◆ **Developed to address**
 - **Growing gout population**
 - **3 to 5 million individuals in the US¹⁻³**
 - **Increasing in incidence and prevalence**
 - **Need for a more effective urate-lowering agent compared to current therapies**
 - **No new gout therapy has been approved in over 40 yrs**

1. Aromdee E, et al. *J Rheumatol*. 2002;29:2403-2406.

2. Roddy E, et al. *Nat Clin Pract Rheumatol*. 2007;3:443-449.

3. Becker and Chohan. *Curr Opin Rheumatol*. 2008;20:167-172.

Febuxostat Proposed Indication

Indication	Dose	Frequency
Treatment of hyperuricemia in patients with gout	40 or 80 mg	Once daily

◆ 80 mg recommended

- Patients with higher serum uric acid (sUA) levels
- Patients with tophi

US Regulatory History (Cycle 1)

- ◆ **Initial febuxostat NDA: December 2004**
 - **One Phase 2 and two Phase 3 studies**
 - **1985 patients**
 - **Febuxostat 80 mg and 120 mg QD**
- ◆ **FDA requested additional information**
 - **Further examine the safety profile of febuxostat (small number of CV events, apparent imbalance)**

US Regulatory History (Cycle 2)

- ◆ Takeda submitted an independent evaluation of all potential CV events in Phase 2 and 3 studies
- ◆ Takeda committed to a Phase 4 Clinical Outcomes study
- ◆ FDA requested additional information
 - More clearly characterize the potential CV risk of 80 mg dose
 - Additional study of safety and efficacy of lower dose (40 mg)

US Regulatory History (Cycle 3)

- ◆ **Takeda conducted an additional Phase 3 study**
 - **2269 patients**
 - **Prospectively designed to**
 - **Evaluate CV events**
 - **Enroll subjects with renal impairment**
 - **Data Monitoring Committee; Cardiovascular Endpoints Committee**
 - **Febuxostat 40 mg QD, Febuxostat 80 mg QD**

Febuxostat Overview

- ◆ **There is a medical need for a new treatment of hyperuricemia in patients with gout**
- ◆ **Febuxostat did not show an increased risk of CV events relative to allopurinol**
 - **Clinical program reflective of the gout population**
 - **No plausible biological mechanism for CV events**
 - **New large Phase 3 study did not substantiate previously observed apparent CV imbalance**
- ◆ **The benefits of febuxostat outweigh the risks and support approval for the proposed indication**

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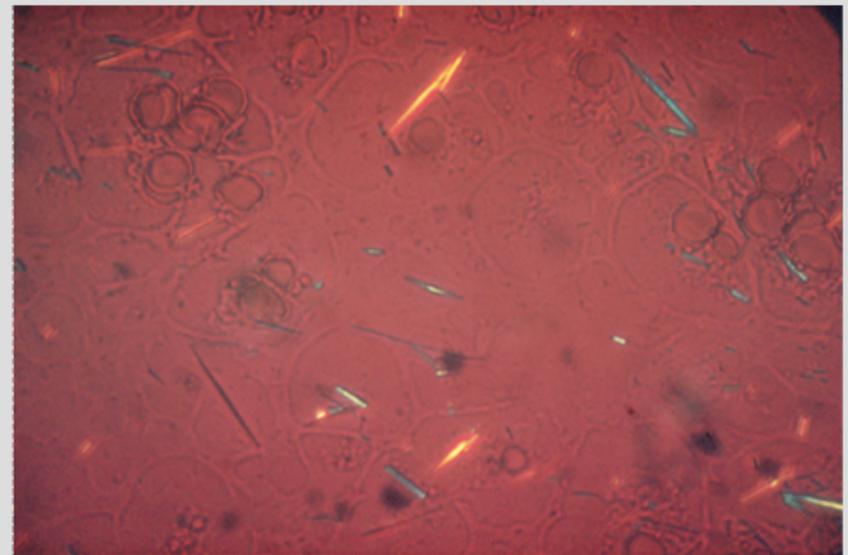
Gout: Disease and Unmet Need

Michael A. Becker, MD

**Professor of Medicine Emeritus
The University of Chicago**

Gout (Urate Crystal Deposition Disease)

- ◆ Gout is increasing in incidence and prevalence¹⁻³
- ◆ Gout symptoms result from responses to urate crystal deposits in tissues, arising from body fluids saturated for urate
- ◆ Hyperuricemia, defined as a serum urate level ≥ 6.8 mg/dL, is the invariable risk factor for gout



1. Aromdee E, et al. *J Rheumatol*. 2002;29:2403-2406.
2. Roddy E, et al. *Nat Clin Pract Rheumatol*. 2007;3:443-449.
3. Becker and Chohan. *Curr Opin Rheumatol*. 2008;20:167-172.

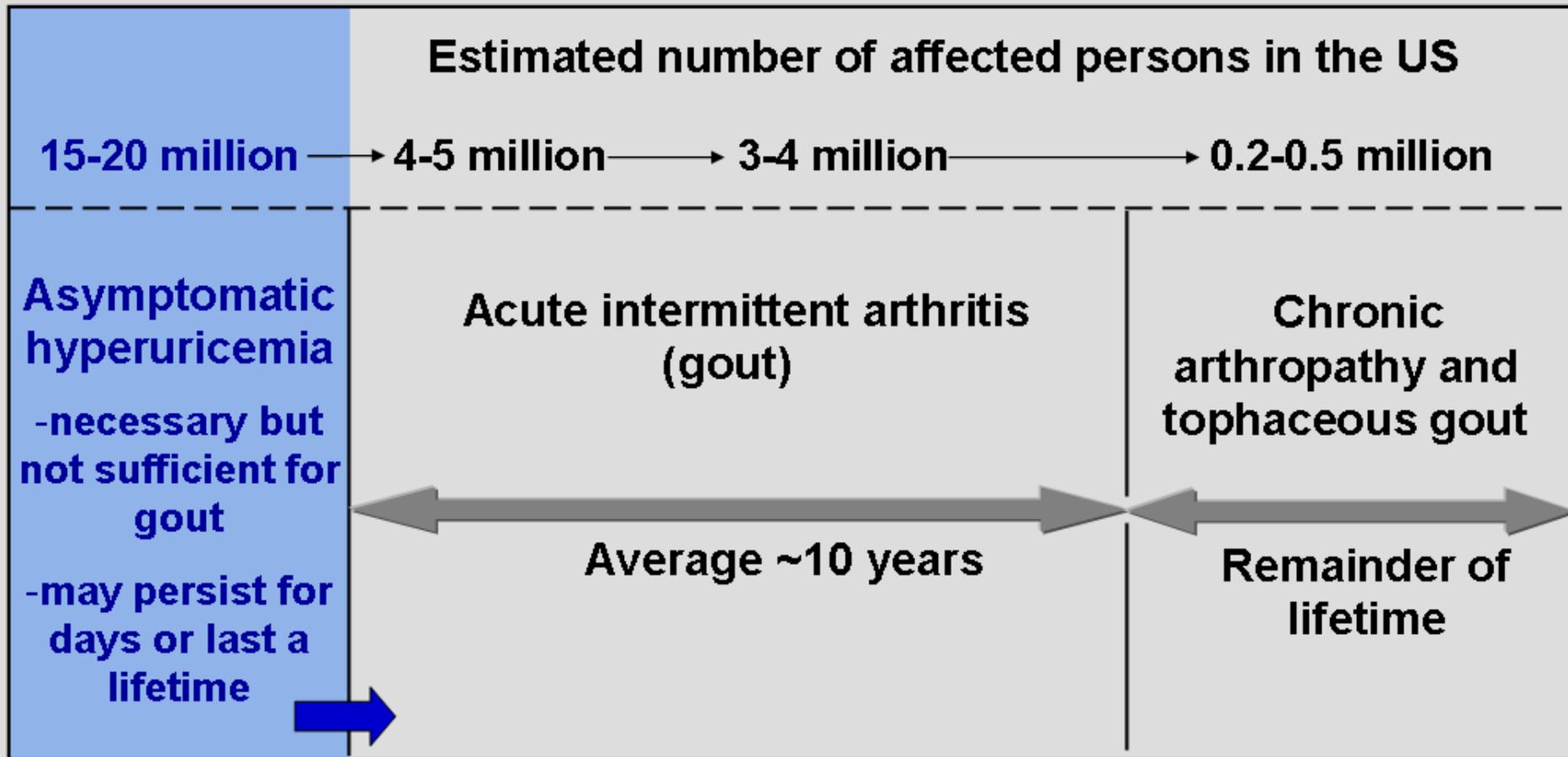
Acute Gouty Inflammation: Urate Crystal Ingested by a Neutrophilic Leukocyte



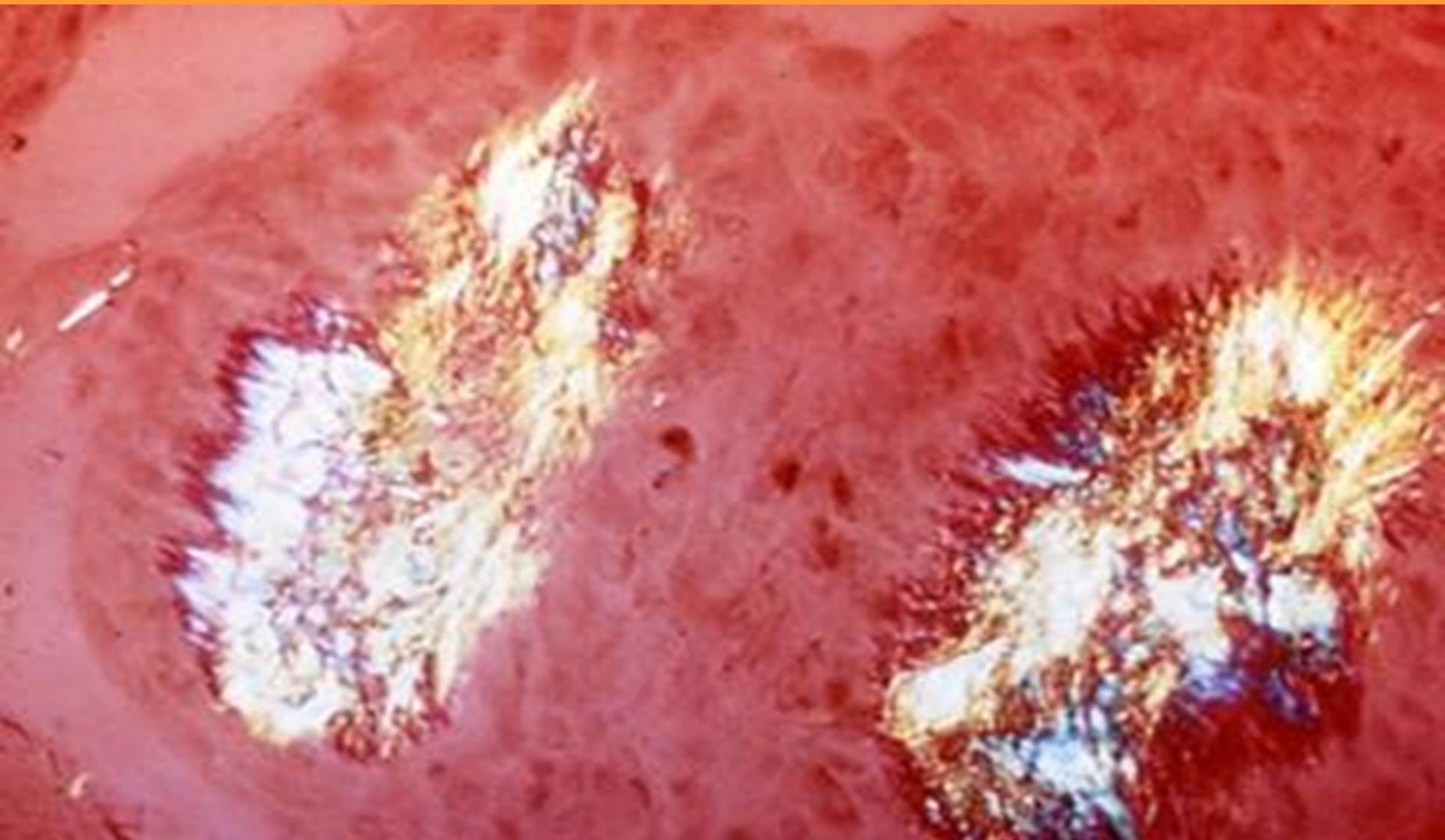
Acute Gouty Arthritis



Gout: A Progressive and Disabling Disease



Chronic Tophaceous Gout: Masses of Urate Crystals in Cartilage/Bone



Chronic Gouty Arthropathy (Hand) and Tophi (Olecranon Bursa; 2nd MCP and PIP Joints)



Chronic Tophaceous Gout: Destructive Arthropathy



Significant Co-morbidities Frequently Accompany Hyperuricemia and Gout

- ◆ Impaired renal function¹
- ◆ Metabolic syndrome²
 - Hyperlipidemia³
 - Obesity³
 - Diabetes mellitus⁴
- ◆ Cardiovascular disease⁵
 - Myocardial infarction
 - Stroke
 - Peripheral artery disease
- ◆ Heart failure⁶
- ◆ Hypertension⁷

1. Vazquez-Mellado, et al. *Best Practice Res Clin Rheumatol*. 2004;18:111.

2. Ford, et al. *JAMA*. 2002;287:356.

3. Nakanishi, et al. *Int J Epidemiol*. 1999;28:888.

4. Boyko, et al. *Diabetes Care*. 2000;23:1242.

5. Niskanen, et al. *Arch Intern Med*. 2004;164:1546.

6. Anker, et al. *Circulation*. 2003;107:1991.

7. Gavin, et al. *Am J Cardiovasc Drugs*. 2003;3:309.

Current Urate-lowering Management of Gout

Maintenance of serum urate in a sub-saturating range (< 6.0 mg/dL) to:

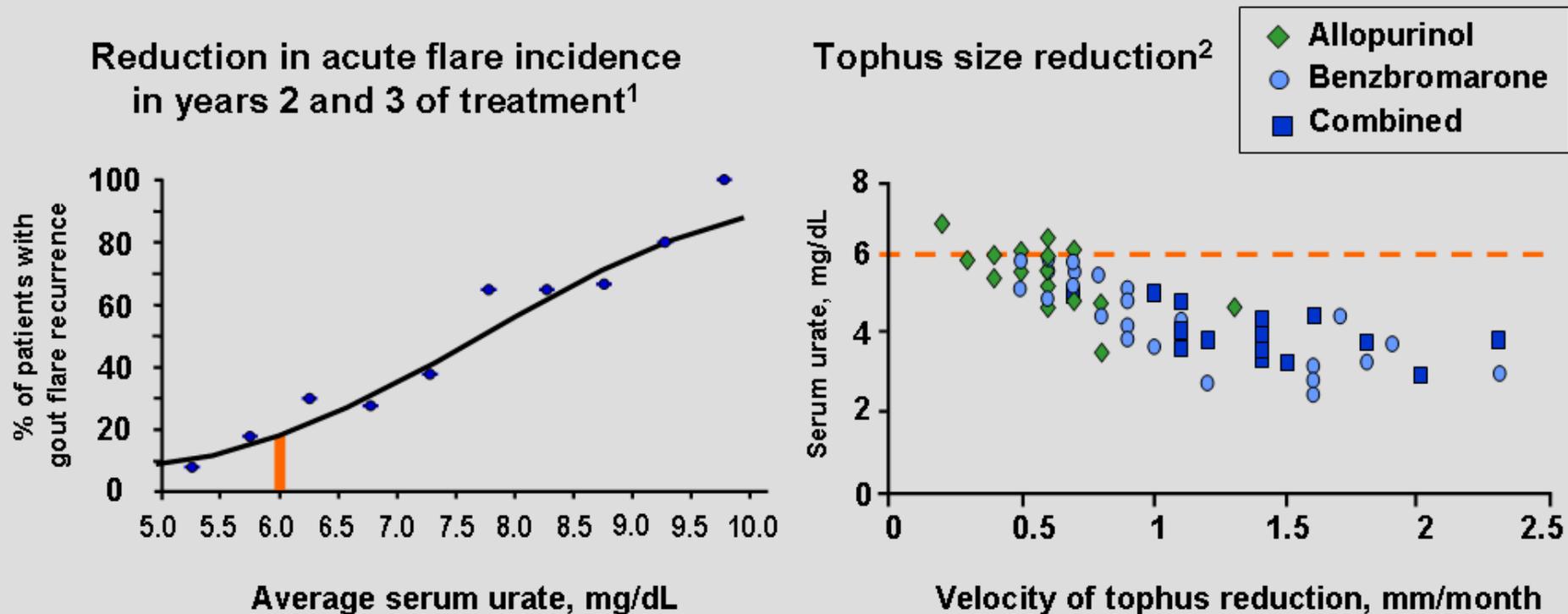
- Reduce body urate pool
- Dissolve crystals¹
- Prevent/reverse gout symptoms and progression to disability and impaired quality of life^{2,3}

1. Li-yu, et al. *J Rheumatol*. 2001;28:577-580.

2. Shoji, et al. *Arthritis Rheum*. 2004;51:321-325.

3. Perez-Ruiz, et al. *Arthritis Rheum*. 2002;47:356-360.

Lowering Serum Urate Decreases Acute Flares and Reduces Tophus Size



1. Shoji, et al. *Arthritis Care Res.* 2004;51:321-325.

2. Perez-Ruiz, et al. *Arthritis Rheum.* 2002;47:356.

Treatment Initiated Flares

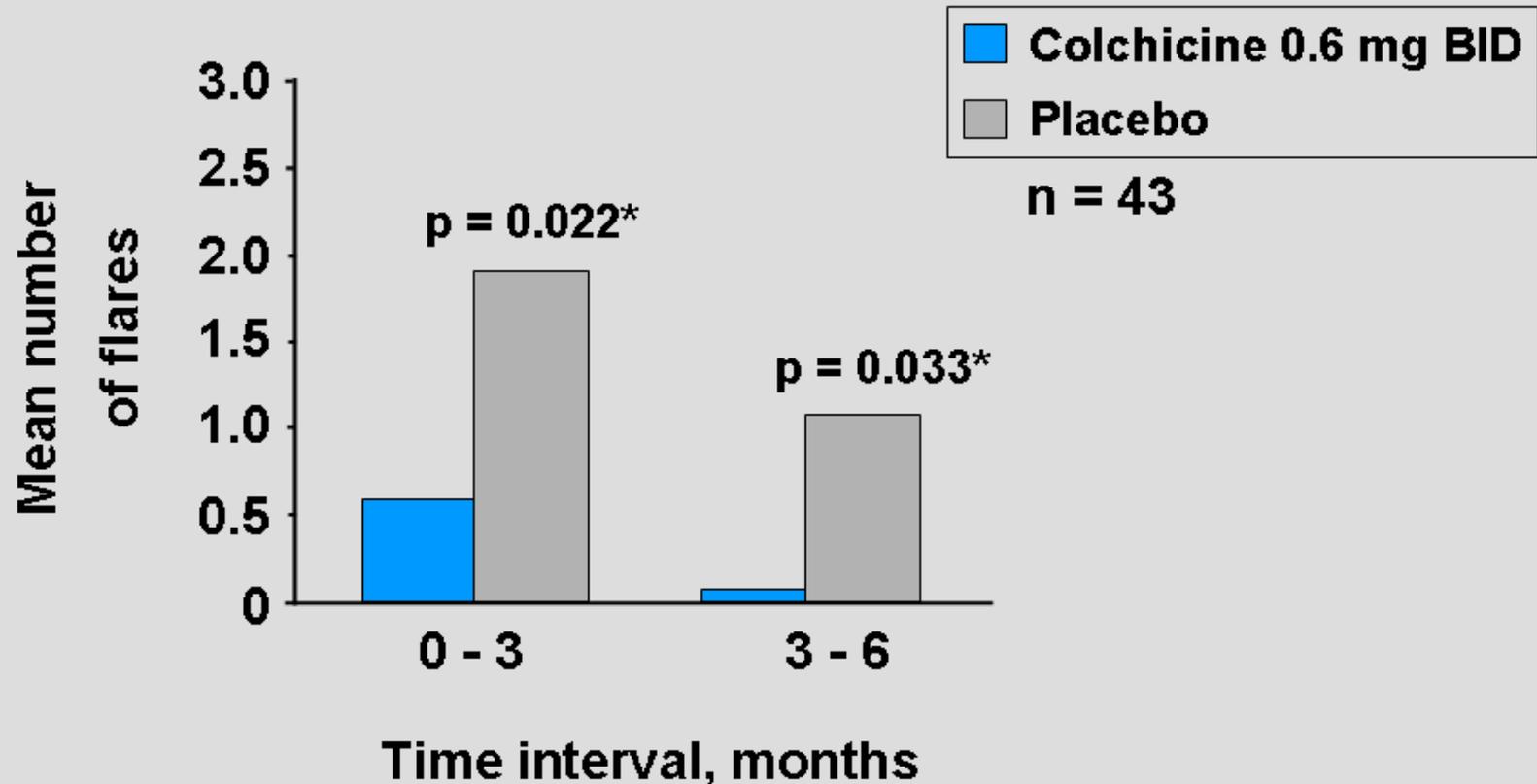
- ◆ An increase in gout flares occurs early in urate-lowering therapy¹⁻⁶
- ◆ Treatment initiated flares have an impact on patient adherence to therapy
- ◆ Mechanism is speculative but may be due to “activation” of deposited crystals

1. Rundels. *Ann Intern Med.* 1966;64:229-258. 2. Fam. *Clin Rheum.* 1990;4:177-192.

3. Paulus. *Arth Rheum.* 1974;17:609-614. 4. Emmerson. *N Engl J Med.* 1996;334:445-450.

5. Yamanka et al. *Adv Exp Med Biol.* 1998;431:13-18. 6. Hollingsworth. *Ann Rheum Dis.* 1980;39:529-530.

Efficacy of Colchicine Prophylaxis During Urate-Lowering with Allopurinol



* p-values for the difference between colchicine and placebo groups.
Borstad, et al. *J Rheum.* 2004;31:2429.

