

**EFFICACY AND SAFETY OF A RANGE OF DOSES  
OF RDEA594, A NOVEL URICOSURIC AGENT, AS  
MONOTHERAPY IN GOUT PATIENTS:  
RANDOMIZED, DOUBLE-BLIND, PLACEBO-  
CONTROLLED, PHASE 2 EXPERIENCE**

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Z. Shen, J. Miner, M. Nguyen, D. Wilson, L. Yeh, B. Quart

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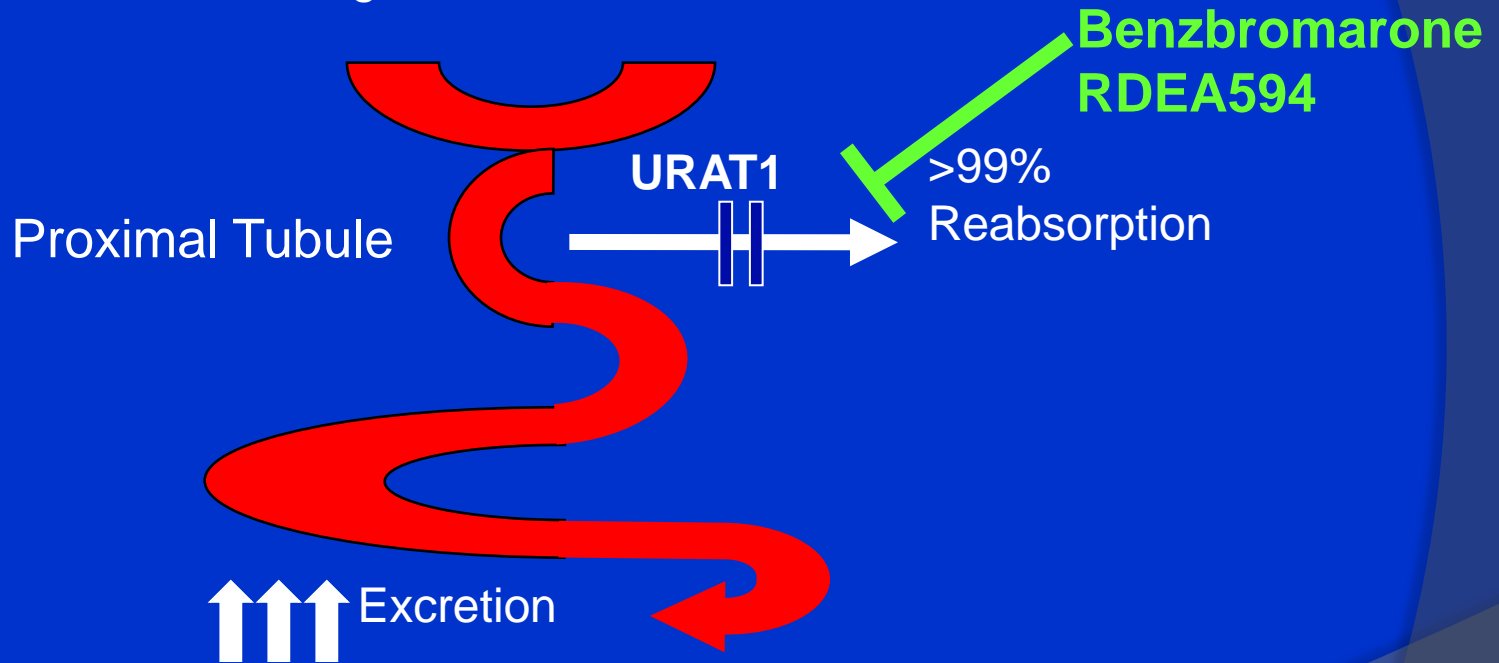
*Rome*

# Disclosures

- F. Perez-Ruiz: Consultant for Ardea Biosciences, Novartis Pharmaceuticals, and Menarini.
- V Hingorani: Consultant for Ardea Biosciences, Inc.
- J. Welp, B. Sheedy, K. Manhard, Z. Shen, J. Miner, M. Nguyen, D. Wilson, L. Yeh, and B. Quart: Employees, Ardea Biosciences, Inc.

# URAT1 Inhibitors Increase the Urinary Excretion of Uric Acid

~100% of uric acid is initially filtered through glomerular filtration



Enomoto; Urat1 identification in Nature May2002  
D Levinson & L Sorensen; Renal Handling of Uric Acid

