Journal Club

10/13/2017

Nada Elmagboul, MD

Case

- 66 yo veteran with multiple comorbidities including gout
- Recurrent hospital admissions 2/2 gout flares
- Difficult to control with mean SUA 8
  - Non compliance
  - intolerance to Allopurinol > 100 mg, Febuxostat and Probenecid
- Started Lesinurad 200 mg with Allopurinol 100 mg
  - Good tolerance
  - Last SUA 5.7

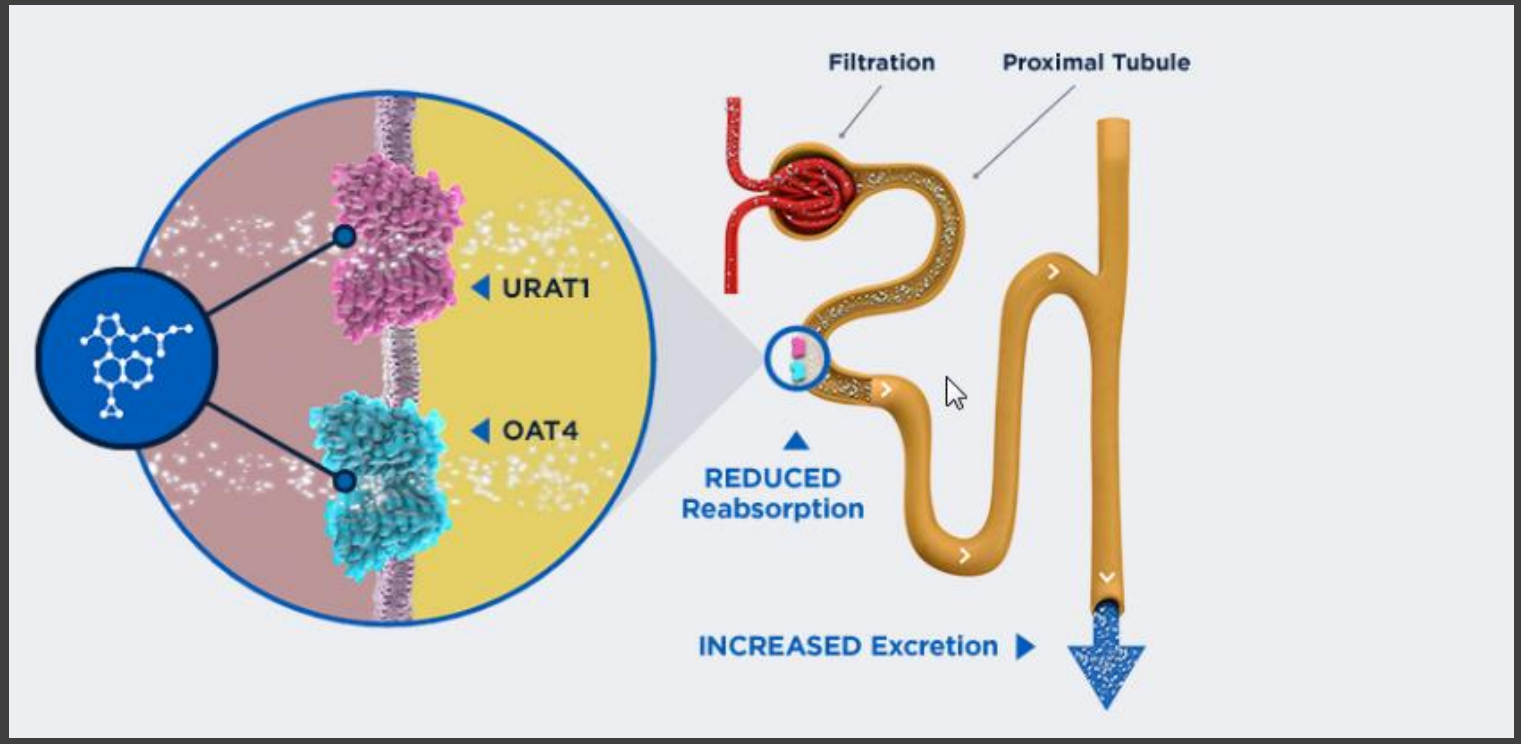
Introduction

- Treatment goal SUA
  - <6 mg/dl
  - <5 mg/dl in severe/ Tophaceous gout

- ULT
  - Xanthine oxidase inhibitors (XOI)
  - uricosuric agents

Lesinurad

- FDA approved 2015 as Combination treatment with XOI
- Oral selective inhibitor of the URAT1 and OAT4 uric acid (UA) transporters