Allopurinol

Xanthine oxidase inhibitor: reduces urate formation

◆ Available since 1966

- Approved at doses from 100 to 800 mg/day, but
 - 95% of dosing in US is at 300 mg/day or less¹
 - Less than 50% of gout patients reach goal serum urate at 300 mg/day^{2, 3}
 - Dosage reduction is recommended with renal functional impairment^{4, 5}
- Minimal RCT evidence (1 trial, 17 subjects) for safety and efficacy of allopurinol at doses > 300 mg/day⁶

1. Sarawate, et al. *Mayo Clin Proc.* 2006;81:925-934. 2. Perez-Ruiz, et al. *Ann Rheum Dis.* 1998;57:545-549. 3. Becker, et al. *N Engl J Med.* 2005;353:2450-2461. 4. Hande, et al. *Am J Med.* 1984;76:47-56. 5. Dalbeth, et al. *J Rheumatol.* 2006;33:1646-1650. 6. Reinders, et al. *Ann Rheum Dis.* 2008; Published online:doi10.1136/ard.2008.091462.

Allopurinol (2)

- ◆ Intolerance in up to 20% of patients^{1,2}
 - Rare (< 1 in 1000 patients) allopurinol hypersensitivity syndrome or severe rashes that can be fatal¹

1. Arellano and Scristan. *Ann Pharmacother.* 1993;27:337-343.
2. Wortmann. *Current Opinion Rheum.* 2005;17:319-24.



Lee, et al. *Singapore Med J.* 2008;49(5):384.

New Urate-Lowering Therapy

- ◆ **Safety and clinical efficacy in all patients with gout**
- ◆ **Requires no dose reduction in patients with mild to moderate renal functional impairment**
- ◆ **Improves convenience and compliance through once daily dosing**

Conclusions

- ◆ Gout is an increasingly common, often progressive, and disabling disease
- ◆ Although available urate-lowering therapies benefit many gout patients, there is a documented need¹⁻⁴ for safe new urate-lowering options to prevent unnecessary acute disability and long-term disease progression in the broader range of current gout patients

1. Sarawate, et al. *Mayo Clin Proc.* 2006;81:925-934. 2. Pascual and Sivera. *Ann Rheum Dis.* 2007;66:1269-1270. 3. Becker and Chohan. *Curr Opin Rheumatol.* 2008;20:167-172. 4. Edwards. *Arthritis Rheum.* 2008;58:2587-2590.

Febuxostat Development Program

Nancy Joseph-Ridge, MD

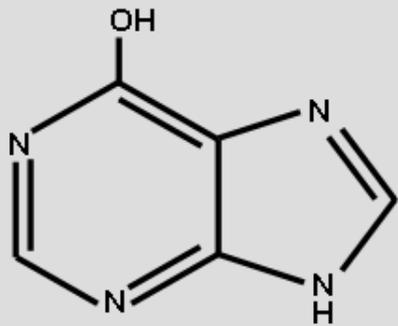
President

**Takeda Global Research & Development
Center, Inc. (US)**

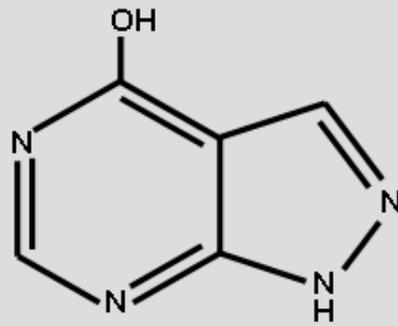
Efficacy Agenda

- ◆ **PK/PD Background**
- ◆ **Overview of Clinical Program**
- ◆ **Clinical Results**
 - **Reduction in Serum Urate (sUA)**
 - **Flares and Tophi**
- ◆ **Long-Term Extension Studies**
- ◆ **Conclusion**

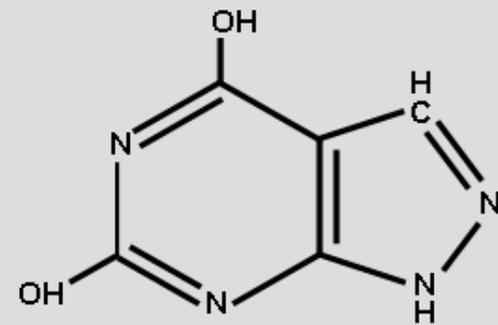
Febuxostat – Nonpurine Selective XO Inhibitor



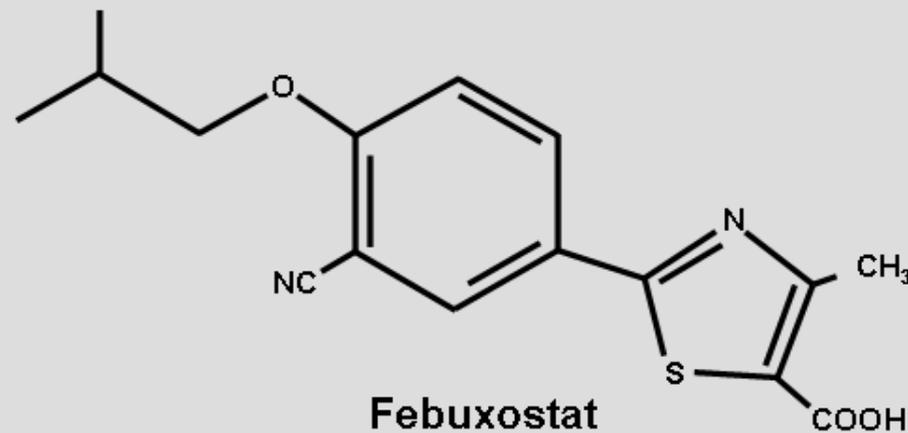
Hypoxanthine



Allopurinol



Oxypurinol



Febuxostat

Pharmacokinetics

- ◆ Rapidly and well absorbed
- ◆ Dose proportional
- ◆ No accumulation ($t_{1/2}$ 5 to 8 hrs)
- ◆ Extensive hepatic metabolism
- ◆ Renal excretion of febuxostat and active metabolites < 10% of dose
- ◆ Can be safely administered with colchicine, indomethacin, naproxen, hydrochlorothiazide, or warfarin

Pharmacodynamics

- ◆ **Decrease in sUA**
 - **Steady-state within 1 wk**
- ◆ **No clinically relevant differences**
 - **Food**
 - **Age or gender**
 - **Mild to moderate hepatic or renal impairment**

Clinical Program

- ◆ **Reduction of sUA to < 6 mg/dL**
 - **Treatment guidelines¹ have established sUA < 6 mg/dL as target level**
 - **Goal of treatment for clinical manifestations of gout is the correction of hyperuricemia²**
 - **Maintenance of sUA < 6 mg/dL associated with reduction of gout flare³ and tophi⁴**

1. Zhang, et al. *Ann Rheum Dis*. 2006;65(10):1312-1324. (EULAR Guidelines).

2. Wortman, et al. *Kelley's Textbook of Rheumatology*. 2001;1339-1376.

3. Shoji, et al. *Arthritis Rheum*. 2004;51:321-325.

4. Perez-Ruiz, et al. *Arthritis Rheum*. 2002;47:356-360.

Clinical Program

- ◆ **Doses ranged from 10 mg to 300 mg**
 - **25 Phase 1 studies**
 - **6 Phase 2/3 studies (40, 80, 120, 240 mg)**

Randomized-Controlled Studies and Long-Term Extension Studies

Phase 2

- Dose-Ranging (TMX-00-004)

Phase 3

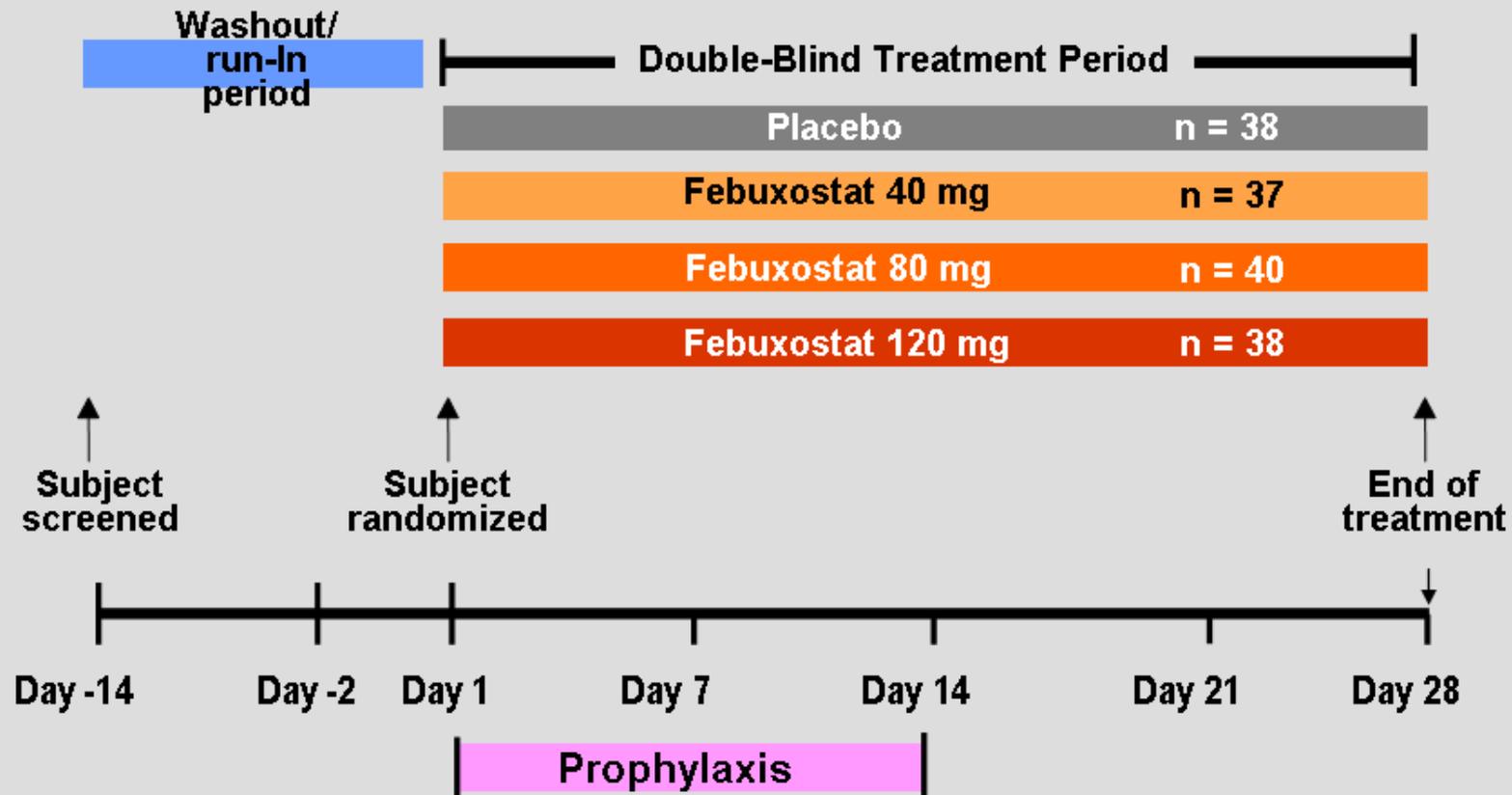
- FACT (C02-010)
- APEX (C02-009)
- CONFIRMS (F-GT06-153)

Long-Term Open-Label Extension

- Phase 2 – FOCUS (TMX-01-005)
- Phase 3 – EXCEL (C02-021)

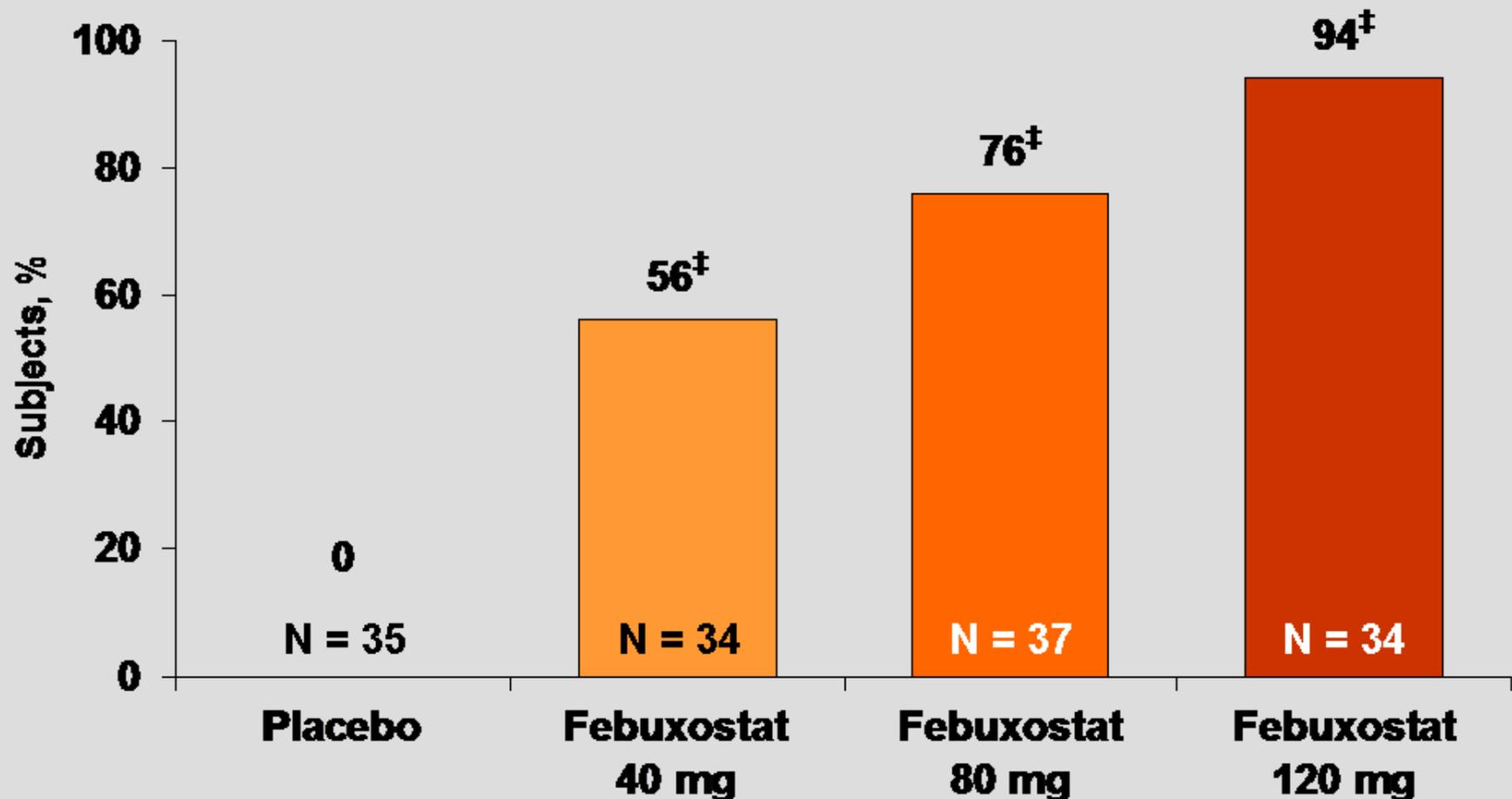
FACT (Febuxostat and Allopurinol Controlled Trial); APEX (Allopurinol and Placebo Evaluation of Febuxostat); CONFIRMS (Confirmation of Febuxostat in Reducing and Maintaining Serum Urate); FOCUS (Febuxostat Open Label Clinical Trial of Urate Lowering Safety and Efficacy); EXCEL (Febuxostat/Allopurinol Comparative Extension Long Term Study).

Phase 2 Dose-Ranging Study Design



sUA < 6 mg/dL at Final Visit

Phase 2 Dose Ranging Study

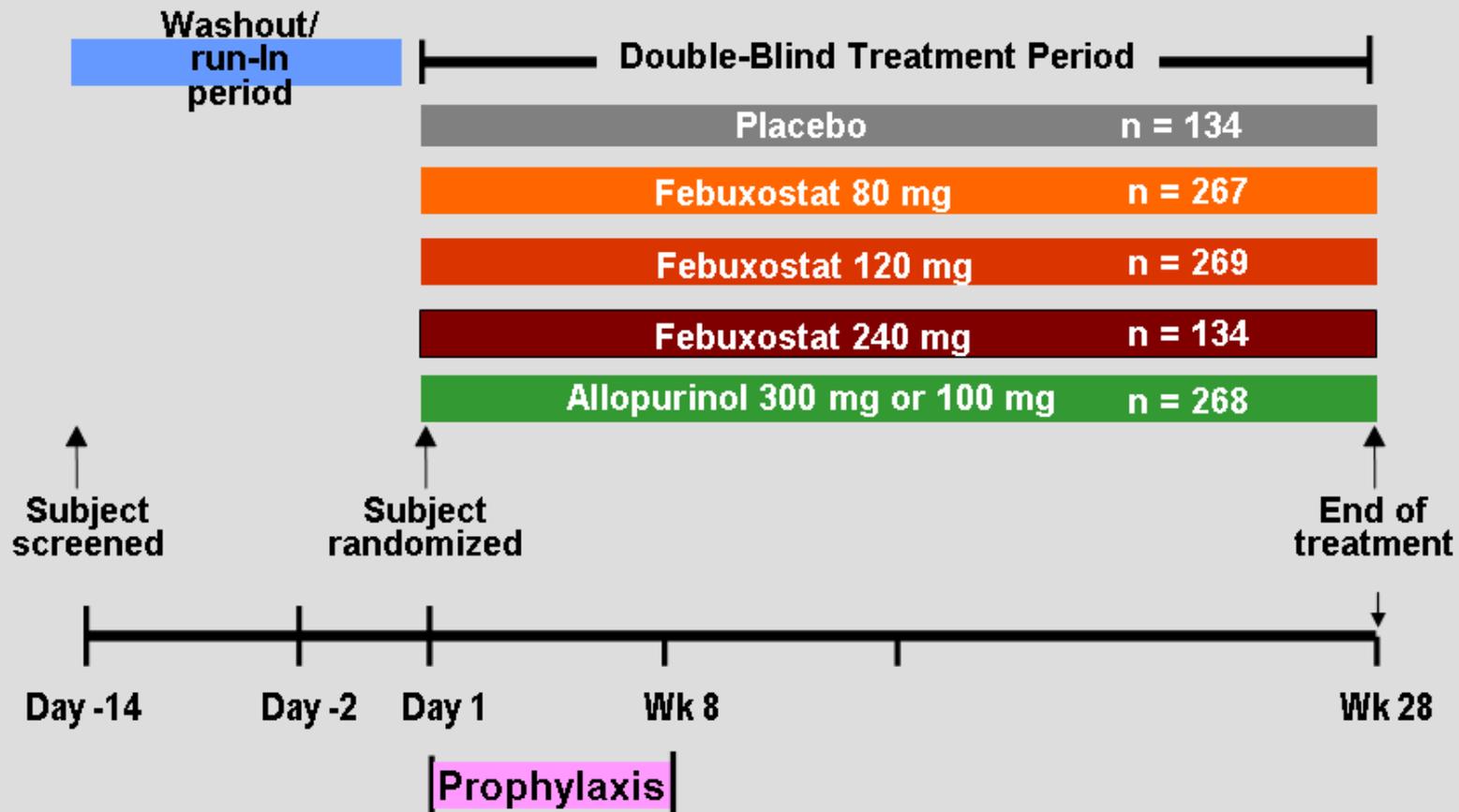


[‡] p < 0.001 vs placebo.

Becker, et al. *Arth Rheum.* 2005;52:916-923.