# Overview of RDEA594

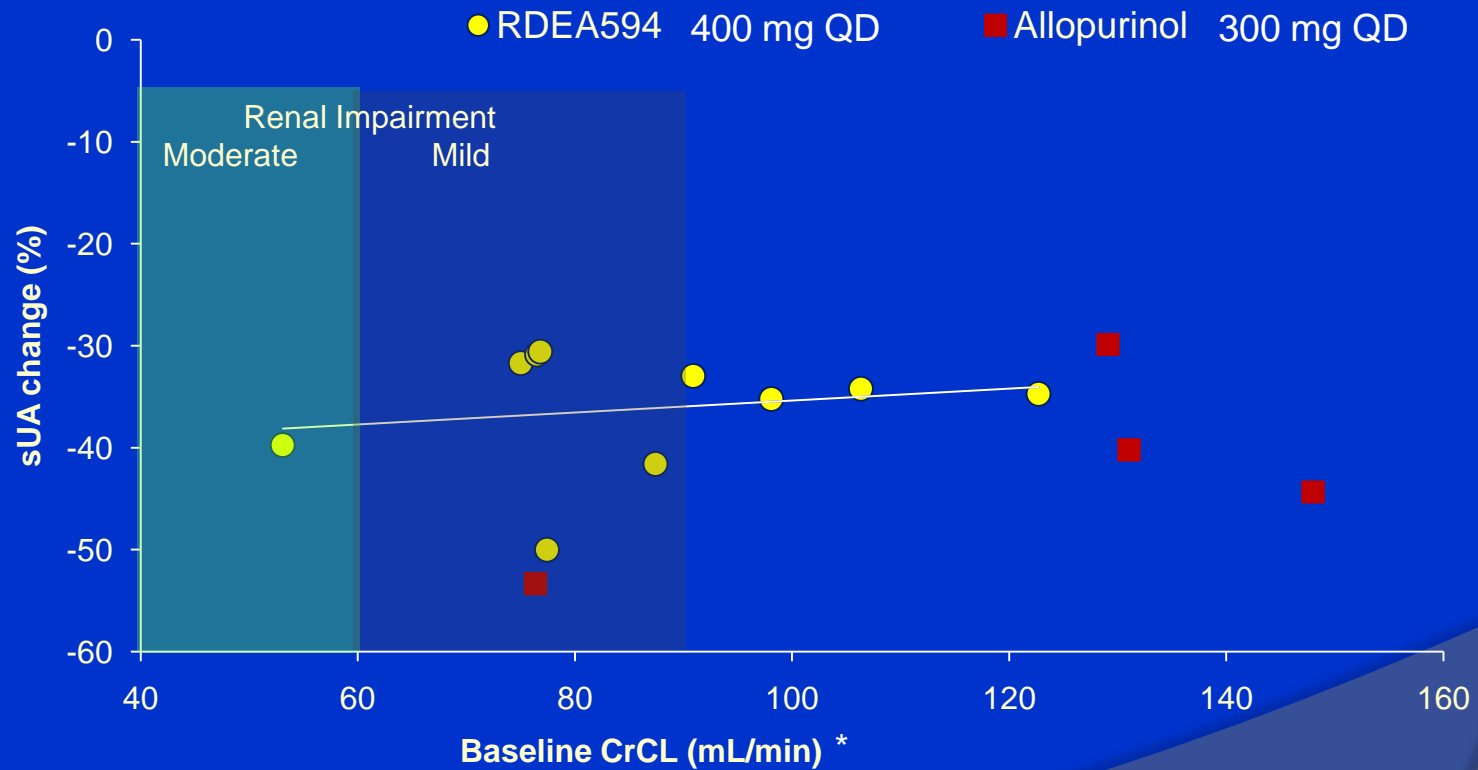
- Main metabolite of RDEA806 (HIV NNRTI)
- Attributes of RDEA594:
  - Inhibitor of URAT1
  - No activity in purine catabolism pathways
  - No activity against HIV
  - Linear PK with high bioavailability
  - No mitochondrial toxicity, little oxidative metabolism and no activity against multiple nuclear receptor targets seen with other uricosuric drugs

# Summary of Results From Phase 2a

- Phase 2a results for reduction of serum urate (sUA) with RDEA594:
  - 200 mg QD:
    - 40% response (sUA < 6 mg/dL) after one week
  - 400 mg QD:
    - 60% response after one week
    - 83% response for patients with mild to moderate renal impairment
    - 100% response with combination allopurinol 300 mg

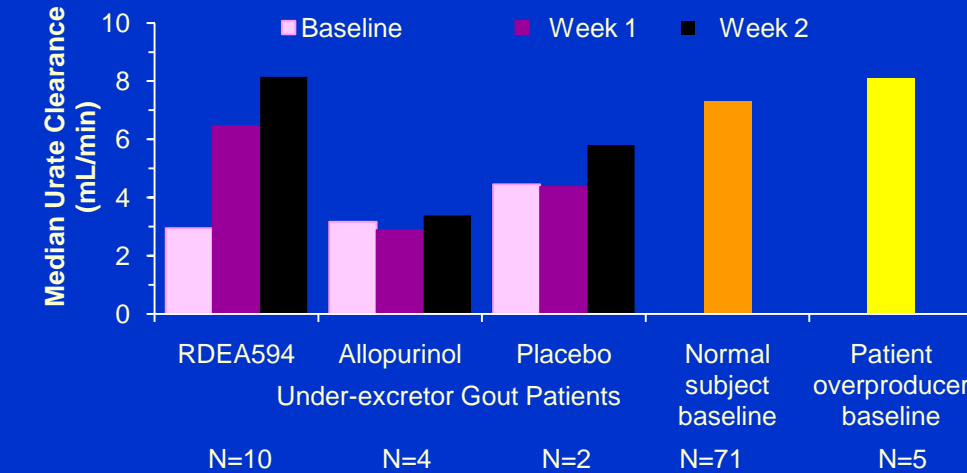
# Phase 2a - Consistent Response in Mild to Moderate Renal Impairment with RDEA594

Week 2 Serum Urate (sUA) Reduction by Baseline Estimated CrCl



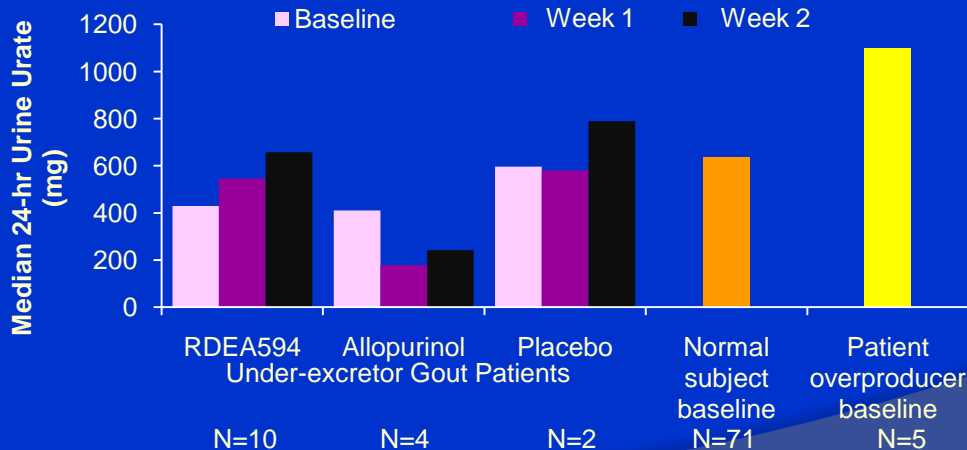
\*estimated by Cockcroft-Gault (C-G)