2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis

DINESH KHANNA,[1] PUJA P. KHANNA,[1] JOHN D. FITZGERALD,[2] MANJIT K. SINGH,[3] SANGMEE BAE,[2] TUHINA NEOGI,[4] MICHAEL H. PILLINGER,[5] JOAN MERILL,[6] SUSAN LEE,[7] SHRADDHA PRAKASH,[2] MARIAN KALDAS,[2] MANEESH GOGIA,[2] FERNANDO PEREZ-RUIZ,[8] WILL TAYLOR,[9] FRÉDÉRIC LIOTÉ,[10] HYON CHOI,[4] JASVINDER A. SINGH,[11] NICOLA DALBETH,[12] SANFORD KAPLAN,[13] VANDANA NIYYAR,[14] DANIELLE JONES,[14] STEVEN A. YAROWS,[15] BLAKE ROESSLER,[1] GAIL KERR,[16] CHARLES KING,[17] GERALD LEVY,[18] DANIEL E. FURST,[2] N. LAWRENCE EDWARDS,[19] BRIAN MANDELL,[20] H. RALPH SCHUMACHER,[21] MARK ROBBINS,[22] NEIL WENGER,[2] AND ROBERT TERKELTAUB[7]

2016 updated EULAR evidence-based recommendations for the management of gout.

Richette P[1], Doherty M[2], Pascual E[3], Barskova V[4], Becce F[5], Castañeda-Sanabria J[6], Coyfish M[7], Guillo S[6], Jansen TL[8], Janssens H[9], Lioté F[1], Mallen C[10], Nuki G[11], Perez-Ruiz F[12], Pimentao J[13], Punzi L[14], Pywell T[7], So A[15], Tausche AK[16], Uhlig T[17], Zavada J[18], Zhang W[2], Tubach F[6], Bardin T[1].

If target SUA cannot be achieved with XOI, a uricosuric or combining a XOI with a uricosuric should be considered

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 203–212
DOI 10.1002/art.39840
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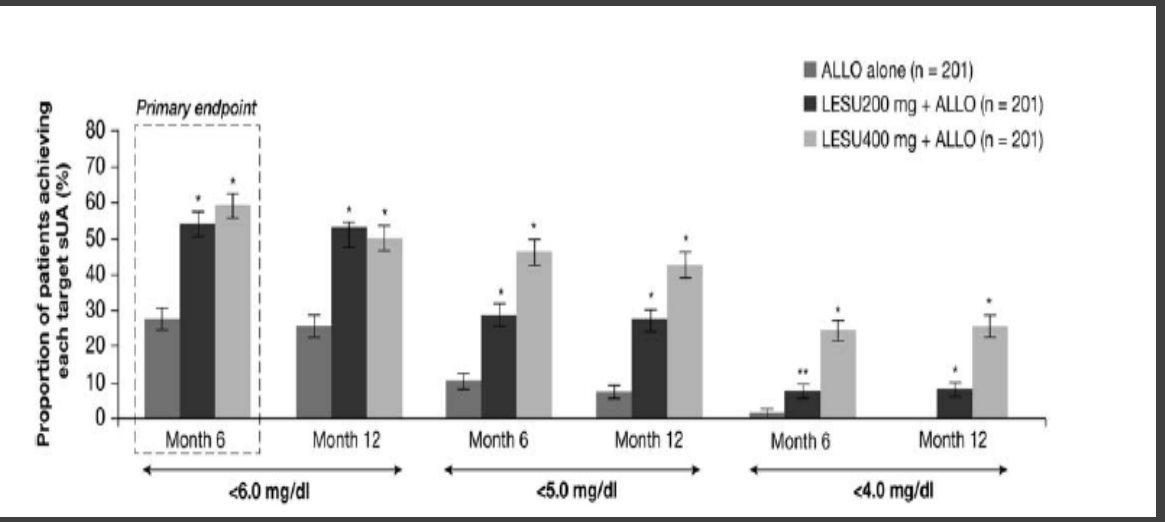
Lesinurad Combined With Allopurinol

A Randomized, Double-Blind, Placebo-Controlled Study in Gout Patients With an Inadequate Response to Standard-of-Care Allopurinol (a US-Based Study)