Phase 3 Double-Blind Study Design

APEX

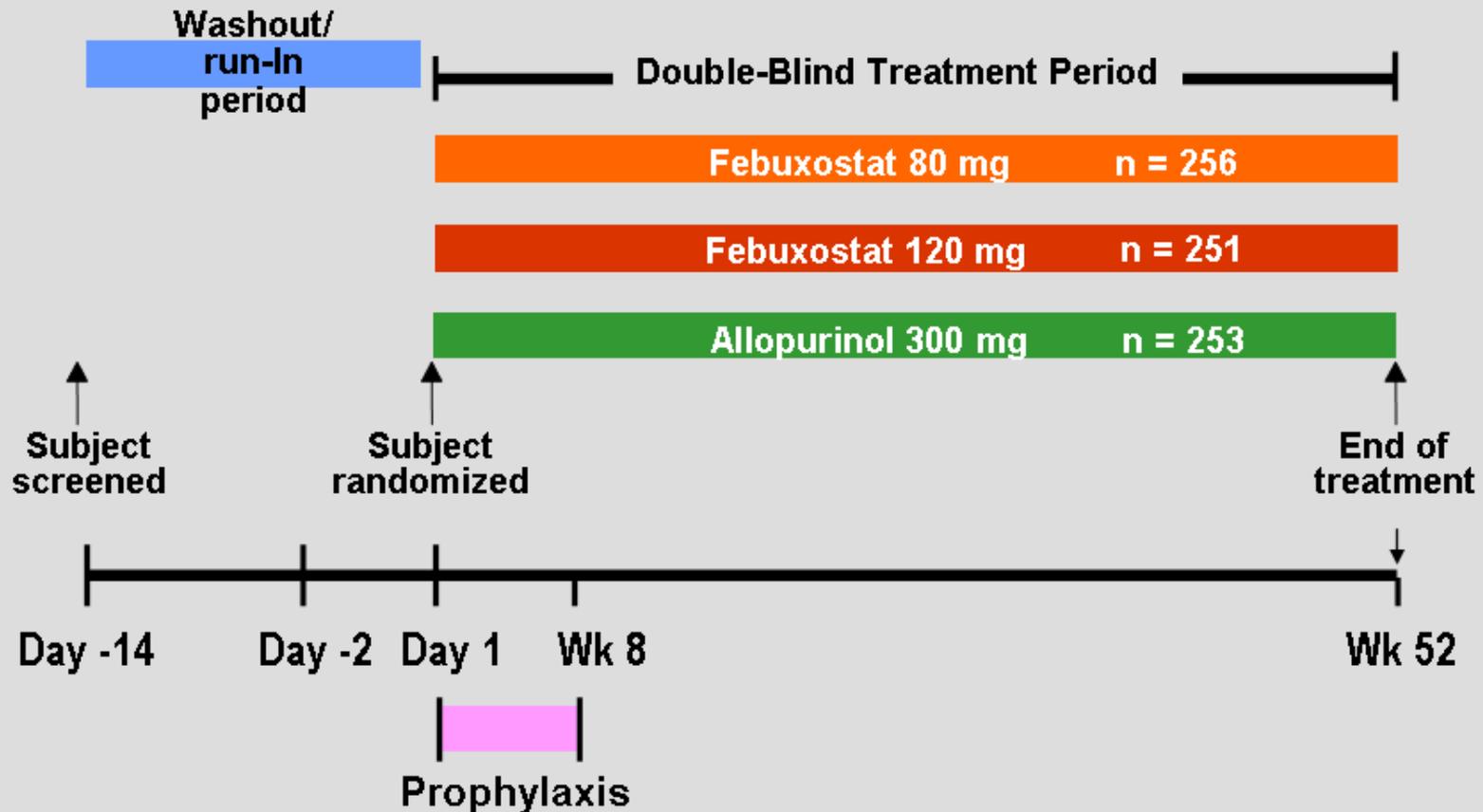


Allopurinol dose based on renal function.

n = 10 for 100 mg (serum creatinine > 1.5 mg/dL and ≤ 2.0 mg/dL).

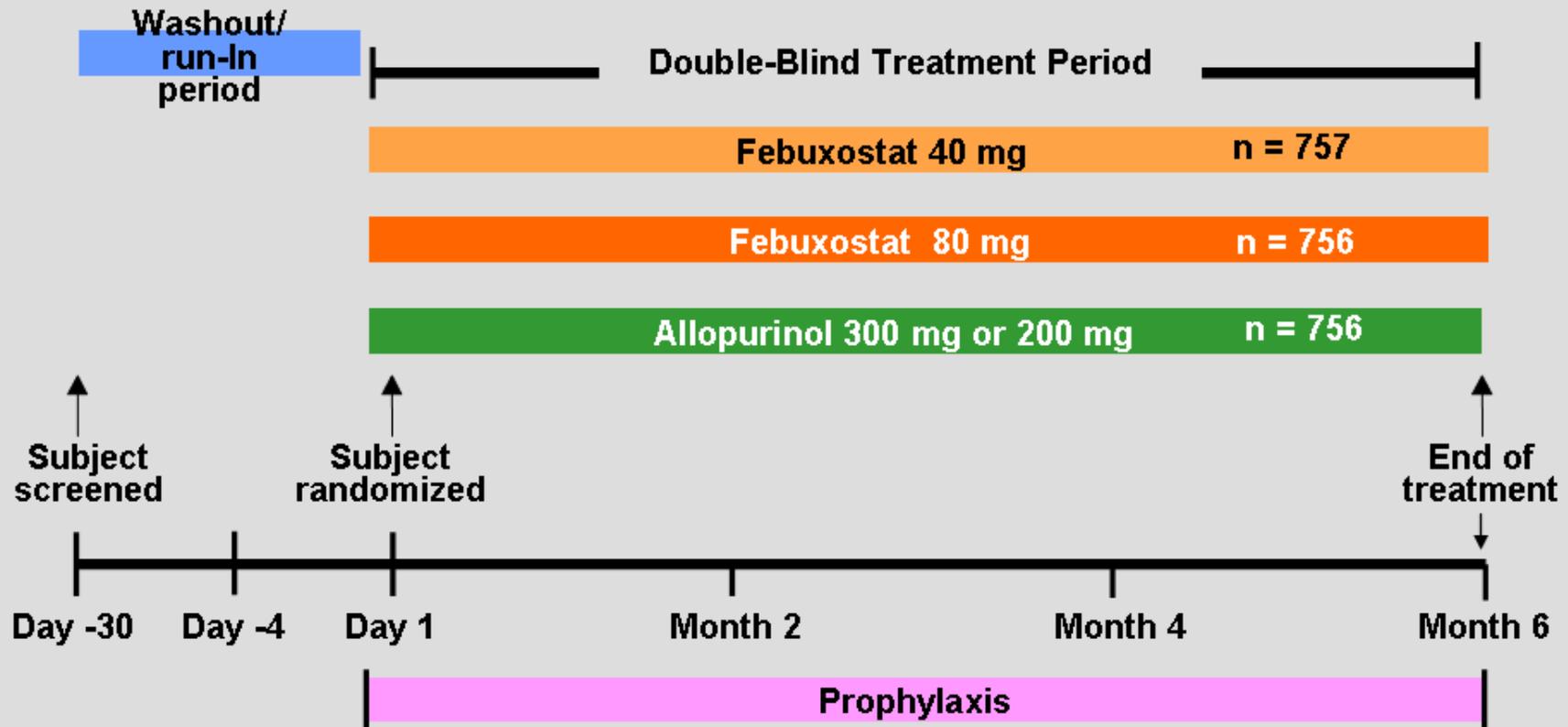
Phase 3 Double-Blind Study Design

FACT



Phase 3 Double-Blind Study Design

CONFIRMS



Allopurinol dose based on renal function.
n = 145 for 200 mg (estimated CrCL 30 to 59 mL/min).

Phase 3 Enrollment Criteria

APEX, FACT, CONFIRMS

Inclusion criteria

- ◆ Must meet ARA criteria¹ for gout
- ◆ Men and women ages 18 to 85 inclusive
- ◆ sUA level \geq 8 mg/dL at baseline

Exclusion criteria

- ◆ Secondary hyperuricemia
- ◆ Severe renal impairment
- ◆ Active liver disease
- ◆ Significant medical condition

1. Wallace, et al. *Arthritis Rheum.* 1977;20(3):895-900.

Demographics

APEX, FACT, CONFIRMS

	All subjects		
	APEX N = 1072	FACT N = 760	CONFIRMS N = 2269
Male, n (%)	1005 (94)	729 (96)	2141 (94)
Race, n (%)			
Caucasian	835 (78)	587 (77)	1863 (82)
Black	120 (11)	62 (8)	228 (10)
Asian	26 (2)	25 (3)	88 (4)
Mean age, yr	51.6	51.8	52.8
Mean BMI (kg/m ²)	32.7	32.5	32.8
Presence of tophi	299 (28)	186 (24)	478 (21)
Mean yr with gout	10.9	11.9	11.6
Mean baseline sUA (mg/dL)	9.9	9.8	9.6

Medical History

APEX, FACT, CONFIRMS

Medical condition	All subjects, n (%)		
	APEX N = 1072	FACT N = 760	CONFIRMS N = 2269
Renal function¹ CrCL (mL/min)			
30 - 59 (moderately impaired)	154 (14)	94 (12)	402 (18)
60 - 89 (mildly impaired)	377 (35)	295 (39)	1081 (48)
≥ 90 (normal)	541 (51)	371 (49)	786 (35)
Hypertension	502 (47)	331 (44)	1199 (53)
Hyperlipidemia	349 (33)	255 (34)	942 (42)
Diabetes	90 (8)	53 (7)	312 (14)
Atherosclerotic disease	145 (14)	75 (10)	261 (12)
Use of low-dose aspirin < 325 mg/day	183 (17)	128 (17)	405 (18)

1. Kidney Disease Outcome Quality Initiative; Chronic Kidney Disease.
Am J Kidney Dis. 2002;39:S46-S75.

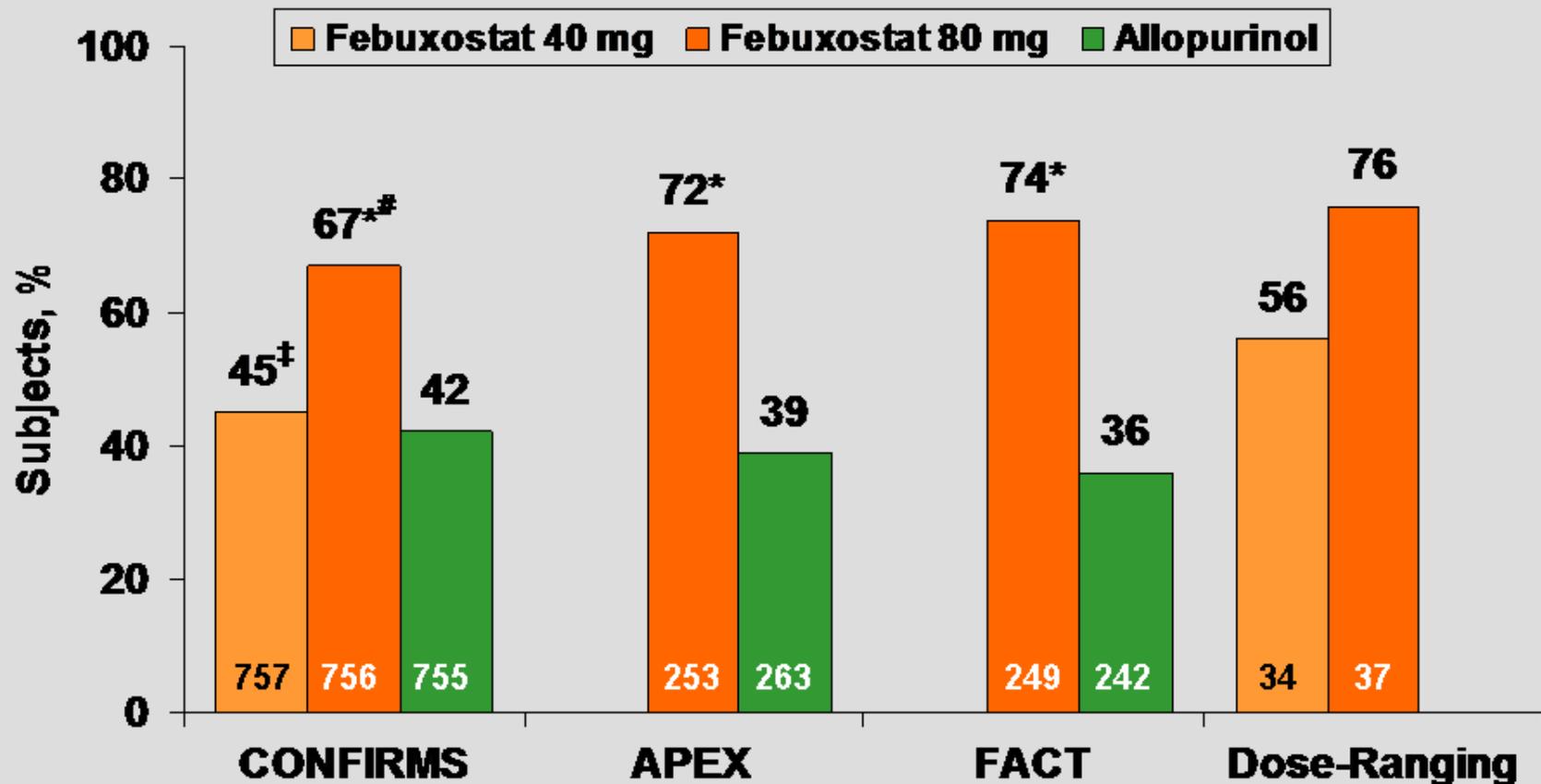
Phase 3 Efficacy Endpoints

APEX, FACT, CONFIRMS

- ◆ **Primary endpoint of proportion of subjects with sUA < 6 mg/dL at**
 - **FACT and APEX: last 3 visits**
 - **CONFIRMS: final visit**
- ◆ **Secondary endpoints**
 - **FACT and APEX:**
 - **sUA < 6 mg/dL at final visit**
 - **Proportion of subjects requiring treatment for gout flares**
 - **Percent reduction in primary tophus size**
 - **CONFIRMS: Proportion of subjects with renal impairment with sUA < 6 mg/dL at final visit**

sUA < 6 mg/dL at Final Visit

CONFIRMS, APEX, FACT, Dose-Ranging

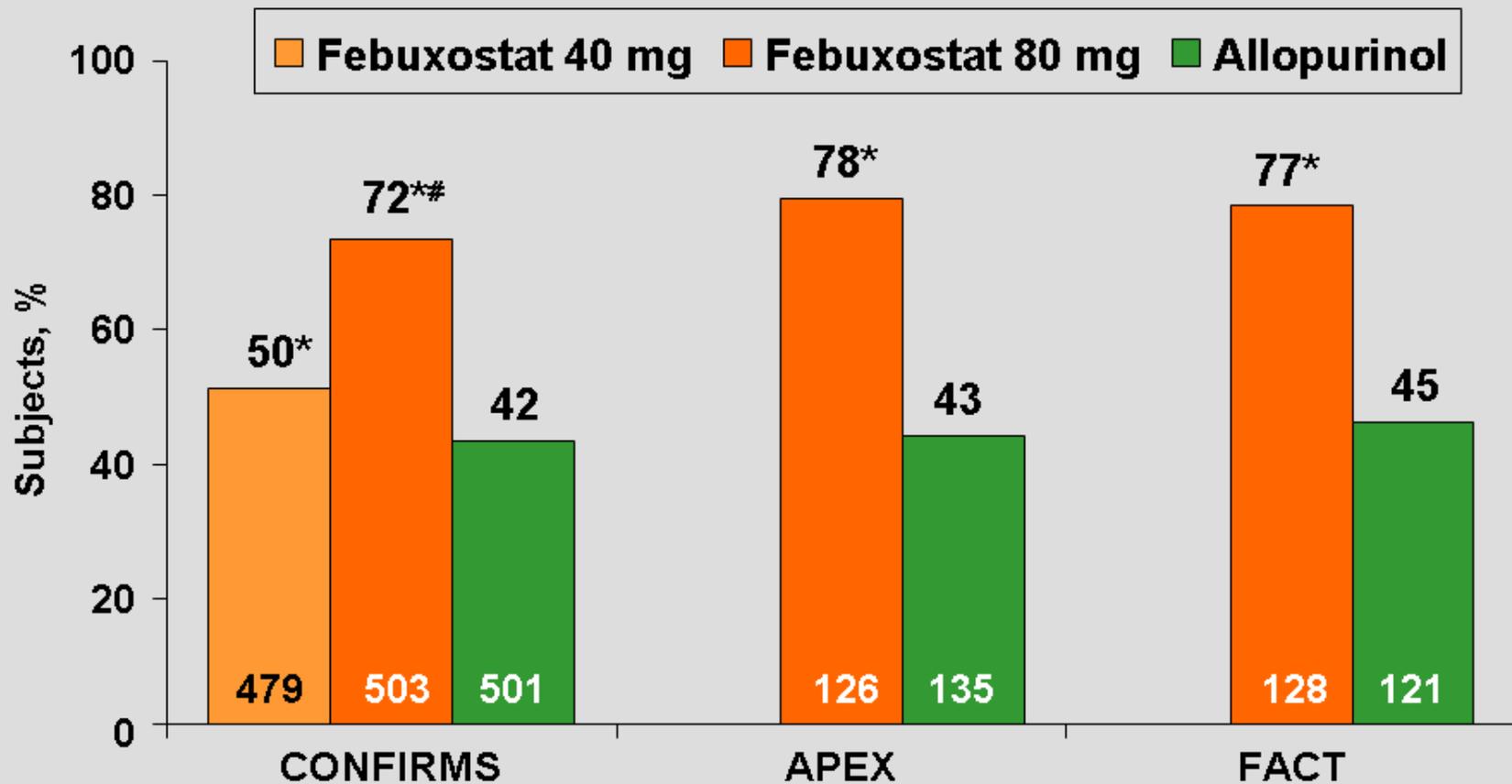


* p < 0.001 vs allopurinol.

p < 0.001 vs febuxostat 40 mg.

‡ Non-inferior to allopurinol.

sUA < 6 mg/dL at Final Visit Mild/Moderate Renal Impairment CONFIRMS, APEX, FACT



* $p < 0.05$ vs allopurinol.

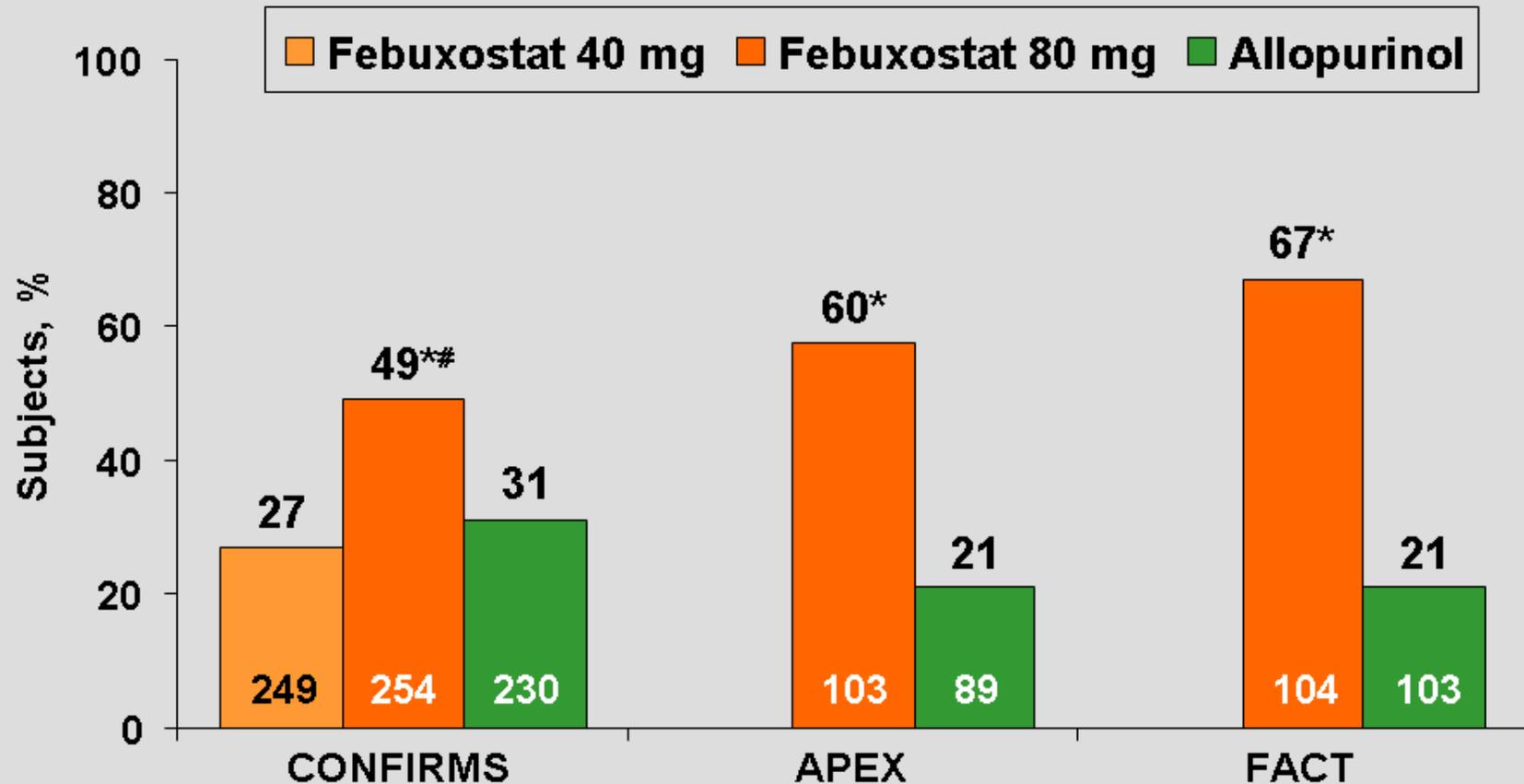
$p < 0.05$ vs febuxostat 40 mg.