# Phase 2a - RDEA594 Normalizes Uric Acid Excretion with Increasing Doses



## WEEK 1

- RDEA594 200 mg
- Allopurinol 300 mg
- Placebo



## WEEK 2

- RDEA594 400 mg
- Allopurinol 300 mg
- Placebo

# RDEA594-202

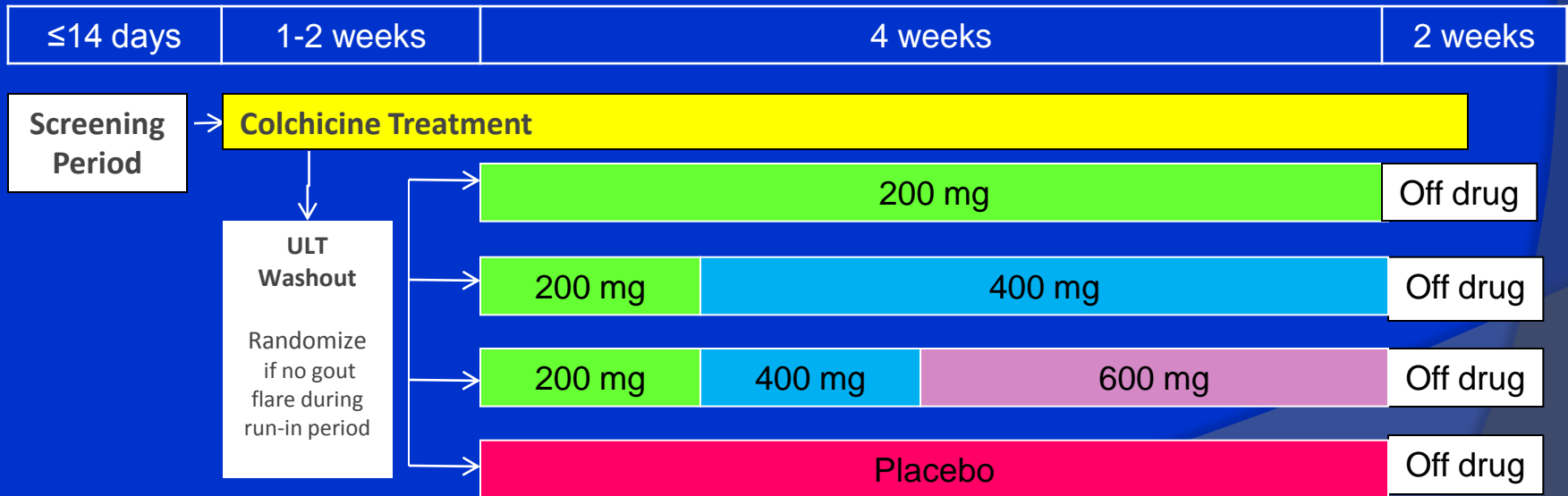
**Phase 2b, Randomized, Double-Blind,  
Multicenter, Placebo-Controlled, Safety and  
Efficacy Study of RDEA594 Versus Placebo in  
the Treatment of Hyperuricemia in Patients with  
Gout**

# Study Design

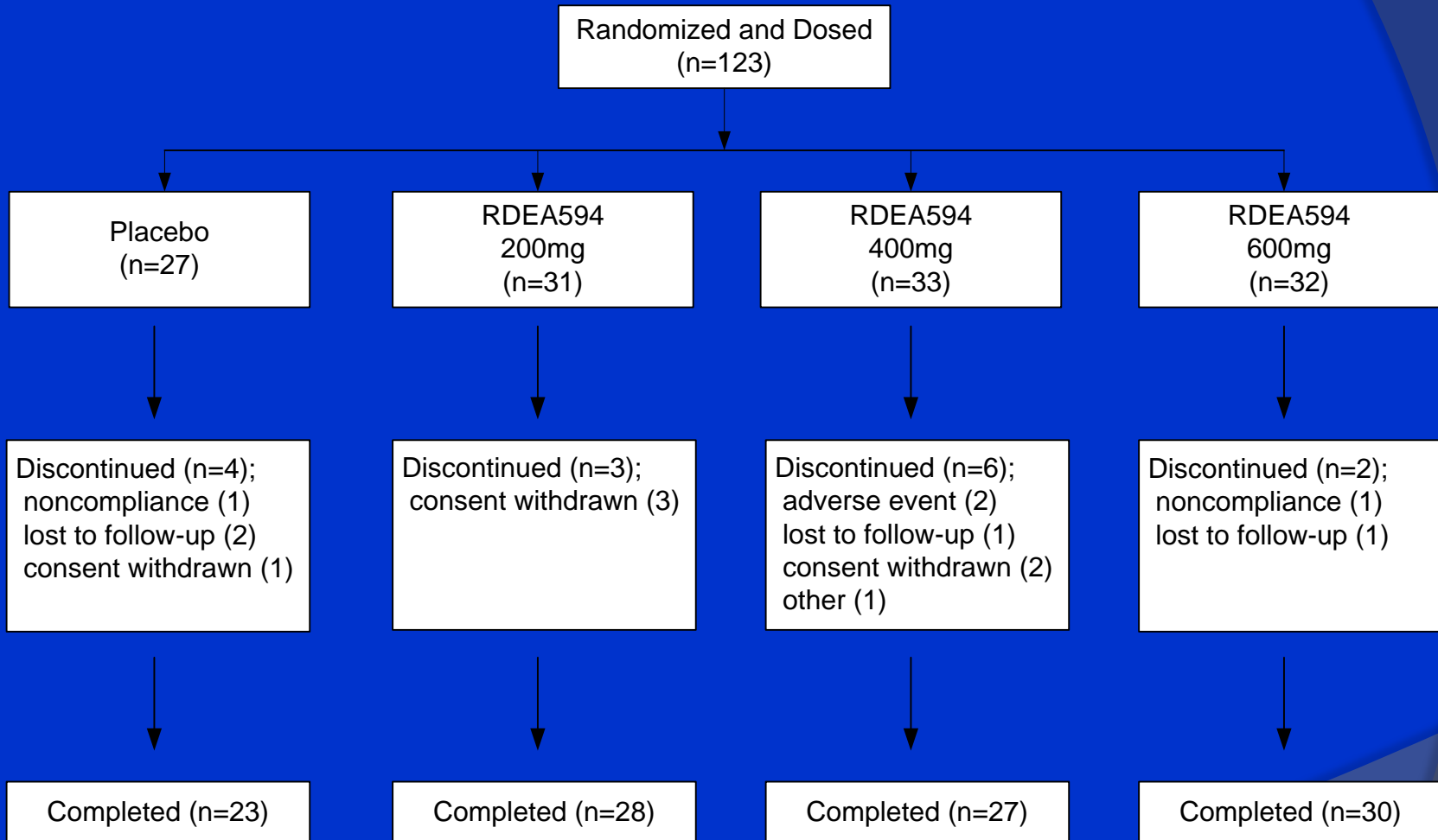
- Study Population
  - 123 patients with sUA  $\geq$  8 mg/dL (480  $\mu$ mol/L) at screening
  - Diagnosis of gout: ARA criteria (1977)
  - Underexcretors of uric acid (UaCl  $<$  6.0 mL/min)
  - Estimated CrCl by C-G method  $\geq$  60 mL/min
- Endpoints:
  - *Primary* - proportion of subjects whose urate level is  $<$  6.0 mg/dL (360  $\mu$ mol/L) following 4 weeks of dosing by randomized treatment group
  - *Secondary* - absolute and percent reduction from baseline in sUA levels at each weekly visit, and incidence of gout flares
  - *Methods* – direct LC-MS/MS method in plasma and indirect UV method in serum for analysis of urate levels in blood

# Study Timeline and Dose Titration Schema

- Screening & Run-in Period – 2-4 weeks:
  - urate lowering therapy (ULT) washout
  - initiate colchicine
- Treatment Period – 4 weeks:
  - weekly titration up to randomized dose for higher doses



# Patient Disposition

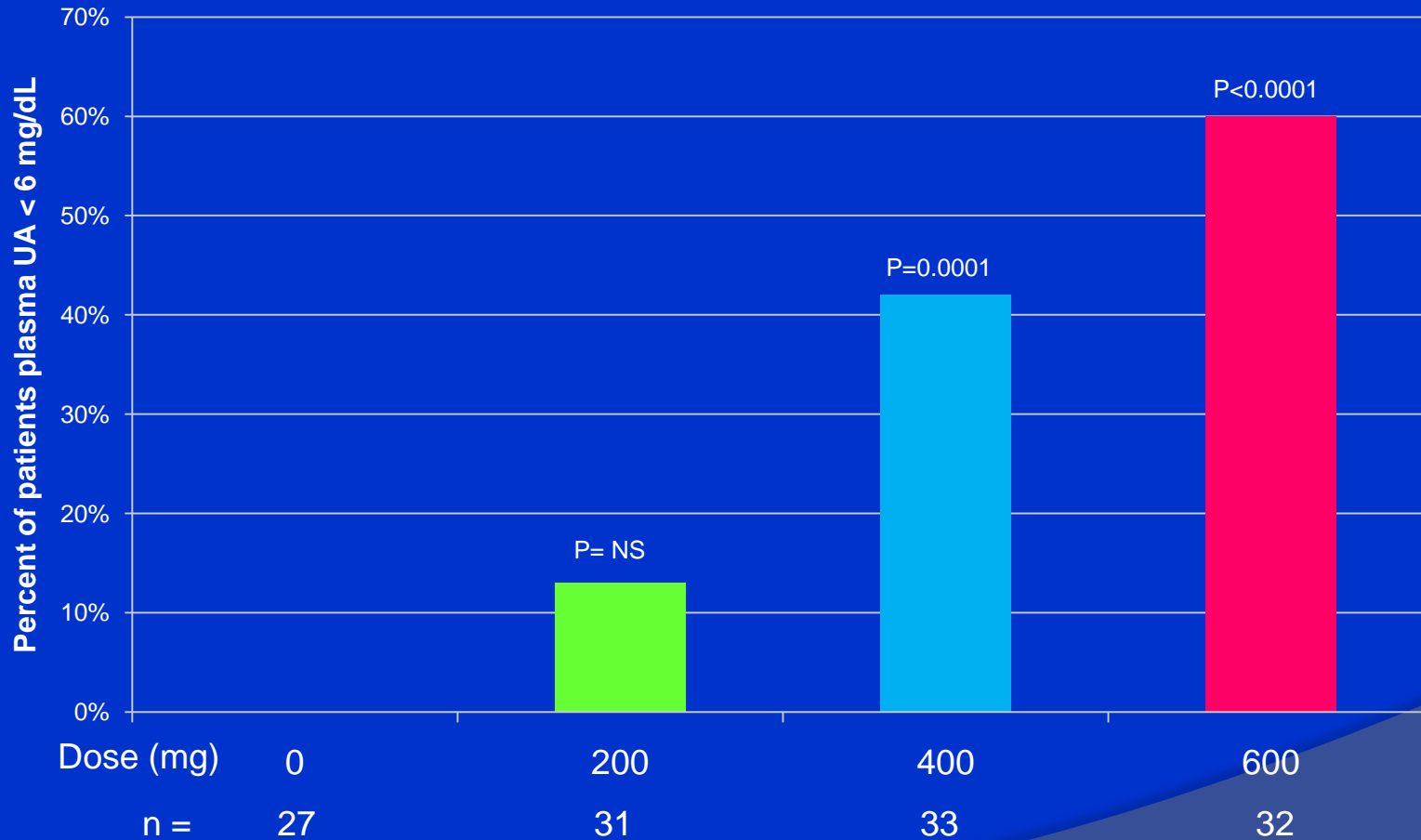


# Subject Characteristics

Baseline Parameter	200 mg Group	400 mg Group	600 mg Group	Placebo
	N=31	N=33	N=32	N=27
Mean age (years)	51	53	53	50
Male (%)	100	97	97	100
Caucasian (%)	97	97	94	96