CrCL > 30 to < 89 mL/min.

sUA < 6 mg/dL at Final Visit

Baseline sUA ≥ 10 mg/dL

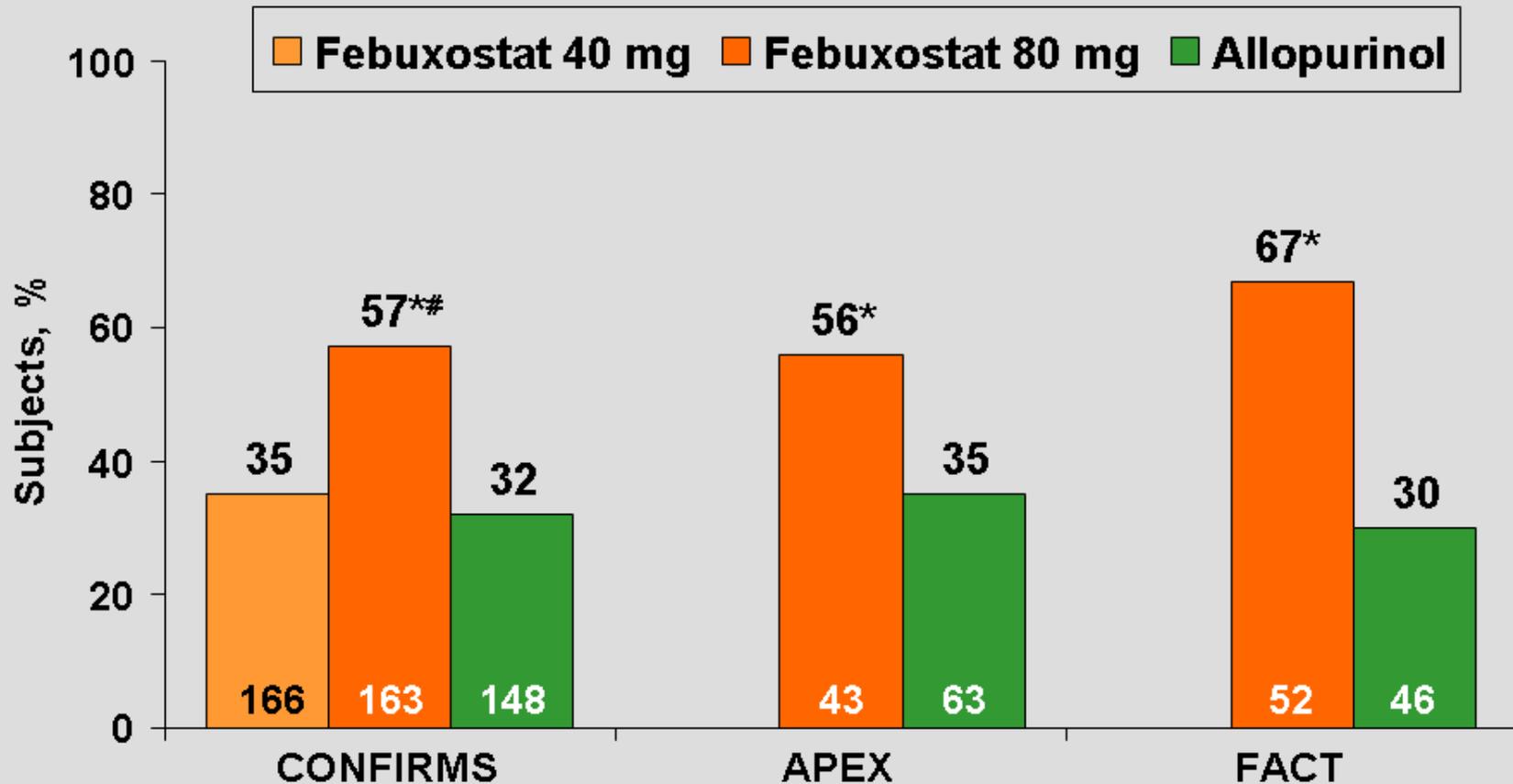
CONFIRMS, APEX, FACT



* p < 0.05 vs allopurinol.

p < 0.05 vs febuxostat 40 mg.

sUA < 6 mg/dL at Final Visit Subjects with Tophi at Baseline CONFIRMS, APEX, FACT



* $p < 0.05$ vs allopurinol.

$p < 0.05$ vs febuxostat 40 mg.

Treatment Initiated Gout Flares

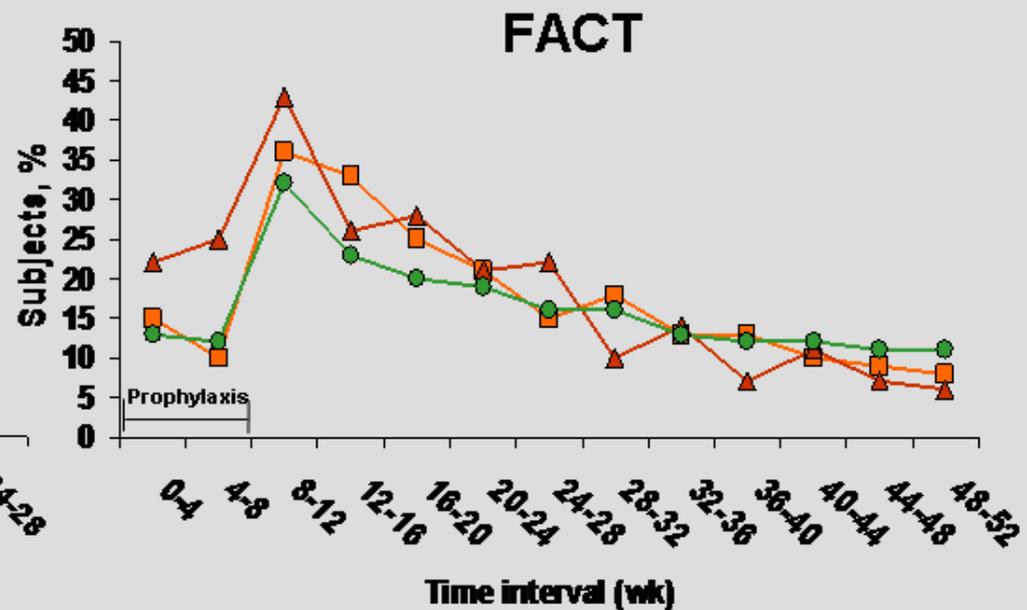
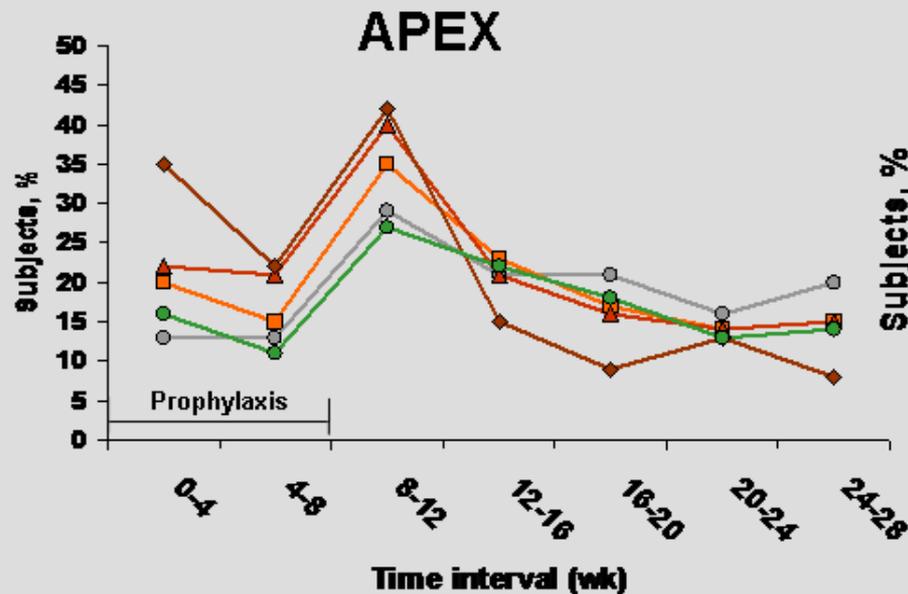
CONFIRMS, APEX, FACT

- ◆ Flares occurred in all treatment groups
- ◆ More flares with higher doses of febuxostat
- ◆ Flares gradually decreased over time
- ◆ Increase in flares after end of 8 wk prophylaxis in APEX and FACT
- ◆ Fewer flares in CONFIRMS when prophylaxis given for 6 months¹

Reduction in Gout Flares

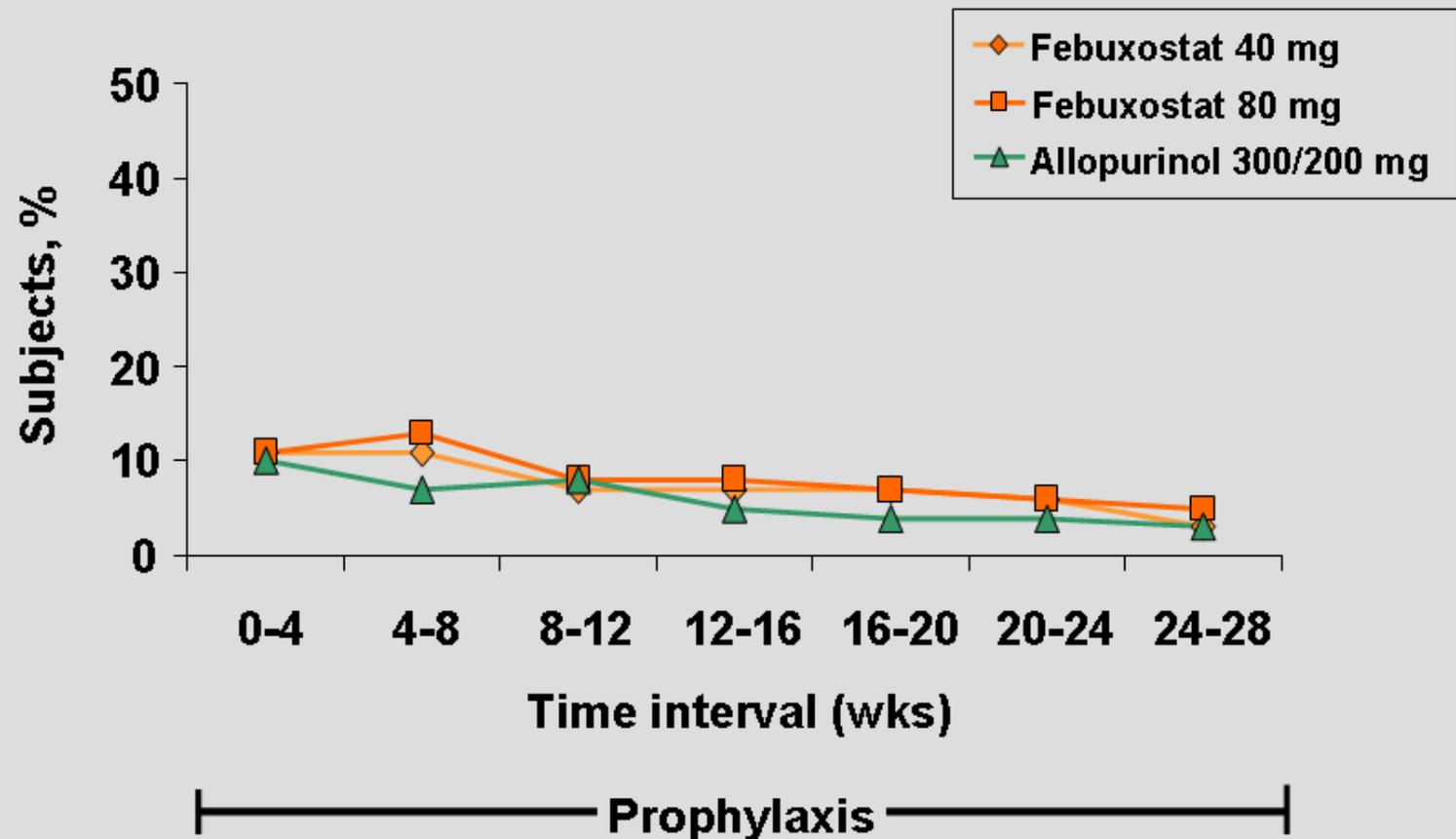
APEX, FACT

● Placebo
 ■ Febuxostat 80 mg
 ▲ Febuxostat 120 mg
 ◆ Febuxostat 240 mg
 ● Allopurinol



Reduction in Gout Flares

CONFIRMS



Reductions in Tophus Size

APEX, FACT

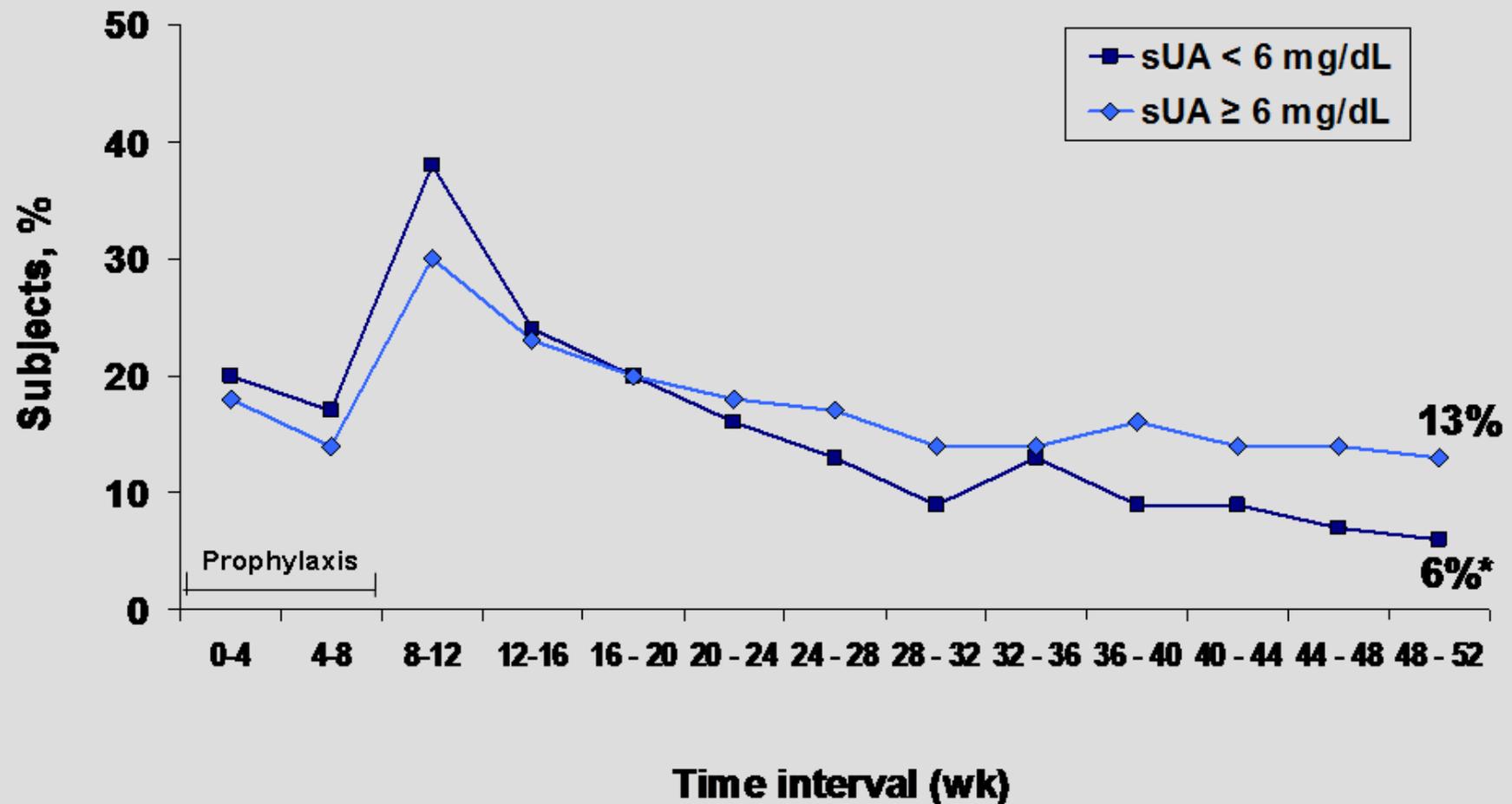
- ◆ ~ 20% of subjects with tophi
- ◆ Reductions in tophus size noted in all treatment groups
 - 30 to 50% after 6 months (n = 239)
 - 50 to 80% after 1 yr (n = 88)

Reductions in Gout Flares and Tophus Size by sUA (< 6 vs \geq 6 mg/dL)

APEX, FACT

- ◆ Grouped subjects by average postbaseline sUA level (< 6 vs \geq 6 mg/dL) regardless of treatment
- ◆ Summarized proportion of subjects with flares and percent reduction in tophus size
- ◆ Fewer flares with sUA < 6 mg/dL by Wks 20 to 24 interval; difference statistically significant during Wks 48 to 52 of FACT study
- ◆ Larger reduction in tophus size also noted with sUA < 6 mg/dL

Reductions in Gout Flares by sUA (< 6 vs \geq 6 mg/dL) APEX, FACT



* $p < 0.05$

Long-Term Open-Label Extension Studies

Phase 2
Trials

Dose Ranging
n = 153
1 mo



FOCUS
Open-Label
Extension Study
n = 116
5 yr

Phase 3
Trials

APEX
n = 1072
6 mo



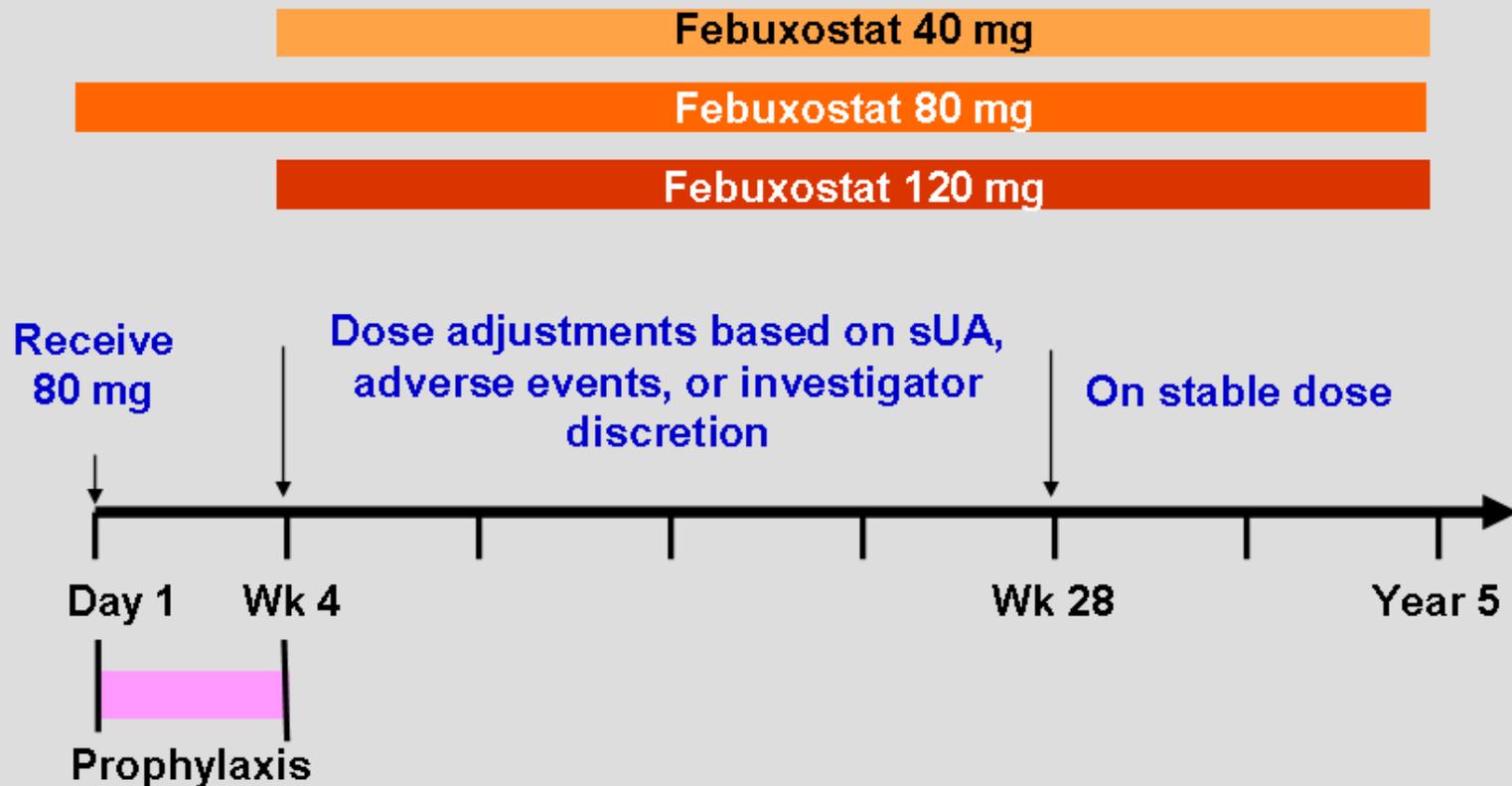
EXCEL
Open-Label
Extension Study
n = 1086
3 yr

FACT
n = 760
1 yr

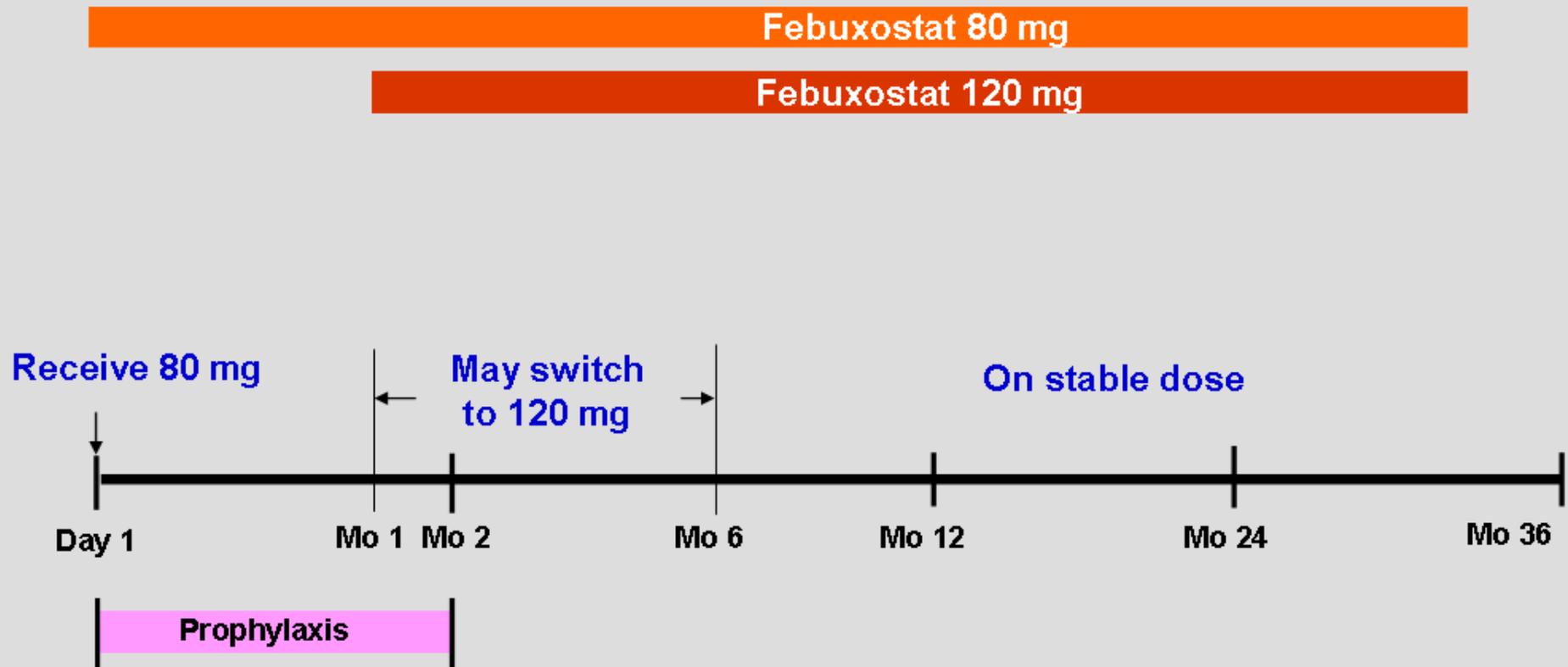


Phase 2 Long-Term Open-Label Extension Study Design

FOCUS



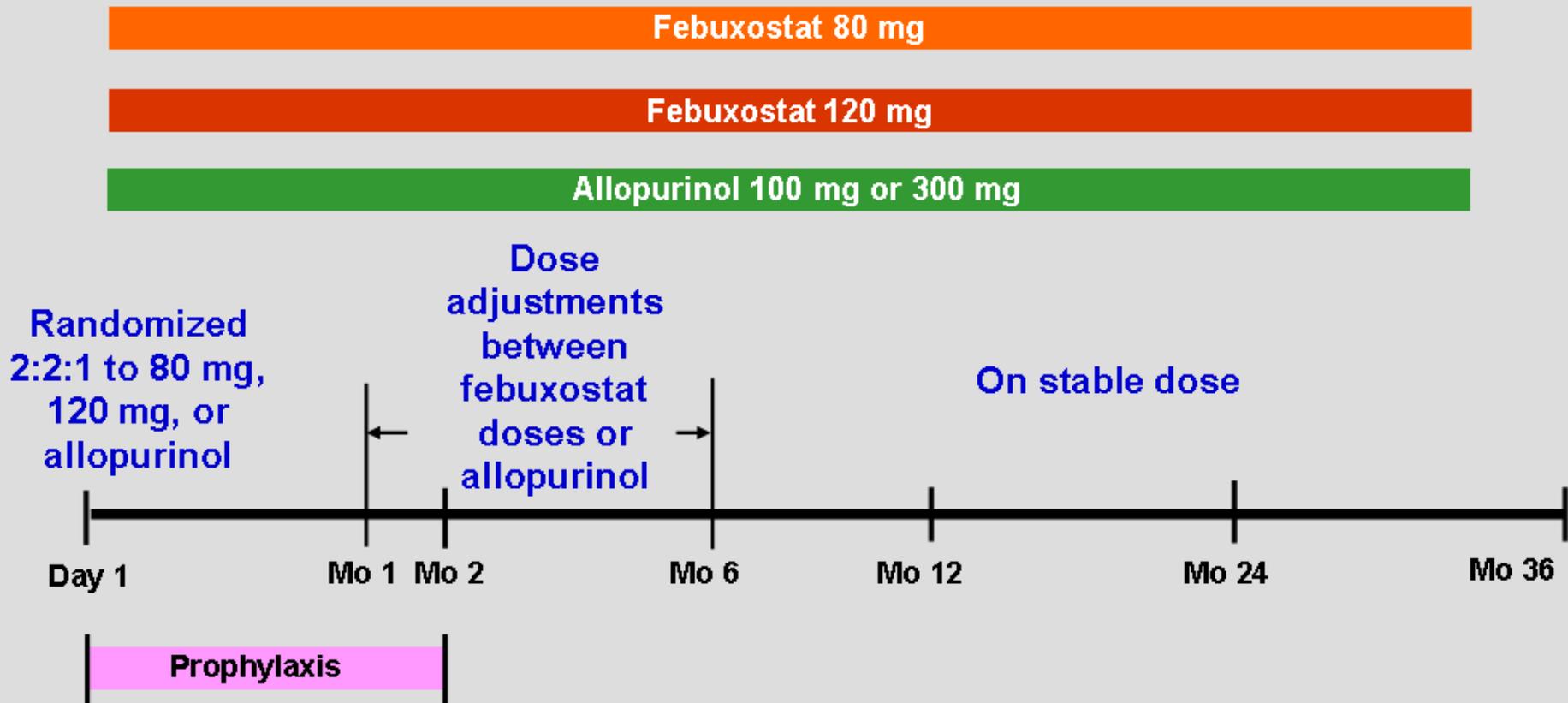
Phase 3 Long-Term Open-Label Extension Study Design EXCEL (Original Protocol)



351 subjects enrolled under original protocol.

Phase 3 Long-Term Open-Label Extension Study Design

EXCEL (Amended Protocol)

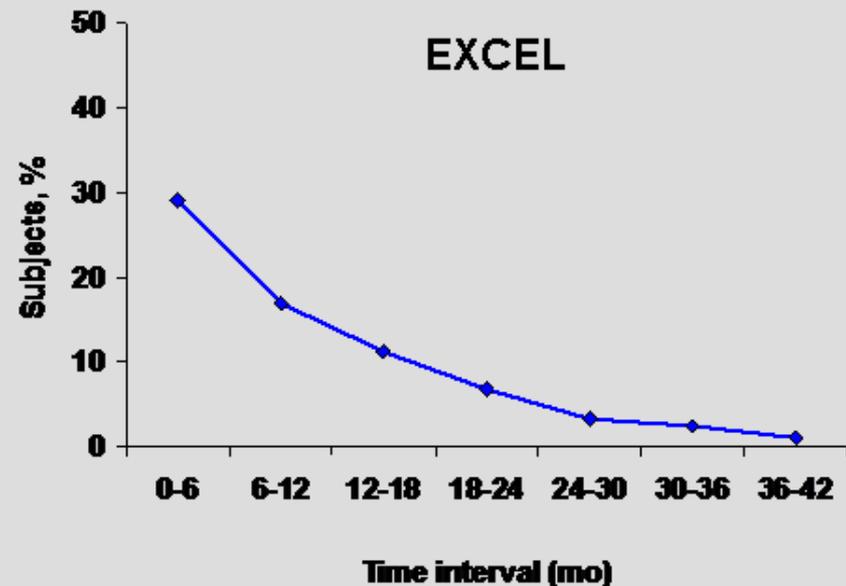
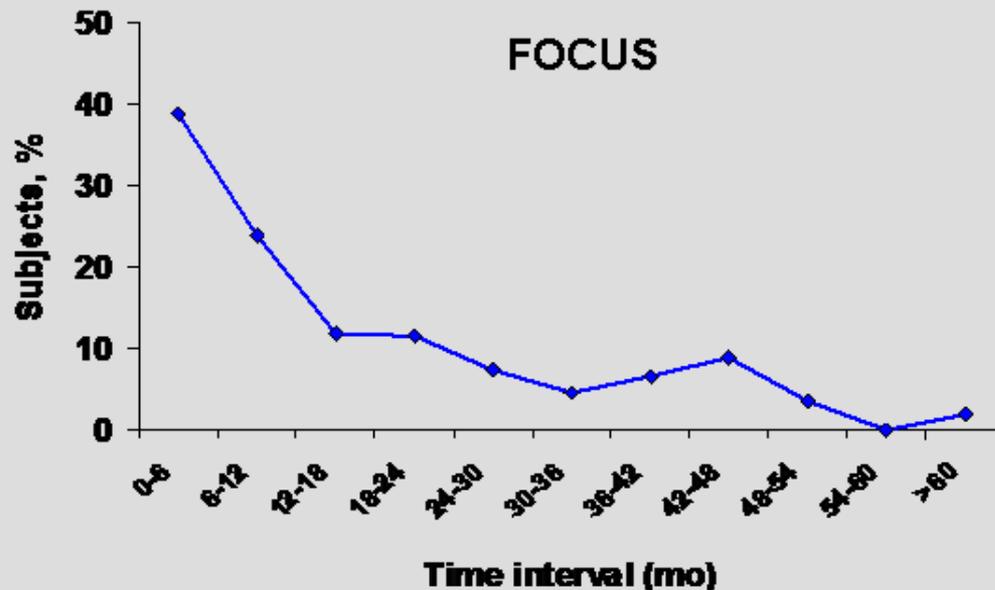


735 subjects enrolled under amended protocol.

Long-Term Open-Label Extension Studies

FOCUS, EXCEL

- ◆ 80% maintained sUA < 6 mg/dL on febuxostat
- ◆ Majority remained on 80 mg
- ◆ ~ 50% switched from allopurinol
- ◆ Tophi resolved in ~ 50% of subjects after 2 yrs
- ◆ Reduction of gout flares over time



Efficacy Conclusions

- ◆ Febuxostat 40 mg and 80 mg effectively lower and maintain sUA < 6 mg/dL
- ◆ 80 mg superior to both 40 mg and allopurinol, including in subjects with high sUA or tophi
- ◆ Both 40 mg and 80 mg effective in subjects with renal impairment without dose adjustment
- ◆ Maintenance of sUA < 6 mg/dL demonstrated decreases in gout flares and tophi resolution

Safety

Safety Agenda

- ◆ Exposure
- ◆ Discontinuations
- ◆ AEs and SAEs
- ◆ Other Areas of Interest
 - Cardiovascular
 - Renal
 - Hepatic
 - Hypersensitivity Reactions
- ◆ Additional Safety Information
- ◆ Conclusion

Safety Overview

- ◆ 4072 subjects exposed to febuxostat doses of 10 mg to 300 mg
 - Greatest exposure to febuxostat 40, 80, and 120 mg
- ◆ Subjects enrolled representative of gout population
 - Multiple CV comorbidities and risk factors
 - > 50% of population with renal impairment
- ◆ Long-term treatment up to 5 yrs
- ◆ Well-characterized safety profile of febuxostat

Safety Groups

- ◆ **Phase 3 Randomized-Controlled Studies**
 - **APEX, FACT, & CONFIRMS**
 - **Results in percent of subjects**
- ◆ **Long-Term Extension Studies**
 - **Phase 2 FOCUS and Phase 3 EXCEL**
 - **Results in 100 patient-yr**

Summary of Exposure

Phase 3 Randomized-Controlled Studies

	Placebo	Febuxostat mg				Allopurinol
		40	80	120	240	
Subjects, n	134	757	1279	520	134	1277
Mean exposure, days	163	166	184	214	147	192
Maximum, days	210	233	385	394	212	389

Summary of Exposure

Long-Term Extension Studies‡

	Febuxostat mg				Allopurinol
	40	80	120	Total	
Subjects, n	12	917	524	1143	178
Patient-yr	38	1746	878	2661	172
Mean exposure, days	1146	695	612	850	353
Maximum, days	1935	2088	2038	2095	1099

‡ Treatment and dose changes based on sUA levels, AEs, and investigator discretion (per protocol for first 6 months of studies).

Discontinuations

Phase 3 Randomized-Controlled Studies

	Subjects, n (%)					Allopurinol N = 1277
	Placebo	Febuxostat mg				
	N = 134	40 N = 757	80 N = 1279	120 N = 520	240 N = 134	
Total discontinued	33 (24.6)	125 (16.5)	339 (26.5)	167 (32.1)	48 (35.8)	258 (20.2)
Most common reasons						
Adverse event	5 (3.7)	49 (6.5)	95 (7.4)	39 (7.5)	11 (8.2)	90 (7.0)
Lost to follow-up	10 (7.5)	28 (3.7)	77 (6.0)	35 (6.7)	9 (6.7)	66 (5.2)
Personal reason(s)	9 (6.7)	12 (1.6)	59 (4.6)	29 (5.6)	9 (6.7)	31 (2.4)
Other‡	3 (2.2)	8 (1.1)	34 (2.7)	22 (4.2)	6 (4.5)	30 (2.3)
Gout flare	0	3 (0.4)	30 (2.3)	34 (6.5)	8 (6.0)	12 (0.9)

‡ “Other” included withdrew consent, noncompliance, and lack of efficacy.

Treatment Emergent AEs ($\geq 7\%$ any Group)

Phase 3 Randomized-Controlled Studies

MedDRA High Level Term	Placebo N = 134	Subjects, n (%)				Allopurinol N = 1277
		40 N = 757	80 N = 1279	120 N = 520	240 N = 134	
Total subjects with ≥ 1 AE	97 (72)	429 (57)	797 (62)	372 (72)	98 (73)	848 (66)
Upper respiratory tract infections	21 (16)	71 (9)	169 (13)	103 (20)	27 (20)	182 (14)
Musculoskeletal and connective tissue signs and symptoms	14 (10)	43 (6)	99 (8)	72 (14)	14 (10)	99 (8)
Diarrhea (excl infective)	12 (9)	45 (6)	94 (7)	45 (9)	20 (15)	91 (7)
Liver function analyses	3 (2)	63 (8)	82 (6)	26 (5)	6 (4)	77 (6)
Joint related signs and symptoms	6 (4)	31 (4)	81 (6)	43 (8)	7 (5)	77 (6)
Headaches	7 (5)	21 (3)	53 (4)	38 (7)	12 (9)	62 (5)

Treatment-Emergent Serious AEs ($\geq 0.3\%$ any Group)

Phase 3 Randomized-Controlled Studies

MedDRA High Level Term	Subjects, n (%)					Allopurinol N = 1277
	Placebo N = 134	Febuxostat mg				
		40 N = 757	80 N = 1279	120 N = 520	240 N = 134	
Total subjects with ≥ 1 SAE	2 (1.5)	19 (2.5)	49 (3.8)	28 (5.4)	5 (3.7)	56 (4.4)
Ischemic coronary artery disorders [‡]	0	1 (0.1)	6 (0.5)	4 (0.8)	0	3 (0.2)
Pain and discomfort	0	1 (0.1)	4 (0.3)	1 (0.2)	0	2 (0.2)
Heart failure	0	2 (0.3)	3 (0.2)	1 (0.2)	0	1 (< 0.1)
Coronary artery disorders [#]	1 (0.7)	2 (0.3)	2 (0.2)	0	0	6 (0.5)
Intestinal ulcers and perforation	0	2 (0.3)	1 (< 0.1)	1 (0.2)	0	1 (< 0.1)
Abdominal and gastrointestinal infections	0	2 (0.3)	0	1 (0.2)	0	4 (0.3)
Disturbances in consciousness [§]	0	0	0	1 (0.2)	0	4 (0.3)
Cholecystitis and cholelithiasis	0	0	0	0	0	4 (0.3)

[‡] Preferred Terms: Angina pectoris, unstable angina, myocardial infarction, acute myocardial infarction, acute coronary syndrome.

[#] Preferred Terms: Arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery atherosclerosis.

[§] Preferred Terms: Loss of consciousness, syncope.

Treatment-Emergent AEs Leading to Discontinuations ($\geq 0.8\%$ any Group)

Phase 3 Randomized-Controlled Studies

MedDRA High Level Term	Placebo N = 134	Subjects, n (%)				Allopurinol N = 1277
		40 N = 757	80 N = 1279	120 N = 520	240 N = 134	
Total subjects with ≥ 1 AE	7 (5.2)	47 (6.2)	98 (7.7)	44 (8.5)	13 (9.7)	87 (6.8)
Liver function analyses	0	14 (1.8)	18 (1.4)	10 (1.9)	0	12 (0.9)
Diarrhea (excl infective)	0	6 (0.8)	10 (0.8)	1 (0.2)	4 (3.0)	9 (0.7)
Rashes, eruptions and exanthems	1 (0.7)	2 (0.3)	7 (0.5)	4 (0.8)	0	3 (0.2)
Nausea and vomiting symptoms	0	3 (0.4)	3 (0.2)	0	4 (3.0)	3 (0.2)
Neurological signs and symptoms (dizziness)	0	0	2 (0.2)	0	3 (2.2)	1 (< 0.1)

Discontinuations due to LFTs were associated with low levels of transaminase elevations.

All-Cause Mortality

Phase 3 Randomized-Controlled Studies

Cause of Death	Subjects, n					Total	Allopurinol
	Placebo	Febuxostat mg					
		40	80	120	240		
	N = 134	N = 757	N = 1279	N = 520	N = 134	N = 2690	N = 1277
Total deaths, n (%)	0	1 (0.13)	3 (0.23)	2 (0.38)	0	6 (0.22)	3 (0.23)
Retroperitoneal hemorrhage			1			1	
Respiratory failure			1			1	
Respiratory failure/ anoxic encephalopathy				1		1	
Colon cancer				1		1	
Anaphylactic reaction [‡]		1				1	
Brain edema/COPD			1			1	
Hypertensive heart disease							1
Sudden death							1
Lung adenocarcinoma/ pneumonia necrotizing/ sepsis							1

[‡] Due to multiple ant bites.

During screening there was 1 additional death (myocardial infarction).

Treatment-Emergent AEs, SAEs, and Discontinuations

Long-Term Extension Studies

- ◆ Incidence rates for AEs, SAEs and discontinuations due to AEs did not increase over time
- ◆ Types of AEs and SAEs in the long-term extension studies were similar to those in the Phase 3 randomized-controlled studies
- ◆ For discontinuations due to AEs, there were no trends based on timing or type of event

All-Cause Mortality

Subjects, n

Cause of death	Randomized-controlled studies						Long-term studies	
	Placebo	Febuxostat mg				Allopurinol	Febuxostat mg	
	N=134 PY=60	40 N=757 PY=343	80 N=1279 PY=644	120 N=520 PY=305	240 N=134 PY=54	Total N=2690 PY=1346	N=1277 PY=671	Total N=1143 PY=2661
Total deaths, n [n per 100-PY]	0	1 [0.29]	3 [0.47]	2 [0.66]	0	6 [0.45]	3 [0.45]	10 [0.38]
Anaphylactic reaction [‡]		1				1		
Brain edema/COPD			1			1		
Cancer [#]				1		1	1	2
CHF, respiratory failure, cardio-respiratory arrest								1
Hypertensive heart disease							1	
Myocardial infarction								5
Retroperitoneal hemorrhage			1			1		1
Respiratory failure			1			1		
Respiratory failure/anoxic encephalopathy				1		1		
Sepsis								1
Sudden death							1	

‡ Due to multiple ant bites. # Bile duct, colon, lung adenocarcinoma. During screening there was 1 additional death (myocardial infarction).
No death on allopurinol in Long-Term studies (PY = 172)

Safety Agenda

- ◆ Exposure
- ◆ Discontinuations
- ◆ AEs and SAEs
- ◆ **Other Areas of Interest**
 - Cardiovascular
 - Renal
 - Hepatic
 - Hypersensitivity Reactions
- ◆ **Additional Safety Information**
- ◆ **Conclusion**

Safety Agenda

- ◆ Exposure
- ◆ Discontinuations
- ◆ AEs and SAEs
- ◆ **Other Areas of Interest**
 - Cardiovascular
 - **Renal**
 - **Hepatic**
 - **Hypersensitivity Reactions**
- ◆ **Additional Safety Information**
- ◆ **Conclusion**

Renal Laboratory Analyses

Serum Creatinine

Phase 3 Randomized-Controlled Studies

	Subjects, % (n/N)					
	Placebo	Febuxostat mg				Allopurinol
		40	80	120	240	
> 30% increase from baseline and > ULN ^{1,2}	7 (9/129)	3 (24/711)	3 (36/1205)	5 (23/506)	6 (7/127)	3 (36/1200)

1. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis.* 2004;43:S101-106.

2. Bakris and Weir. *Arch Intern Med.* 2000;160:685-693.

Renal Laboratory Analyses

Serum Creatinine

Long-Term Extension Studies

	Subjects, [rate per 100 PY]				Allopurinol
	Febuxostat mg			Total	
	40	80	120		
	N = 12 PY = 37.7	N = 898 PY = 1744.8	N = 506 PY = 877.0	N = 1121 PY = 2660.2	N = 173 PY = 172.0
> 30% increase from baseline and > ULN ^{1,2}	1 [2.7]	87 [5.0]	34 [3.9]	117 [4.4]	7 [4.1]

1. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis.* 2004;43:S101-106.