BMI (kg/m <sup>2</sup> )	31	30	31	31
Median sUA	9.6	9.6	10.0	9.2
Mean calculated CrCL from 24-hr urine (mL/min)	99	96	87	108*
Presence of tophus (%)	16	27	16	19
Prior ULT (%)	26	45	31	37
Mean gout flares in prior year (n, range)	3.0 (0-8)	3.8 (0-30)	3.6 (0-11)	3.6 (0-11)

\*p<0.05 compared to pooled RDEA594

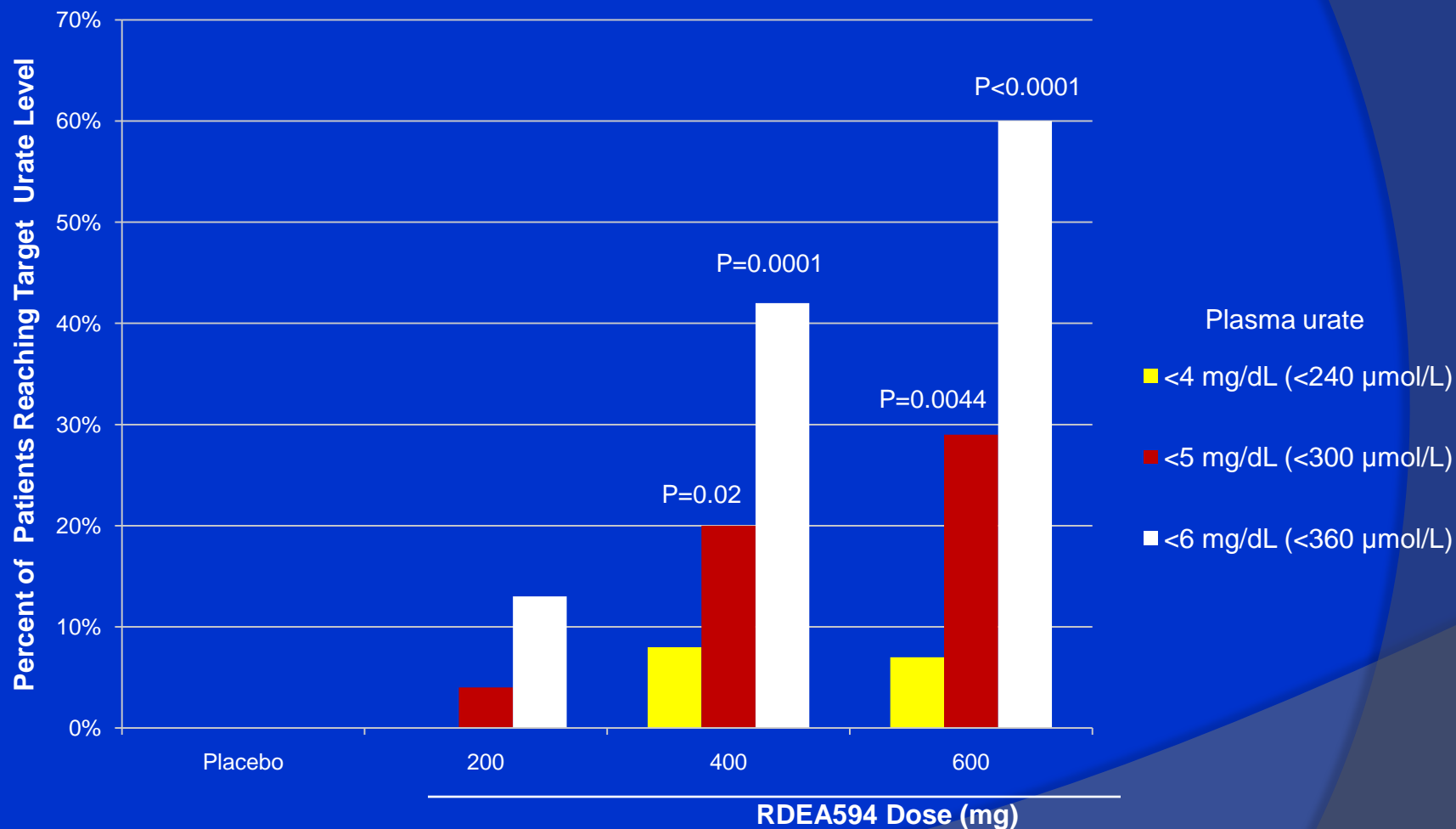
# Primary Endpoint – Percent of Patients < 6 mg/dL (360 μmol/L) at Week 4



Plasma urate assay using direct method of analysis.