2. Bakris and Weir. *Arch Intern Med.* 2000;160:685-693.

Treatment-Emergent AEs by Renal Function

CONFIRMS

- ◆ Overall incidence of AEs similar regardless of renal function
- ◆ Small increase in renal AEs in subjects with moderate impairment
- ◆ Similar findings across all treatment groups
- ◆ Same pattern was observed in the combined Phase 3 randomized-controlled studies

Hepatic Laboratory Analyses

Phase 3 Randomized-Controlled Studies

Laboratory Variable	Subjects, n (%)					Allopurinol N = 1200
	Placebo	Febuxostat mg				
	N = 129	40 N = 711	80 N = 1204	120 N = 506	240 N = 127	
ALT						
≥ 3 - < 5 × ULN	1 (< 1)	20 (3)	36 (3)	23 (5)	1 (< 1)	17 (1)
≥ 5 - < 10 × ULN	0	3 (< 1)	3 (< 1)	1 (< 1)	1 (< 1)	4 (< 1)
≥ 10 × ULN	0	0	0	0	1 (< 1)	2 (< 1)
AST						
≥ 3 - < 5 × ULN	0	7 (< 1)	15 (1)	11 (2)	0	16 (1)
≥ 5 - < 10 × ULN	1 (< 1)	3 (< 1)	1 (< 1)	1 (< 1)	2 (2)	5 (< 1)
≥ 10 × ULN	0	0	0	1 (< 1)	0	3 (< 1)
ALT & AST concurrently						
≥ 3 × ULN	0	8 (1)	10 (< 1)	8 (2)	2 (2)	12 (1)
Total bilirubin						
≥ 2 × ULN	1 (< 1)	1 (< 1)	3 (< 1)	4 (< 1)	2 (2)	8 (< 1)
ALT &/or AST ≥ 3 × ULN with concurrent bilirubin ≥ 2 × ULN	0	0	0	0	1 (< 1)	1 (< 1)

Hepatic Laboratory Analyses

Long-Term Extension Studies

Laboratory Variable	Subjects [rate per 100 PY]				Allopurinol N = 173 PY=172.0
	Febuxostat mg			Total N = 1120 PY=2659.8	
	40 N = 12 PY=37.7	80 N = 898 PY=1744.8	120 N = 505 PY=876.7		
ALT					
≥ 3 - < 5 × ULN	1 [2.7]	31 [1.8]	17 [1.9]	46 [1.7]	2 [1.2]
≥ 5 - < 10 × ULN	0	3 [0.2]	2 [0.2]	5 [0.2]	2 [1.2]
≥ 10 × ULN	0	2 [0.1]	1 [0.1]	3 [0.1]	0
AST					
≥ 3 - < 5 × ULN	0	16 [0.9]	13 [1.5]	27 [1.0]	0
≥ 5 - < 10 × ULN	0	3 [0.2]	1 [0.1]	4 [0.2]	3 [1.7]
≥ 10 × ULN	0	1 [0.1]	1 [0.1]	2 [0.1]	0
ALT & AST concurrently ≥ 3 × ULN	0	13 [0.7]	9 [1.0]	21 [0.8]	3 [1.7]
Total bilirubin ≥ 2 × ULN	0	7 [0.4]	2 [0.2]	9 [0.3]	0
ALT &/or AST ≥ 3 × ULN with concurrent bilirubin ≥ 2 × ULN	0	2 [0.1]	0	2 [0.1]	0

Summary of Hepatic (ALT and/or AST $\geq 3 \times$ ULN^{CS-21} and Concurrent Total Bilirubin $\geq 2.0 \times$ ULN

Phase 3 Randomized-Controlled Studies and Long-Term Extension Studies

Gender/Age	Treatment group, mg	Comments	Causality
Male/61	Febuxostat 240	Cholelithiasis during RCT. Cholecystectomy during LTE study; no recurrence of elevations	Unrelated
Male/61	Allopurinol 300	Cholelithiasis; cholecystectomy performed. Completed RCT and LTE study on febuxostat with no recurrence	Unrelated
Female/73	Febuxostat 80	Bile duct stone on CSD 42. ALT and AST returned to baseline on CSD 58	Unrelated
Male/57	Febuxostat 80	Fatal bile duct cancer CSD=1550 [167 days post-dosing]	Unrelated

Hypersensitivity Reactions

Phase 3 Randomized-Controlled Studies and Long-Term Extension Studies

- ◆ Literature shows rare occurrences of allopurinol hypersensitivity or severe rash can be fatal (< 1 in 1000 patients)¹
- ◆ One serious AE on allopurinol during study
 - Exfoliative rash with desquamation of skin; palms of hands and soles of feet with loss of pigmentation
- ◆ No serious rash or hypersensitivity reaction associated with febuxostat

1. Arellano and Sacristan. *Ann Pharmacother.* 1993;27:337-343.

Safety Agenda

- ◆ Exposure
- ◆ Discontinuations
- ◆ AEs and SAEs
- ◆ Other Areas of Interest
 - Cardiovascular
 - Renal
 - Hepatic
 - Hypersensitivity Reactions
- ◆ **Additional Safety Information**
- ◆ **Conclusion**

Additional Safety Information

- ◆ **Other systems/events (lipid metabolism, thyroid, hematology, neurological, GI) evaluated, and no potential risks associated with febuxostat were identified**
- ◆ **No clinically important effects observed in laboratory evaluations (hematology, chemistry, thyroid, or urinalysis)**
- ◆ **Stable measures of renal function associated with maintenance of sUA < 6 mg/dL over 4-yr period¹**

1. Whelton, et al. Abstract 450 (L7). ACR/ARHP Annual Scientific meeting 2008.

General Safety Summary

- ◆ **Subjects reflective of gout population with comorbid conditions**
- ◆ **No change in nature of AEs or increase in frequency over time**
- ◆ **Overall incidence of AEs similar across treatment groups, regardless of renal function**
- ◆ **Hepatic effect similar to allopurinol**
- ◆ **One serious skin reaction associated with allopurinol**

Phase 4 Commitment

Phase 4 Clinical Outcomes Study: Gout Flares

- ◆ A Phase 4, randomized, multi-center study comparing the efficacy and safety of febuxostat to allopurinol in the prevention of gout flares in subjects with gout
 - 3000 to 5000 subjects, 2 to 3 yrs
 - Febuxostat and allopurinol treatment groups (1:1)
 - In addition to impact on gout flares, all aspects of safety will be evaluated to refine label
- ◆ Study design to be developed with FDA

Evaluation of Adjudicated Cardiovascular Events in the Febuxostat Program

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Director, Clinical Trials Unit
University of Connecticut School of Medicine
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CV Regulatory History – 2005

Adjudicated APTC CV Events

APEX and FACT

	Subjects % (n/N)				
	Placebo	Febuxostat mg			Allopurinol
		80	120	240	
APEX	0 (0/134)	0.37 (1/267)	0.37 (1/269)	0 (0/134)	0 (0/268)
FACT	–	1.17 (3/256)	0.80 (2/251)	–	0.40 (1/253)
Total	0 (0/134)	0.76 (4/523)	0.58 (3/520)	0 (0/134)	0.19 (1/521)
95% CI	0.00-2.72	0.21-1.95	0.12-1.68	0.00-2.72	< 0.01-1.07

Note: Small apparent imbalance in APTC events in febuxostat compared to allopurinol. Submitted in NDA Amendment (February 2006).

Evaluation of Cardiovascular Safety 2005 – Present

- ◆ **Review of Non-clinical CV Safety**
- ◆ **Effects on CV Risk Factors**
- ◆ **Cardiovascular Burden in Gout Patients**
- ◆ **Blinded Adjudication Process**
- ◆ **Results of Adjudicated APTC and Non-APTC Events in Clinical Program**

Non-Clinical CV Safety Summary

- ◆ **Xanthine Oxidase inhibition is not known to cause CV adverse effects**
- ◆ **Non-clinical studies identified no biological mechanism for potential CV adverse effects**
 - In-vitro studies show no deleterious effect on various cardiac ion channels and action-potential parameters
 - Febuxostat has no significant effects on coagulation and platelet function
 - No detrimental effects have been observed in animal models of hypertension, metabolic syndrome, myocardial infarction, myocardial hypertrophy, heart failure, and chronic renal diseases

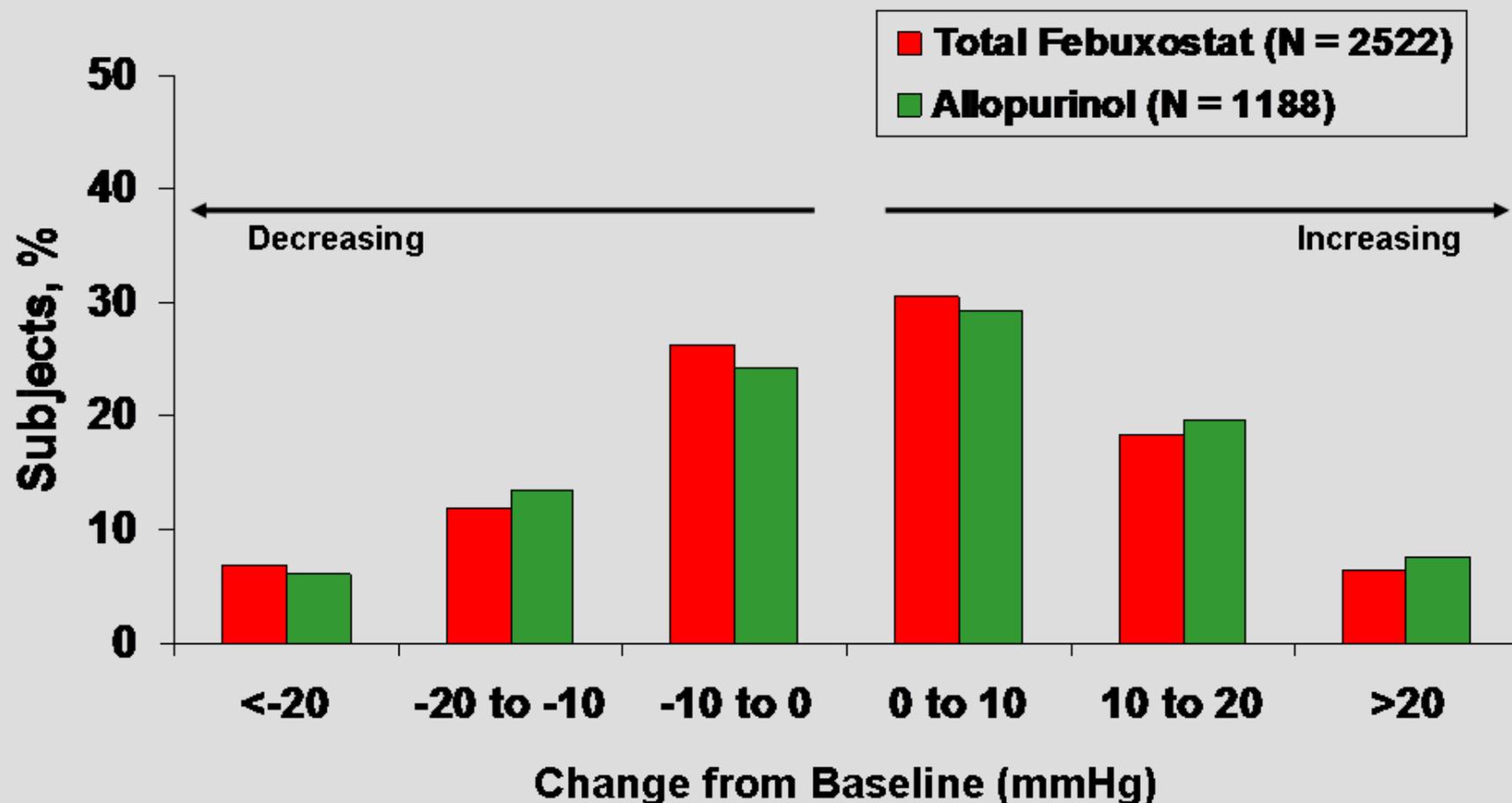
Effects on Cardiovascular Risk Factors

Effects on Cardiovascular Risk Factors

- ◆ **No effects on**
 - **Blood pressure**
 - **Glucose**
 - **Lipids**
 - **Weight**

Change from Baseline to Final Visit in Systolic Blood Pressure

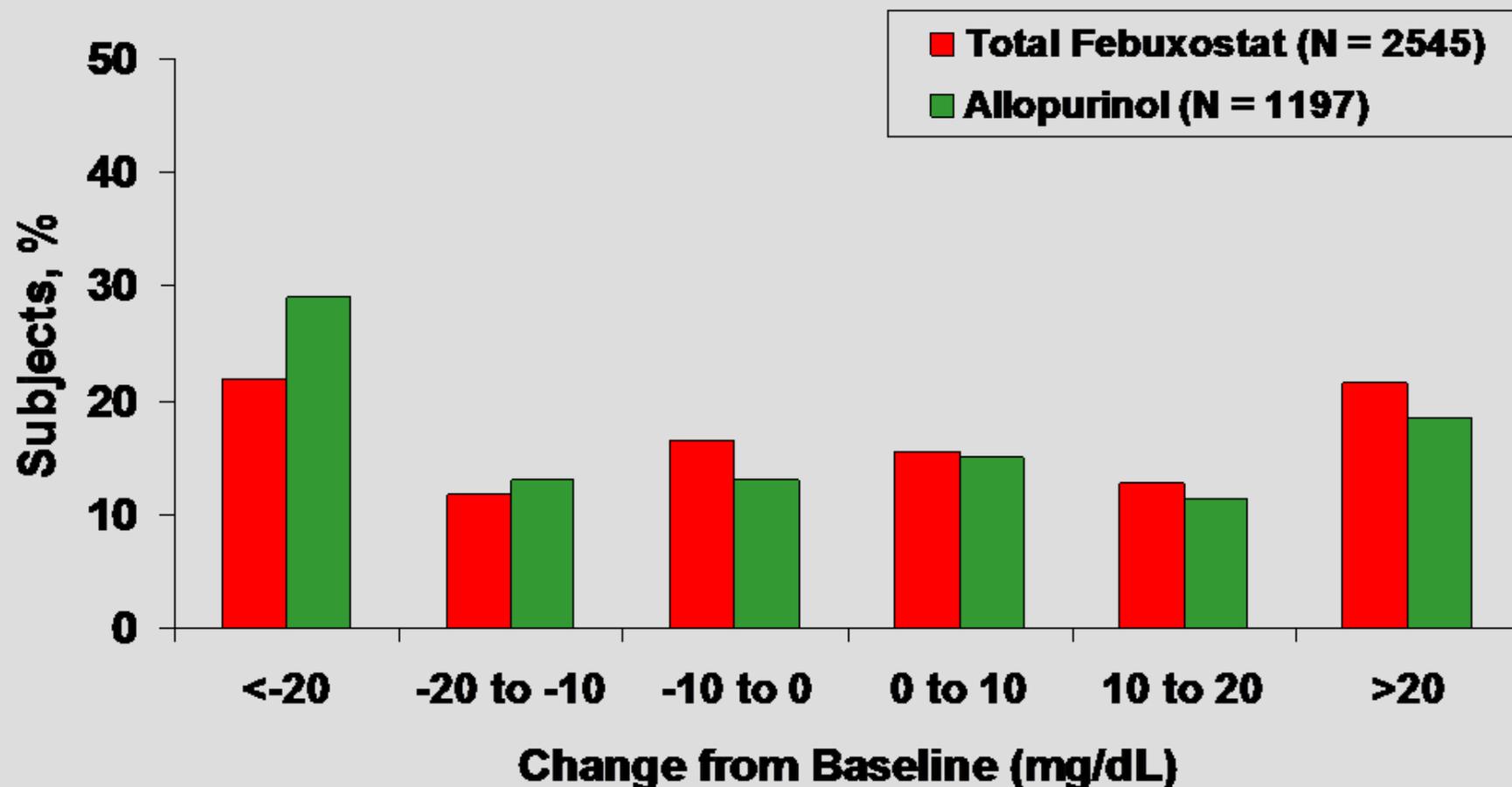
Phase 3 Randomized-Controlled Studies



Mean change \pm SE: Febuxostat, 0.3 ± 0.3 mmHg; Allopurinol, 0.7 ± 0.4 mmHg

Change from Baseline to Final Visit in Total Cholesterol

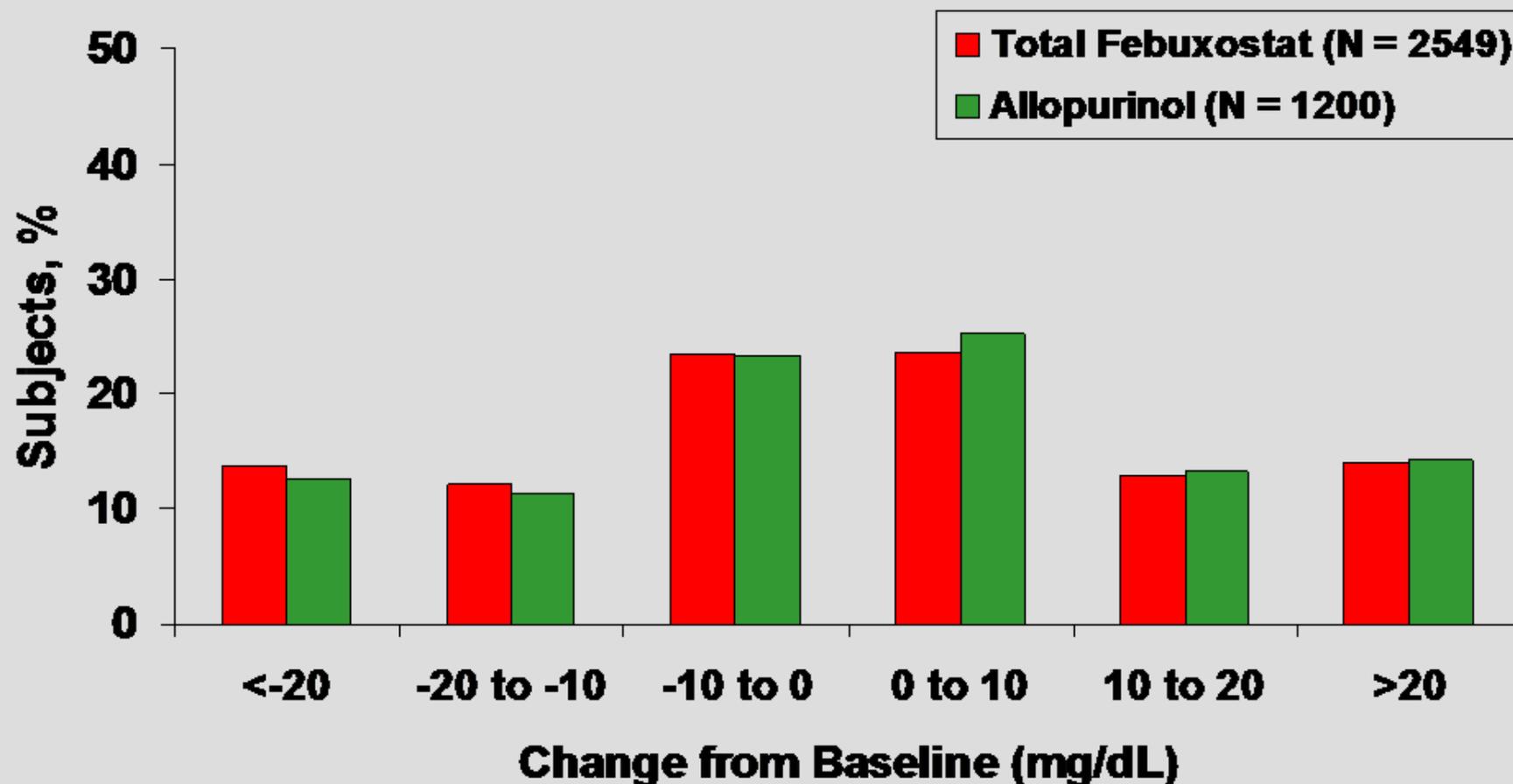
Phase 3 Randomized-Controlled Studies



Mean change \pm SE: Febuxostat, -0.67 ± 0.71 mg/dL; Allopurinol, -6.31 ± 1.01 mg/dL

Change from Baseline to Final Visit in Glucose

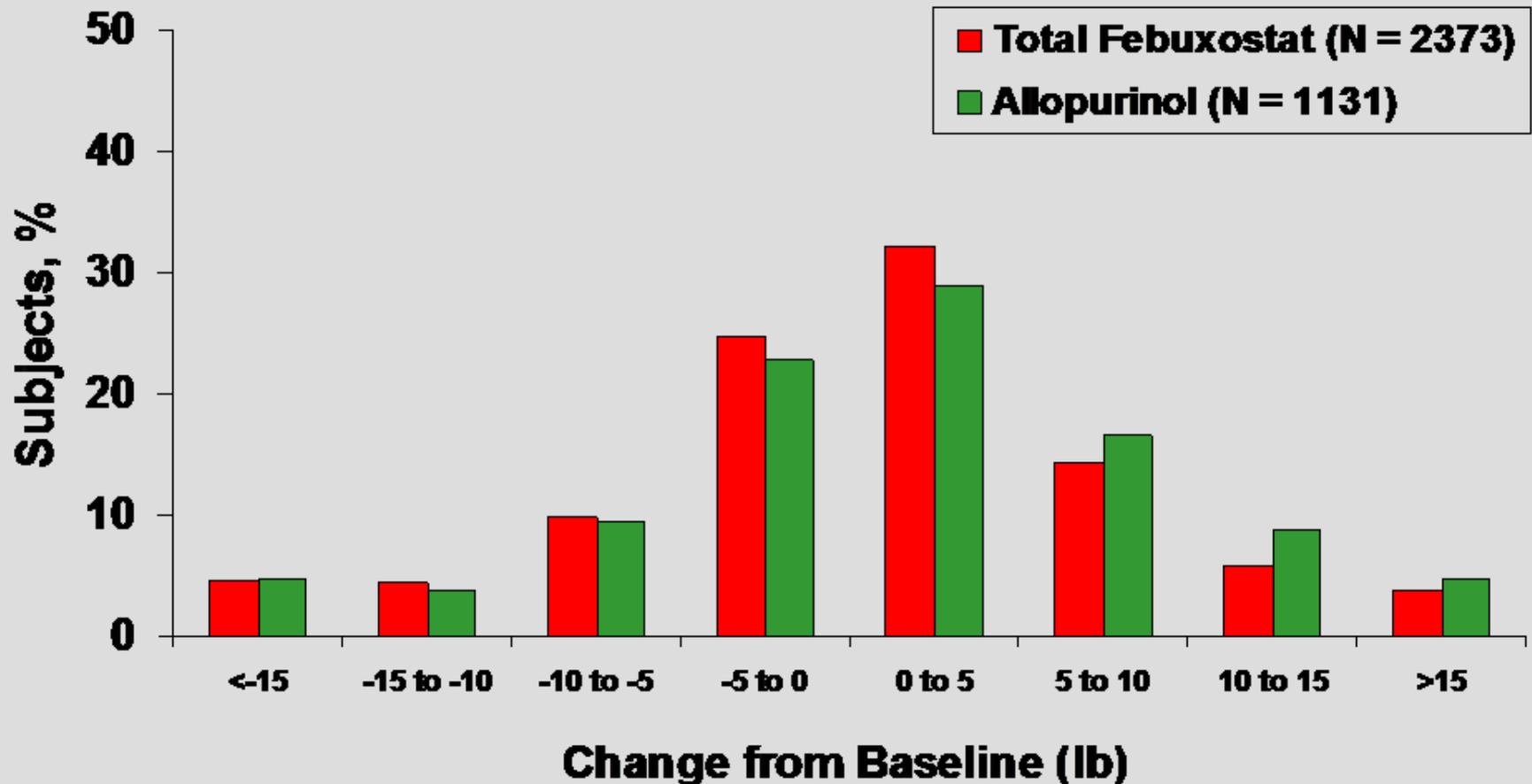
Phase 3 Randomized-Controlled Studies



Mean change \pm SE: Febuxostat, 0.46 ± 0.61 mg/dL; Allopurinol, 0.69 ± 0.78 mg/dL