ITT population

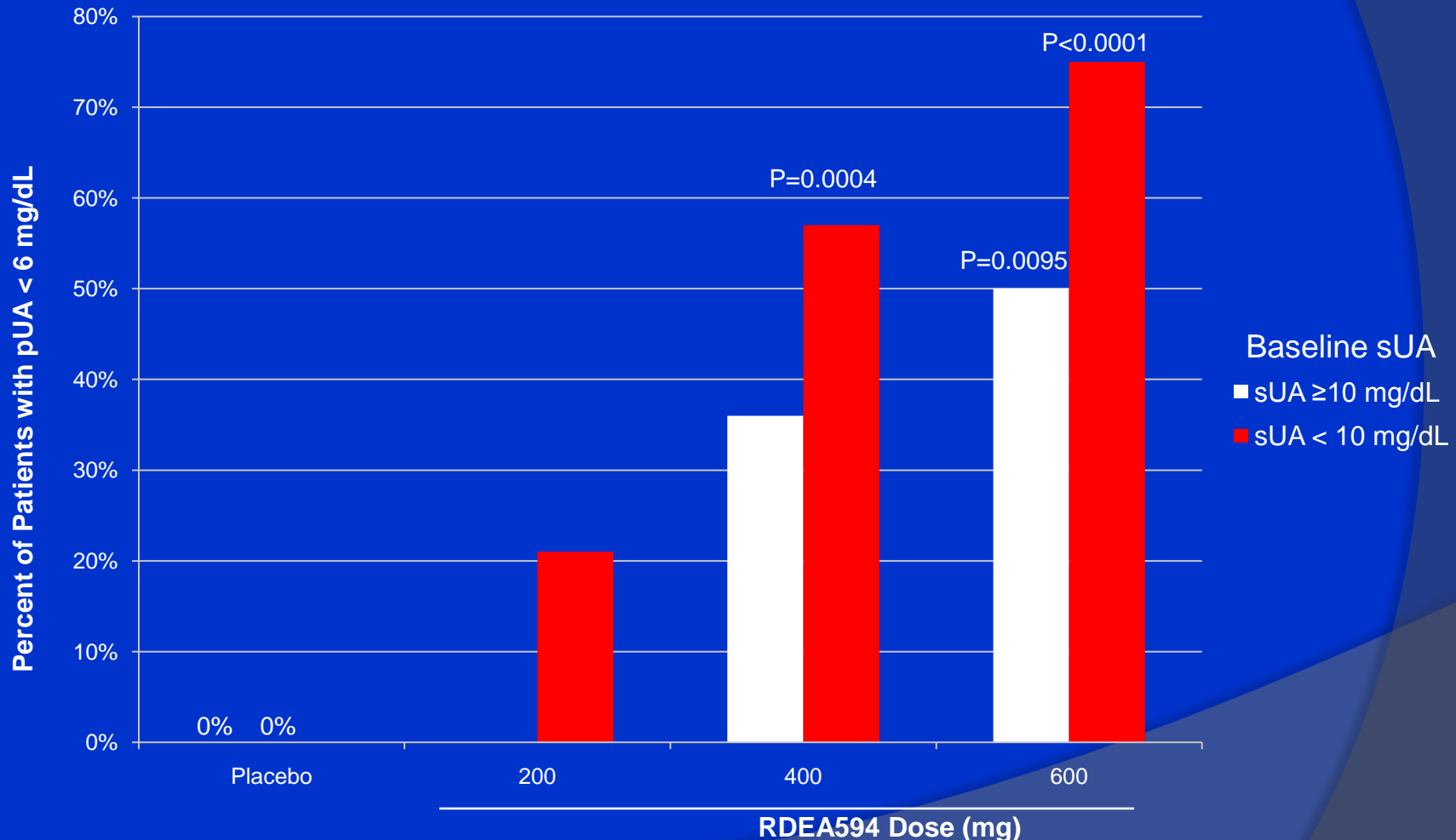
# Proportion of Patients Achieving Target Urate Reduction Levels at Week 4



Plasma urate assay using direct method of analysis.

ITT population

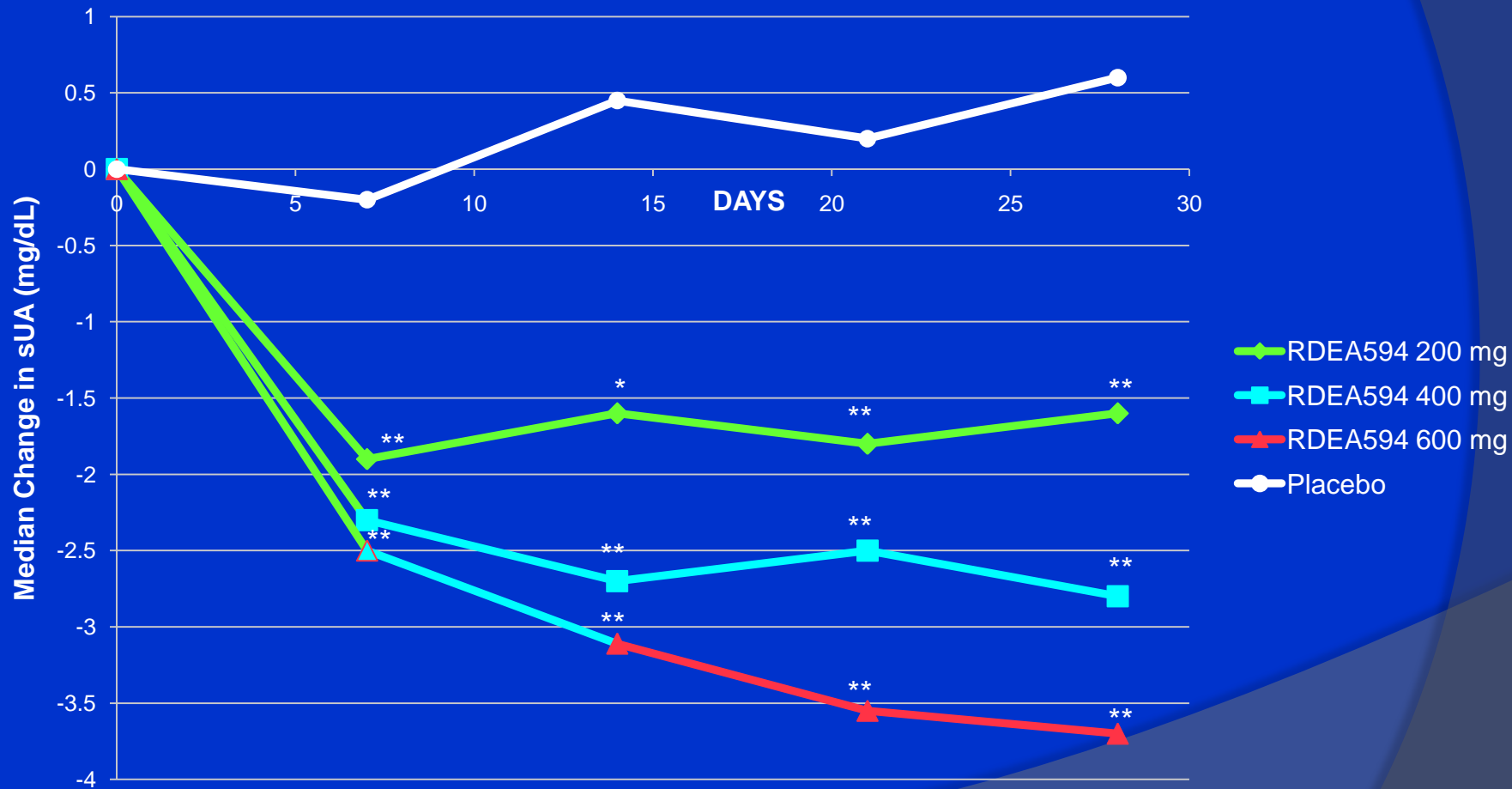
# Response Rates at Week 4 for Urate Reduction by Baseline Urate Levels