Change from Baseline to Final Visit in Body Weight

Phase 3 Randomized-Controlled Studies



Mean change \pm SE: Febuxostat, -0.15 ± 0.26 lbs; Allopurinol, 0.33 ± 0.47 lbs

Background Rates of MI and Deaths in Gout

Person-Yrs	Health Professionals F/U Study ¹		MRFIT Study ^{2,3}	
	Gout	No gout	Gout	No gout
	513,728		~83,629 ² /~15,255 ³	
Nonfatal MI	0.46	0.24	0.43 ²	0.34 ²
CV deaths	0.40	0.16	1.03 ³	0.80 ³
All cause deaths	1.46	0.70	2.09 ³	1.8 ³

1. Choi HK, et al. *Circulation*. 2007;116:894-900.

2. Krishnan E, et al. *Arthritis Rheum*. 2006;54:2688-2696.

3. Krishnan E, et al. *Arch Intern Med*. 2008;168:1104-1110.

High CV Burden In Febuxostat Study Population

Phase 3 Randomized-Controlled Studies

	Subjects, n (%)		
	Placebo N = 134	Total Febuxostat N = 2690	Allopurinol N = 1277
Subjects with ≥ 1 CV disorder and/or risk factor at baseline[‡]	115 (86)	2393 (89)	1150 (90)
1 - 2	75 (56)	1560 (58)	776 (61)
3 - 4	34 (25)	695 (26)	305 (24)
≥ 5	6 (4)	138 (5)	69 (5)

[‡] Included are CV medical disorders and well known CV risk factors (diabetes, hypertension, hyperlipidemia, obesity, smoking).

The CONFIRMS Study

- ◆ Prospectively designed CRF to capture CV history
- ◆ Included a prospective evaluation of CV events
- ◆ CV endpoints defined in the study protocol
- ◆ CV worksheet to ensure collection of essential information
- ◆ Blinded adjudication of potential CV events was performed by an independent committee of experts

Cardiovascular Endpoints Rationale

- ◆ **Antiplatelet Trialists' Collaboration (APTTC)¹ endpoints and non-APTTC CV endpoints²**
 - **Used to evaluate CV safety**
 - **Originally developed to assess safety and efficacy of antiplatelet drugs**
 - **Frame of reference has been developed for APTTC in other studies of noncardiac drugs**

1. Antiplatelet Trialists' Collaboration. *Br Med J*. 1994;308(6921):81-106.

2. White WB, et al. *Am J Cardiol*. 2003;92(4):411-418.

Defined Cardiovascular Endpoints

CONFIRMS

- ◆ **APTC endpoints**
 - Cardiovascular death
 - Nonfatal myocardial infarction
 - Nonfatal stroke
- ◆ **Non-APTC CV endpoints**
 - Arrhythmia with no evidence of ischemia
 - Venous and peripheral arterial vascular thrombotic events
 - Nonfatal congestive heart failure
 - Angina (inclusive of acute coronary syndrome)
 - Coronary revascularization
 - Transient ischemic attack
 - Cerebral revascularization
 - Other non-APTC CV events (eg, severe hypertension)

Adjudication Process

	Retrospective	Prospective
Studies	FACT, APEX, FOCUS, EXCEL	CONFIRMS
Assessments (blinded to treatment group)	CV endpoint expert‡	CV Endpoints Committee (2 cardiologists, 1 stroke neurologist)§
Definitions of APTC and non- APTC CV endpoints	Based on literature	Based on literature (defined by formal charter)

‡ W.B. White, MD.

§ J.S. Borer, MD, P. Gorelick, MD, W.B. White, MD.

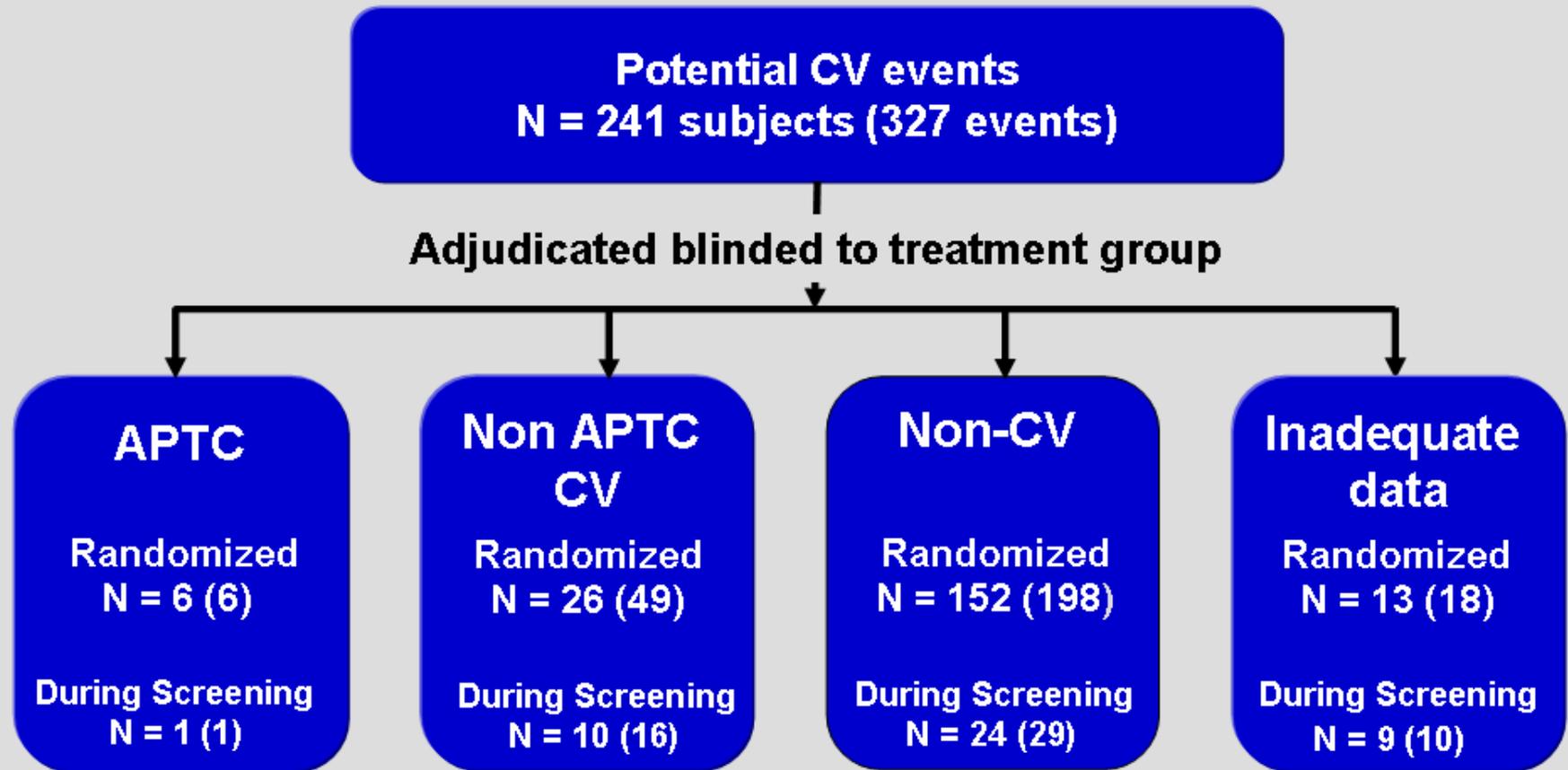
Characteristics of Subjects at Baseline

CONFIRMS

Variable	Febuxostat mg		Allopurinol
	40 N = 757	80 N = 756	N = 756
Age, yrs	52.5	53.0	52.9
Body weight, lb	229.9	227.3	225.5
Systolic/diastolic BP, mmHg	131.0 / 81.3	130.8 / 81.6	130.2 / 80.9
Total cholesterol, mg/dL	204.5	205.2	208.7
Triglycerides, mg/dL	244.9	250.3	264.4
Serum glucose, mg/dL	108.0	108.5	108.1
Concomitant meds, N (%)			
Aspirin	139 (18)	144 (19)	148 (20)
ARBs	254 (34)	275 (36)	289 (38)
ACE inhibitors	176 (23)	187 (25)	186 (25)
Anti-diabetic agents	68 (9)	80 (11)	77 (10)
Beta blockers	142 (19)	124 (16)	154 (20)
NSAIDs	316 (42)	315 (42)	298 (39)
Statins	166 (22)	166 (22)	201 (27)

Disposition of Subjects with Potential CV Events

CONFIRMS



Description of Subjects with Inadequate Data

- ◆ **Subjects not considered serious enough to hospitalize (lack of clinical data)**
- ◆ **Cases balanced among 3 treatment groups**
- ◆ **Only one discontinuation per treatment group**
 - **All other subjects continued on study drug**
- ◆ **During remainder of study, none of these subjects had an APTC event or non-APTC CV event**

Adjudicated APTC CV Events

CONFIRMS

	Subjects, n (%)		
	95% CI		Allopurinol
	Febuxostat mg		
	40 N = 757	80 N = 756	N = 756
All APTC events	0 0.00 - 0.49	3 (0.40) 0.08 - 1.16	3 (0.40) 0.08 - 1.16
CV death‡	0 0.00 - 0.49	0 0.00 - 0.49	2 (0.26) 0.03 - 0.95
Nonfatal MI	0 0.00 - 0.49	1 (0.13) < 0.01 - 0.74	1 (0.13) < 0.01 - 0.74
Nonfatal stroke	0 0.00 - 0.49	2 (0.26) 0.03 - 0.95	0 0.00 - 0.49

‡ 1 death in Febuxostat 40 mg group attributed to allergic reaction to fire ant bites.

Treatment-Emergent APTC CV Events Investigator-Reported vs Adjudicated CONFIRMS

	Subjects, n (%) 95% CI			
	Total febuxostat		Allopurinol	
	Investigator reported	Adjudicated	Investigator reported	Adjudicated
APTC events	N = 1513	N = 1513	N = 756	N = 756
All APTC events	1 (0.07) < 0.01 - 0.37	3 (0.20) 0.04 - 0.58	3 (0.40) 0.08 - 1.16	3 (0.40) 0.08 - 1.16
CV death	0 0.00 - 0.24	0 0.00 - 0.24	2 (0.26) 0.03 - 0.95	2 (0.26) 0.03 - 0.95
Nonfatal MI	1 (0.07) < 0.01 - 0.37	1 (0.07) < 0.01 - 0.37	1 (0.13) < 0.01 - 0.74	1 (0.13) < 0.01 - 0.74
Nonfatal stroke	0 0.00 - 0.24	2 (0.13) 0.02 - 0.48	0 0.00 - 0.49	0 0.00 - 0.49

Adjudicated Non-APTC CV Events CONFIRMS

	Subjects, n (%) 95% CI		
	Febuxostat mg		Allopurinol
	40 N = 757	80 N = 756	N = 756
All non-APTC CV events	10 (1.32) 0.64 - 2.42	9 (1.19) 0.55 - 2.25	7 (0.93) 0.37 - 1.90
Arrhythmia, no evidence of ischemia	3 (0.40)	4 (0.53)	1 (0.13)
Venous & peripheral arterial vascular thrombotic events	0	2 (0.26)	0
Nonfatal CHF	2 (0.26)	0	1 (0.13)
Angina	2 (0.26)	0	0
Coronary revascularization	1 (0.13)	0	1 (0.13)
Transient ischemic attack	1 (0.13)	0	1 (0.13)
Cerebral revascularization	0	0	0
Other non-APTC CV events‡	1 (0.13)	3 (0.40)	3 (0.40)

‡ Treatment emergent hypertension, hypotension, new onset left bundle branch block, syncope.

Adjudicated APTC CV Events

Phase 3 Randomized-Controlled Studies

	Subjects, n (%) 95% CI					
	Placebo	Febuxostat mg				Allopurinol
	N = 134	40 N = 757	80 N = 1279	120 N = 520	240 N = 134	N = 1277
All APTC events	0 0.00-2.72	0 0.00-0.49	7 (0.55) 0.22-1.12	3 (0.58) 0.12-1.68	0 0.00-2.72	4 (0.31) 0.09-0.80
CV death	0 0.00-2.72	0 0.00-0.49	2 (0.16) 0.02-0.56	1 (0.19) < 0.01-1.07	0 0.00-2.72	2 (0.16) 0.02-0.57
Nonfatal MI	0 0.00-2.72	0 0.00-0.49	3 (0.23) 0.05-0.68	2 (0.38) 0.05-1.38	0 0.00-2.72	2 (0.16) 0.02-0.57
Nonfatal stroke	0 0.00-2.72	0 0.00-0.49	2 (0.16) 0.02-0.56	0 0.00-0.71	0 0.00-2.72	0 0.00-0.29

Treatment-Emergent APTC CV Events Investigator-Reported vs Adjudicated Phase 3 Randomized-Controlled Studies

	Subjects, n (%) 95% CI			
	Total febuxostat		Allopurinol	
	Investigator reported	Adjudicated	Investigator reported	Adjudicated
APTC events	N = 2690	N = 2690	N = 1277	N = 1277
Overall	10 (0.37) 0.18 - 0.68	10 (0.37) 0.18 - 0.68	4 (0.31) 0.09 - 0.80	4 (0.31) 0.09 - 0.80
CV death	3 (0.11) 0.02 - 0.33	3 (0.11) 0.02 - 0.33	2 (0.16) 0.02 - 0.57	2 (0.16) 0.02 - 0.57
Nonfatal MI‡	6 (0.22) 0.08 - 0.49	5 (0.19) 0.06 - 0.43	2 (0.16) 0.02 - 0.57	2 (0.16) 0.02 - 0.57
Nonfatal stroke	1 (0.04) < 0.01 - 0.21	2 (0.07) < 0.01 - 0.27	0 0.00 - 0.29	0 0.00 - 0.29

‡ One subject with MI also reported a nonfatal cardiac arrest.

Adjudicated Non-APTC CV Events

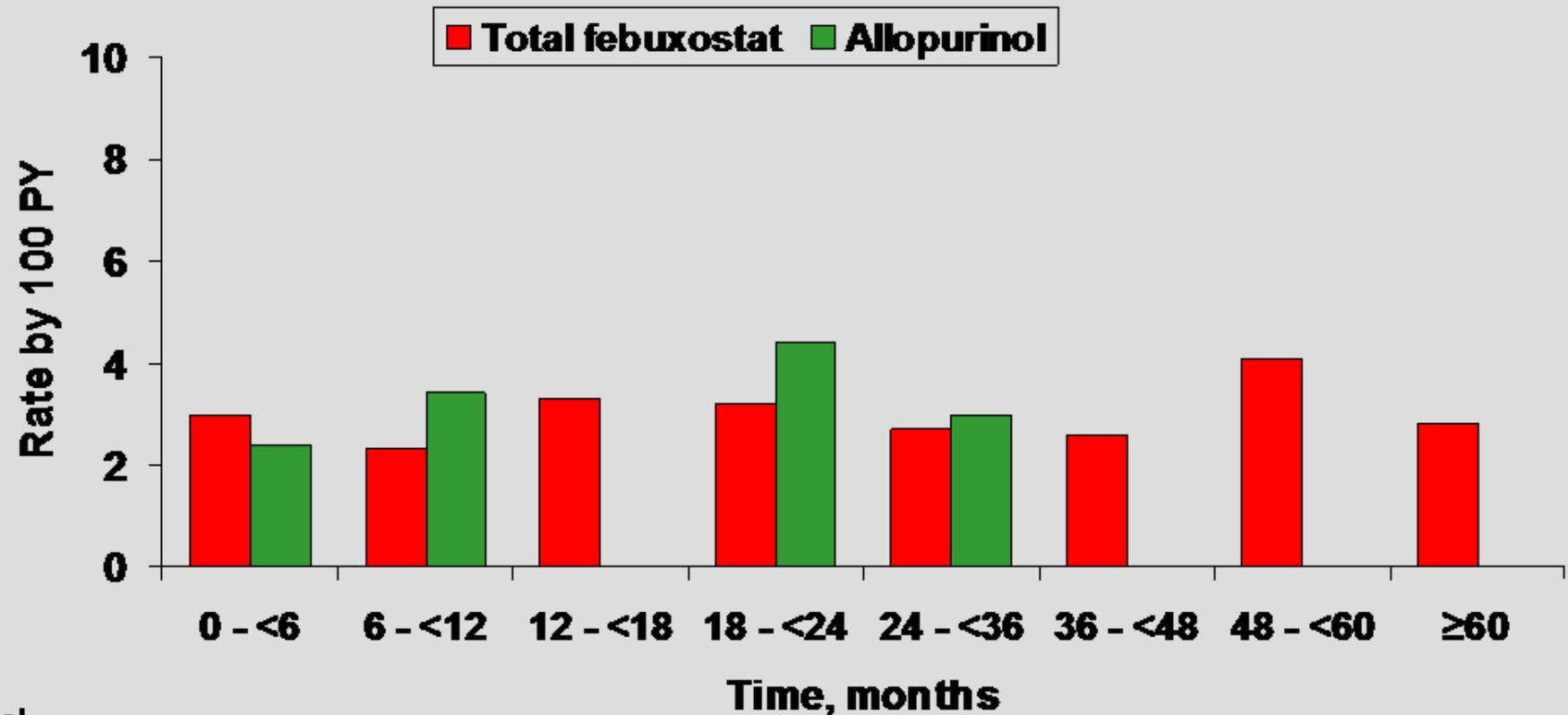
Phase 3 Randomized-Controlled Studies

	Subjects, n (%) 95% CI					Allopurinol N = 1277
	Placebo N = 134	Febuxostat mg				
		40 N = 757	80 N = 1279	120 N = 520	240 N = 134	
All non-APTC CV events	1 (0.75) 0.02-4.09	10 (1.32) 0.64-2.42	15 (1.17) 0.66-1.93	8 (1.54) 0.67-3.01	1 (0.75) 0.02-4.09	12 (0.94) 0.49-1.64
Arrhythmia, no evidence of ischemia	0	3 (0.40)	6 (0.47)	2 (0.38)	1 (0.75)	3 (0.23)
Venous & peripheral arterial vascular thrombotic events	0	0	3 (0.23)	2 (0.38)	0	0
Nonfatal CHF	0	2 (0.26)	0	1 (0.19)	0	1 (0.08)
Angina	1 (0.75)	2 (0.26)	0	0	0	0
Coronary revascularization	0	1 (0.13)	2 (0.16)	2 (0.38)	0	4 (0.31)
Transient ischemic attack	0	1 (0.13)	1 (0.08)	0	0	1 (0.08)
Cerebral revascularization	0	0	0	0	0	0
Other non-APTC CV events [‡]	0	1 (0.13)	3 (0.23)	1 (0.19)	0	3 (0.23)

‡ Treatment emergent hypertension, hypotension, new onset left bundle branch block, cardiomyopathy, syncope.