Plasma urate assay for response using direct method of analysis.

ITT population

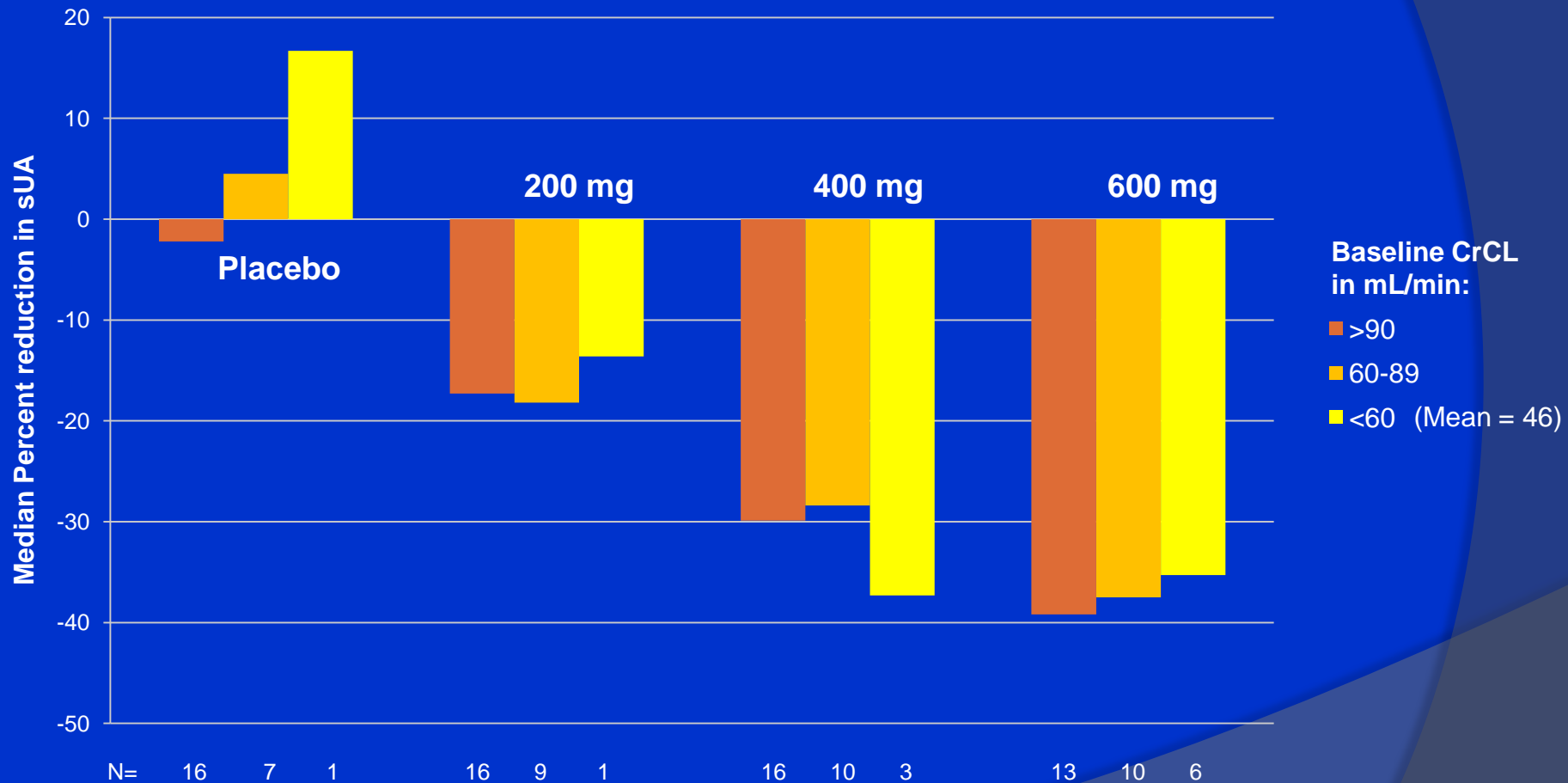
# Secondary Endpoint - Median Change in Serum Urate



\* $p=0.004$ ; \*\* $p<0.0001$  versus placebo

Serum urate assay using indirect method of analysis.