Adjudicated APTC and Non-APTC CV Event Rates by Patient-Yr Over Time

Phase 2/3 Randomized-Controlled Studies and Long-Term Extension Studies



	Time, months							
Total Febuxostat N [PY]	3233 [1360]	2323 [558]	1020 [455]	873 [410]	795 [697]	549 [312]	180 [73]	55 [36]
Allopurinol N [PY]	1398 [590]	1013 [147]	224 [31]	50 [23]	43 [34]	17 [9]	1 [<1]	-

Febuxostat Rates of MI and Deaths in Gout and Background Rates

Per 100 PY	Febuxostat	Health Professionals F/U Study ¹		MRFIT Study ^{2,3}	
Person-Yrs	Gout	Gout	No Gout	Gout	No Gout
	4,007	513,728		~83,629 ² /~15,255 ³	
Non-fatal MI	0.40	0.46	0.24	0.43 ²	0.34 ²
CV Deaths	0.25	0.40	0.16	1.03 ³	0.80 ³
All Cause Deaths	0.40	1.46	0.70	2.09 ³	1.8 ³

1. Choi HK, et al. *Circulation*. 2007;116:894-900.

2. Krishnan E, et al. *Arthritis Rheum*. 2006;54:2688-2696.

3. Krishnan E, et al. *Arch Intern Med*. 2008;168:1104-1110.

Summary of CV Safety of Febuxostat

- ◆ **Non-clinical data did not demonstrate any mechanisms for CV toxicity**
- ◆ **Clinical data showed no alterations in major CV risk factors**
- ◆ **Subjects in clinical program had high risk for CV events, reflective of a population with gout**
- ◆ **CONFIRMS did not show any increase in CV event rates compared to allopurinol**
- ◆ **No dose-related increase in CV event rates in combined randomized-controlled studies**
- ◆ **No increase in CV event rates over time with long-term treatment**

Risk/Benefit

Need for a New Therapeutic Agent

- ◆ **Gout is a progressive disease associated with multiple comorbid conditions**
- ◆ **Limitations of allopurinol**
 - **No prior adequate and well-controlled studies**
 - **Dose adjustment recommended for patients with renal impairment**
 - **Limited use of maximum dose resulting in inability to achieve target level**
 - **Rare severe hypersensitivity reaction**

Potential Risks

◆ Cardiovascular

- **Subjects in clinical trials had significant comorbidities, reflective of gout population**
- **Apparent imbalance in small number of CV events seen in original Phase 3 studies not substantiated in CONFIRMS trial**
- **CONFIRMS**
 - **No APTC events for febuxostat 40 mg**
 - **APTC events were low and similar for febuxostat 80 mg and allopurinol**
- **No underlying mechanism for CV AEs**
- **No change in blood pressure, glucose, lipids, weight**

Potential Risks

- ◆ **Hepatic effects**
 - Percentage of transaminase elevations low and similar with febuxostat and allopurinol
 - No dose response
 - No subject met Hy's Law
- ◆ **Treatment-initiated gout flares**
 - Predictable consequence of urate-lowering therapy
 - More potent agents associated with more paradoxical gout flares
 - Prophylaxis recommended

Benefits

Gout is a progressive disease marked with acute inflammatory arthritis and destructive tophi

- ◆ 40 mg and 80 mg demonstrate effective reduction and maintenance of sUA < 6 mg/dL resulting in
 - Reduction in gout flares
 - Resolution of tophi
- ◆ 80 mg superior to 40 mg
 - Effective in subjects with more severe disease (higher sUA levels or the presence of tophi)

Benefits

- ◆ Both 40 mg and 80 mg were effective in renal impaired patients and no dose adjustment required
- ◆ Effective and well-tolerated treatment option for patients with comorbid conditions
 - No significant drug interactions with commonly used drugs
- ◆ Approval of 40 mg and 80 mg will allow individualized dosing options for physicians
- ◆ The benefits of febuxostat clearly outweigh the risks and support approval of febuxostat

Conclusion

Febuxostat Proposed Indication

Indication	Dose	Frequency
Treatment of hyperuricemia in patients with gout	40 or 80 mg	Once daily

80 mg recommended

- ◆ **Patients with higher serum uric acid (sUA) levels**
- ◆ **Patients with tophi**

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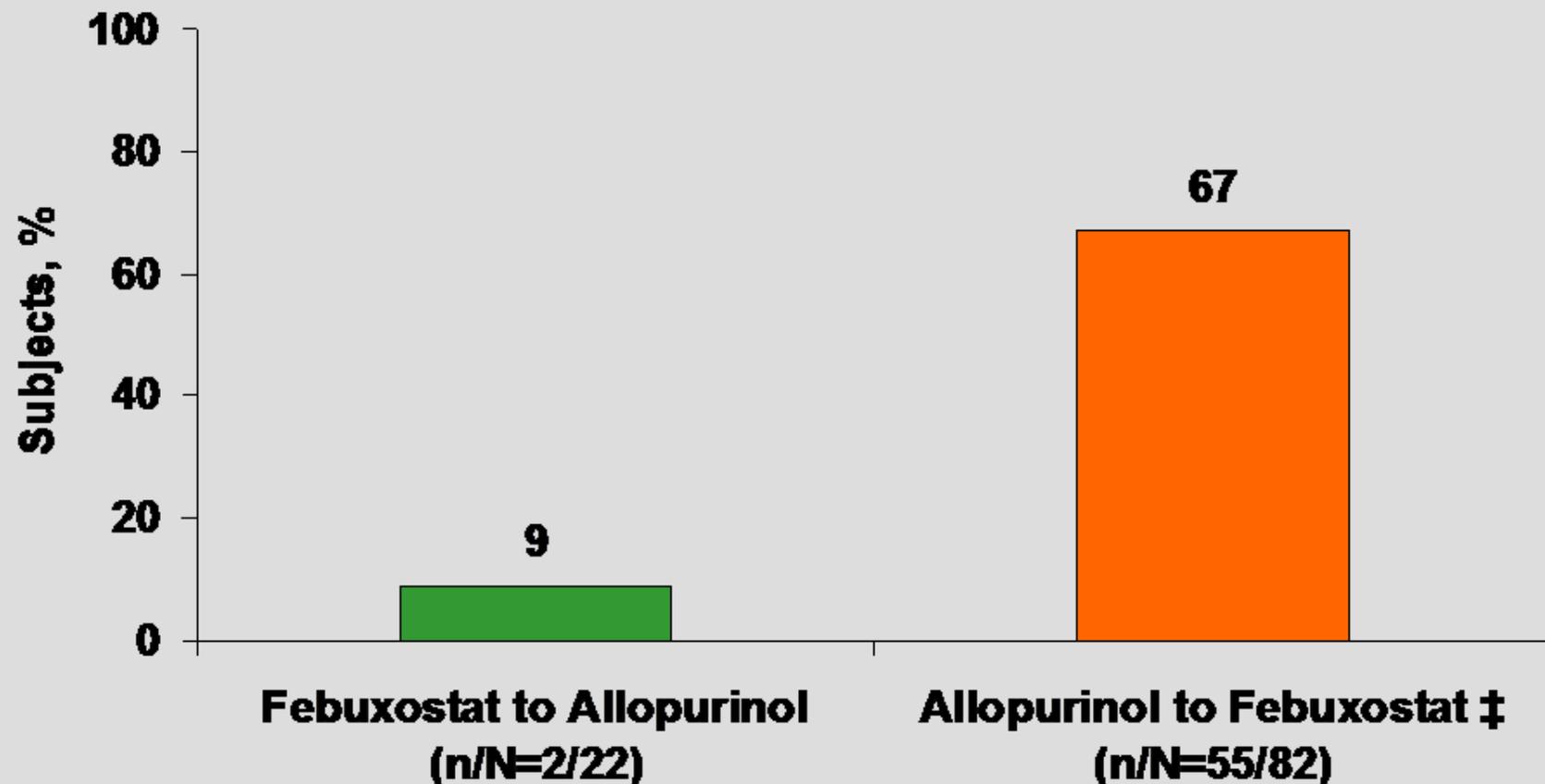
*Professor of Medicine, Cardiology Center
University of Connecticut School of Medicine*

ULORIC[®] (febuxostat) Tablets

**Arthritis Advisory Committee Meeting
November 24, 2008**

sUA < 6 mg/dL After Change in Therapy due to sUA ≥ 6 mg/dL

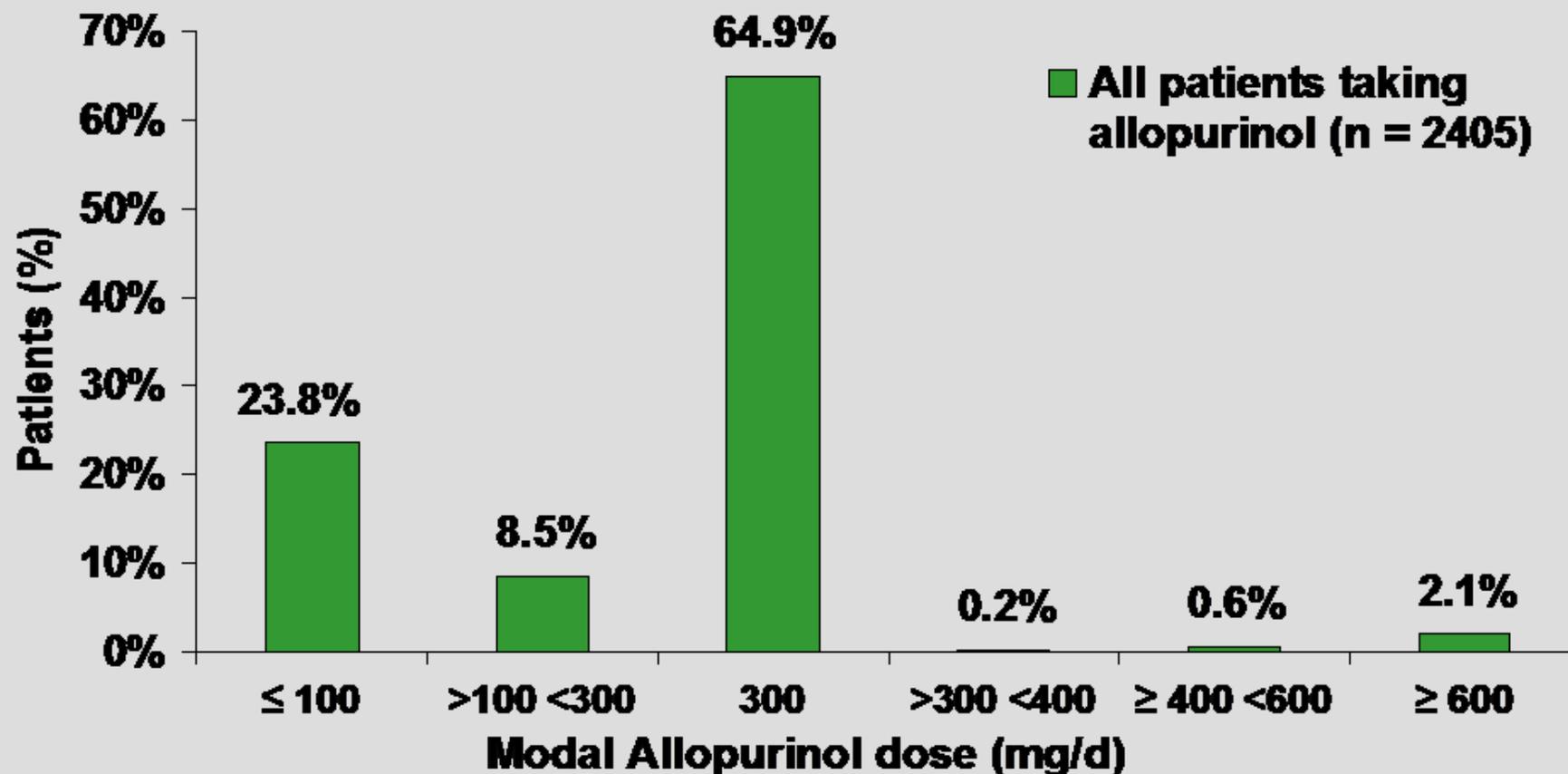
EXCEL



‡ Most subjects changed to febuxostat received 80 mg.

Allopurinol Most Commonly Prescribed Doses

Retrospective Managed Care Claims Analysis



Adjudicated APTC CV Events by NSAIDs/Cox2 Use or Colchicine Use

Phase 3 Randomized-Controlled Studies

	Subjects, n (%)			
	Febuxostat total		Allopurinol	
	Users	Non-users	Users	Non-users
	N = 1528	N = 1162	N = 691	N = 586
NSAIDs/Cox2	6 (0.39)	4 (0.34)	0	4 (0.68)
	N = 2053	N = 637	N = 947	N = 330
Colchicine	10 (0.49)	0	4 (0.42)	0

Myocardial Infarction Deaths

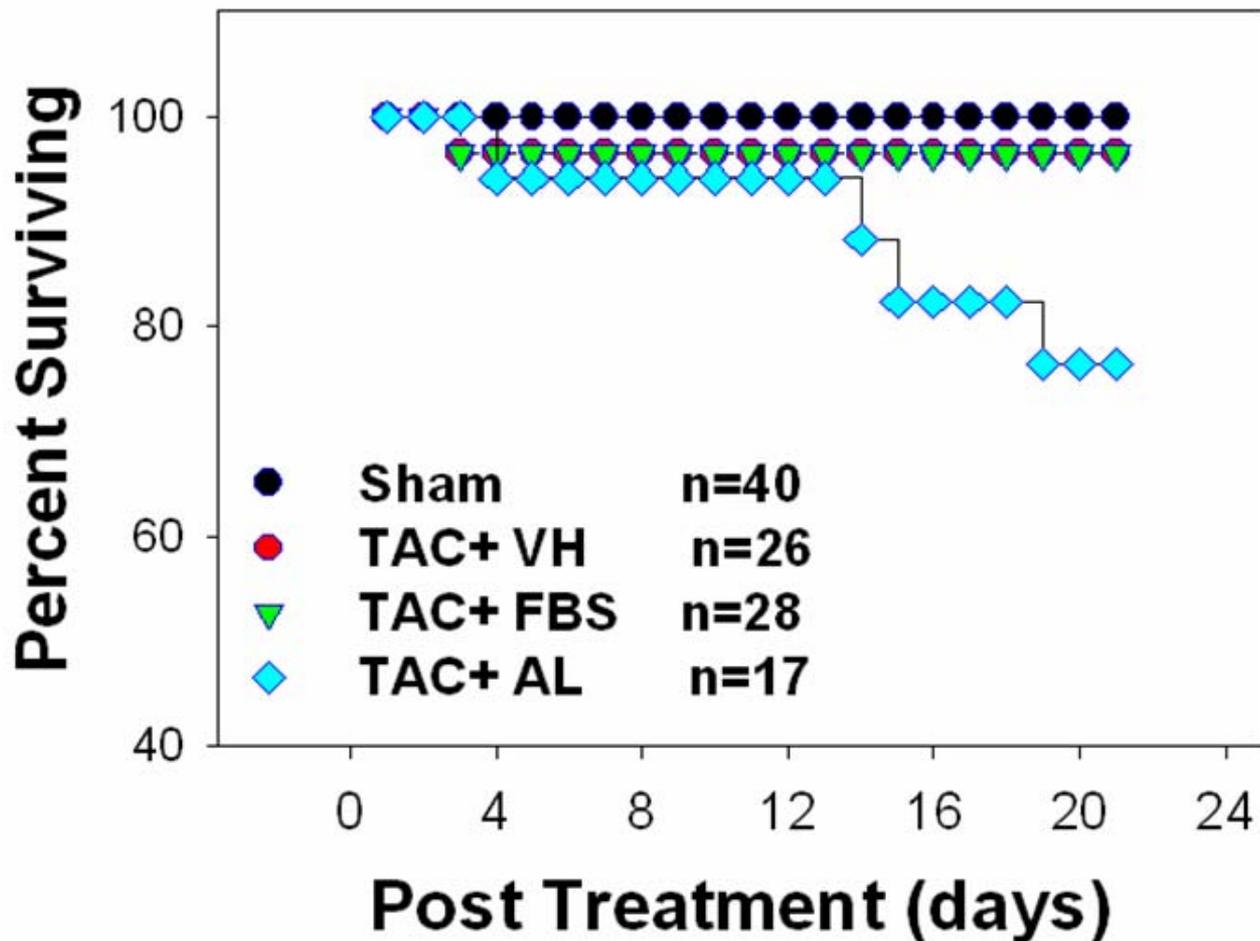
Long-Term Extension Studies

Subject Number/ Gender/Age‡ (Study)	Preferred Term	Day of onset§	Day of death§	Alternative etiology, relevant medical history, and other comments
Febuxostat 80 mg				
4086/M/50 (EXCEL)	Myocardial infarction	1052 (9)	1052 (9)	AltEt: CAD. MedHx: HTN, hyperlipidemia.
4050/M/69 (EXCEL)	Myocardial infarction	1000 (1)	1000 (1)	AltEt: HTN, cardiac arrhythmia, hypercholesterolemia. MedHx: HTN, cardiac arrhythmia-premature ventricular contractions, hyperlipidemia.
4136/M/82 (EXCEL)	Acute myocardial infarction	985 (61)	985 (61)	AltEt: patient on Coumadin in mild prostatitis; history of previous CAD with stent resulting in chronic afib sick sinus syndrome; stents, pacer, multiple previous cardiac events over the last 12 years. MedHx: HTN, cardiac arrhythmia, atrial fibrillation, pacemaker, heart murmur, coronary angioplasty.
Febuxostat 120 mg				
2695/M/58 (EXCEL)	Myocardial Infarction	644 (31)	644 (31)	AltEt: medical history. MedHx: atherosclerotic heart disease, CHF, HTN.
4479/M/75 (EXCEL)	Acute Myocardial Infarction	203	203	AltEt: cardiovascular disease. MedHx: CAD, HTN, hypercholesterolemia.

‡ Age at baseline.

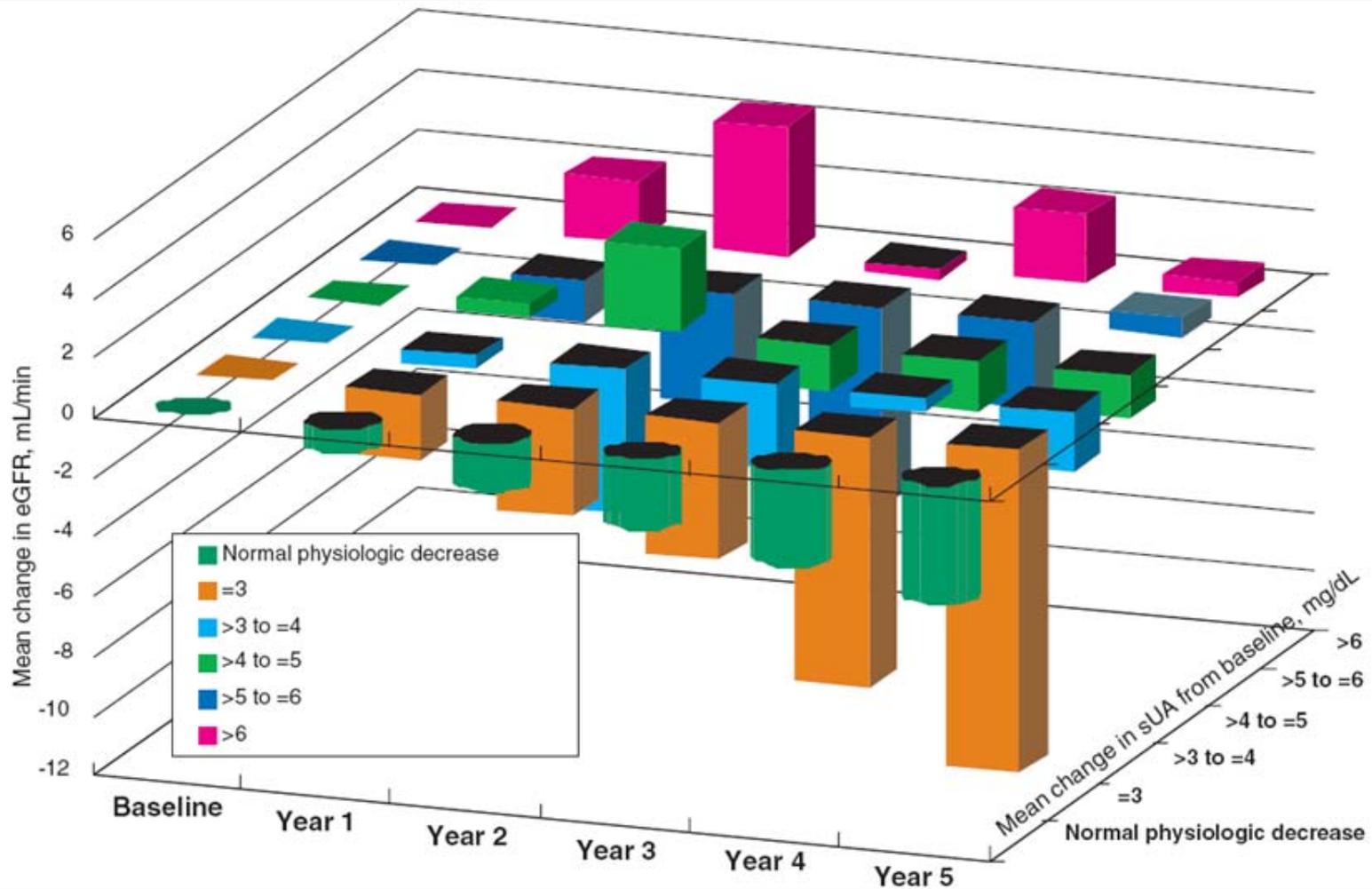
§ Days postdosing are shown in parentheses.

Comparison of Allopurinol and Febuxostat on Mortality in Systolic Overload-induced Heart Failure In Mice



Relationship Between Changes in eGFR and Reductions in sUA Over Time

FOCUS



5.5-Yr Renal Lithiasis Follow-up

FOCUS

- ◆ **18 subjects with a history of gout complicated by renal stone formation (mean gout duration 10 yrs; 1 - > 20 stone episodes per subject) entered a 4-wk double-blind dose ranging study**
 - **15 entered into LTE study with serum urate titrated to < 6.0 mg/dL during the first 6 months of study**
 - **By the end of 3 yrs, 2 subjects had recurrence of nephrolithiasis**
 - **By the end of 5.5 yrs, 1 additional subject excreted a renal stone**
 - **All 3 renal stones were calcium oxylate in composition**
 - **No uric acid stones or xanthine stones were excreted**