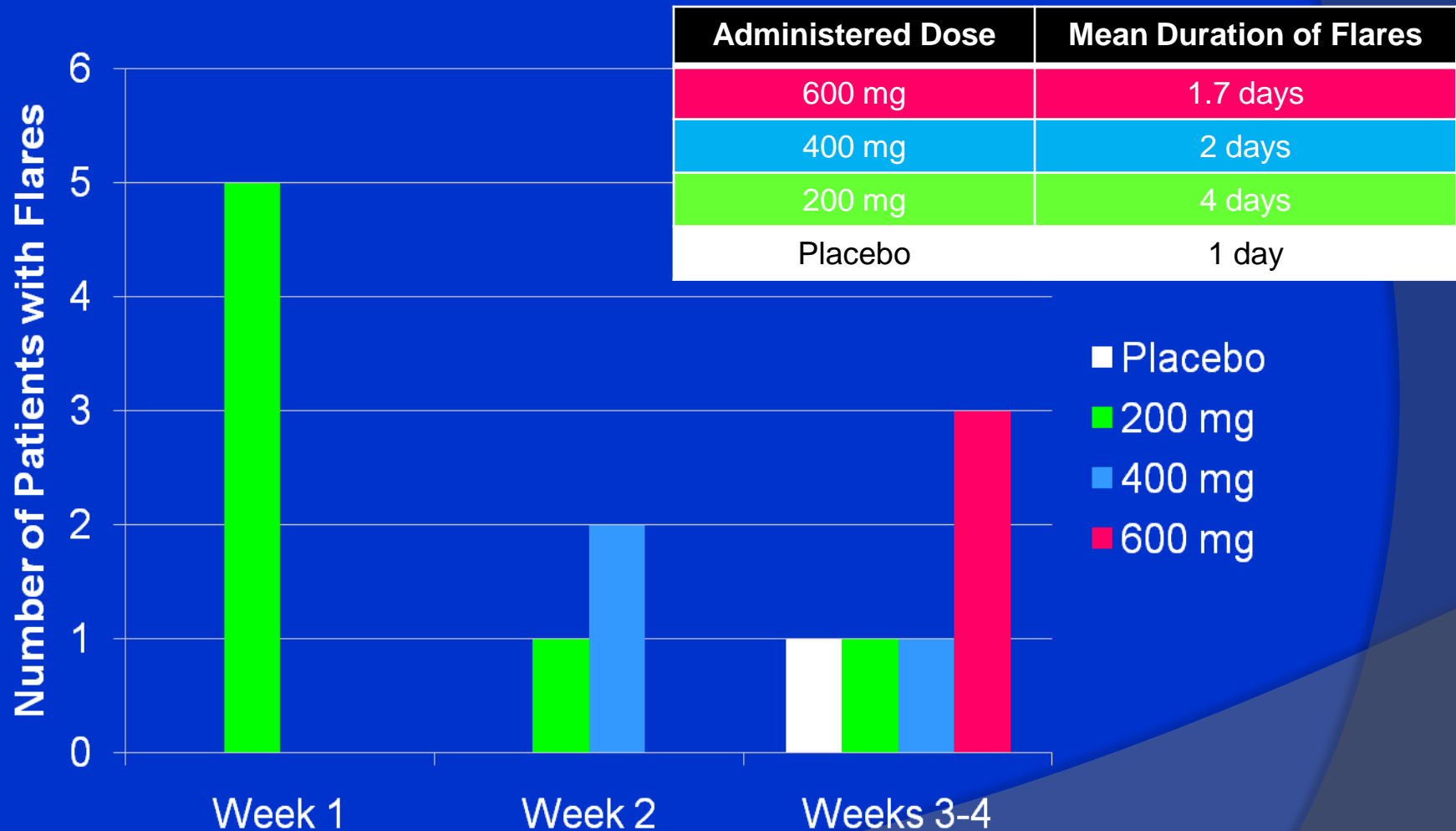
# Consistent sUA Reduction with Reduced Creatinine Clearance\*



Serum urate assay using indirect method of analysis.

\* CrCl calculated from 24-hr urine clearance.

# Number of Patients with Flares by Administered Dose



# Patients with Grade 1-2 Elevations in Serum Creatinine (SCr) and Normal Baselines

	Randomized Dose			
	RDEA594 200 mg (n=31)	RDEA594 400 mg (n=33)	RDEA594 600 mg (n=32)	Placebo (n=27)
Patients with Grade 1-2 Elevations in Serum Creatinine at Day 28	2 (6%)	2 (6%)	2 (6%)	1 (4%)

- Same rate of transient sCR elevations during the screening period
- No grade 3 or 4 elevations
- SCr elevations often associated with flares
- Four patients randomized to RDEA594 had elevated SCr at baseline
  - Two normalized on drug and two remained elevated

# Incidence of the Most Frequent Adverse Events\*

Adverse Events	RDEA594 Dose Group			
	200mg (N=31)	400mg (N=33)	600mg (N=32)	Placebo (N=27)
Any Adverse Event	2 (7%)	5 (15%)	5 (16%)	4 (15%)
Diarrhea	1 (3%)	0	1 (3%)	1 (4%)
Dyspepsia	0	2 (6%)	0	0
Headache	0	1 (3%)	1 (3%)	2 (7%)

\*Adverse events reported by at least 2 subjects that were considered at least possibly related to treatment

- No Serious Adverse Events
- Two discontinuations due to adverse events, both on 400 mg dose:
  - one patient with vertigo, and
  - one patient with elevated sCR that returned to normal range while receiving RDEA594

# Conclusions

- RDEA594 produced rapid and sustained reductions in urate levels, with statistically and clinically significant increases in response rates with the 400 mg and 600 mg doses
- No safety concerns and no dose-related side effects were observed
- Profile of RDEA594 has been consistent across multiple clinical studies
- **Results of this trial demonstrate that RDEA594 is a promising new drug for the treatment of hyperuricemia in gout patients and support the initiation of Phase 3 clinical trials**

# Acknowledgements

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➤ *Investigators and their staff members:*

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