Kenneth G. Saag,[1] David Fitz-Patrick,[2] Jeff Kopicko,[3] Maple Fung,[3] Nihar Bhakta,[3] Scott Adler,[4] Chris Storgard,[3] Scott Baumgartner,[3] and Michael A. Becker[5]

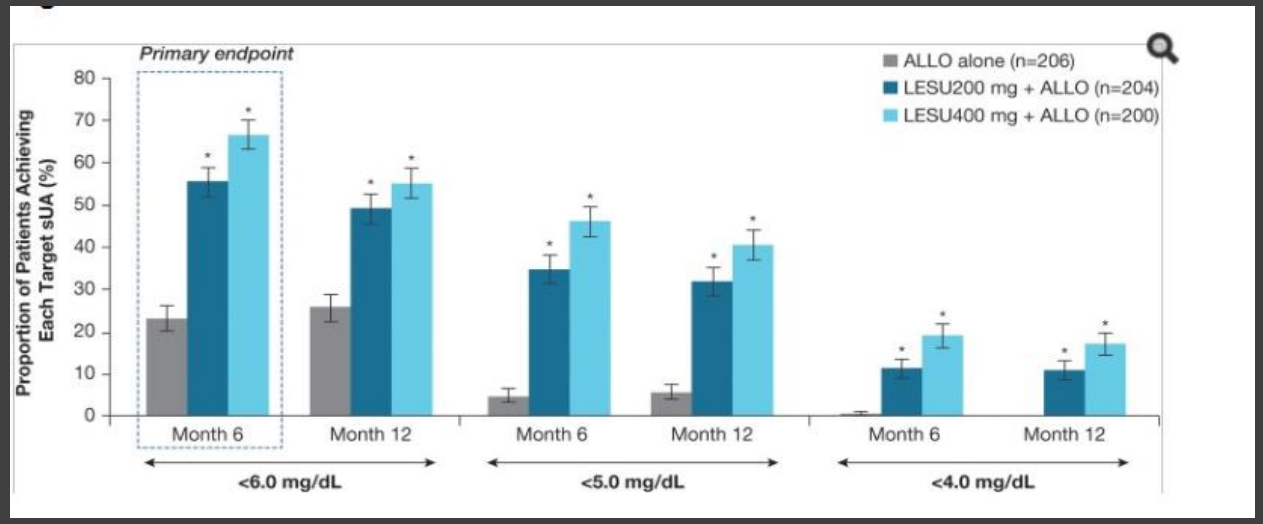


OPEN ACCESS

EXTENDED REPORT

Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study)

Thomas Bardin,[1] Robert T Keenan,[2] Puja P Khanna,[3] Jeff Kopicko,[4] Maple Fung,[5] Nihar Bhakta,[5] Scott Adler,[6] Chris Storgard,[5] Scott Baumgartner,[7] Alexander So[8]



LSU not significantly superior to ALLO alone in terms of the secondary end points.
safety profile of LSU 200-mg dose was comparable to ALLO alone except for higher incidences of reversible elevations of serum creatinine levels.

RHEUMATOLOGY

Rheumatology 2014;53:2167–2174
doi:10.1093/rheumatology/ket487
Advance Access publication 8 February 2014

Original article

Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia

Roy Fleischmann[1], Bradley Kerr[2], Li-Tain Yeh[3], Matt Suster[4], Zancong Shen[3], Elizabeth Polvent[2], Vijay Hingorani[2], Barry Quart[4], Kimberly Manhard[5], Jeffrey N. Miner[6] and Scott Baumgartner[4], on behalf of the RDEA594-111 Study Group

- Phase IB, multicenter, open-label, multiple-dose study of pts with sUA >8 mg/dl
- Febuxostat 40 or 80 mg/day plus Lesinurad 400 or 600 mg/day resulted in 100% of subjects achieving sUA <6 mg/dl and up to 100% achieving sUA <5 mg/dl.
- Combination was well tolerated.

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 9, September 2017, pp 1903–1913
DOI 10.1002/art.40159
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Lesinurad, a Selective Uric Acid Reabsorption Inhibitor, in Combination With Febuxostat in Patients With Tophaceous Gout

Findings of a Phase III Clinical Trial

Nicola Dalbeth,[1] Graeme Jones,[2] Robert Terkeltaub,[3] Dinesh Khanna,[4] Jeff Kopicko,[5] Nihar Bhakta,[5] Scott Adler,[6] Maple Fung,[5] Chris Storgard,[5] Scott Baumgartner,[5] and Fernando Perez-Ruiz[7]

THE CRYSTAL TRIAL

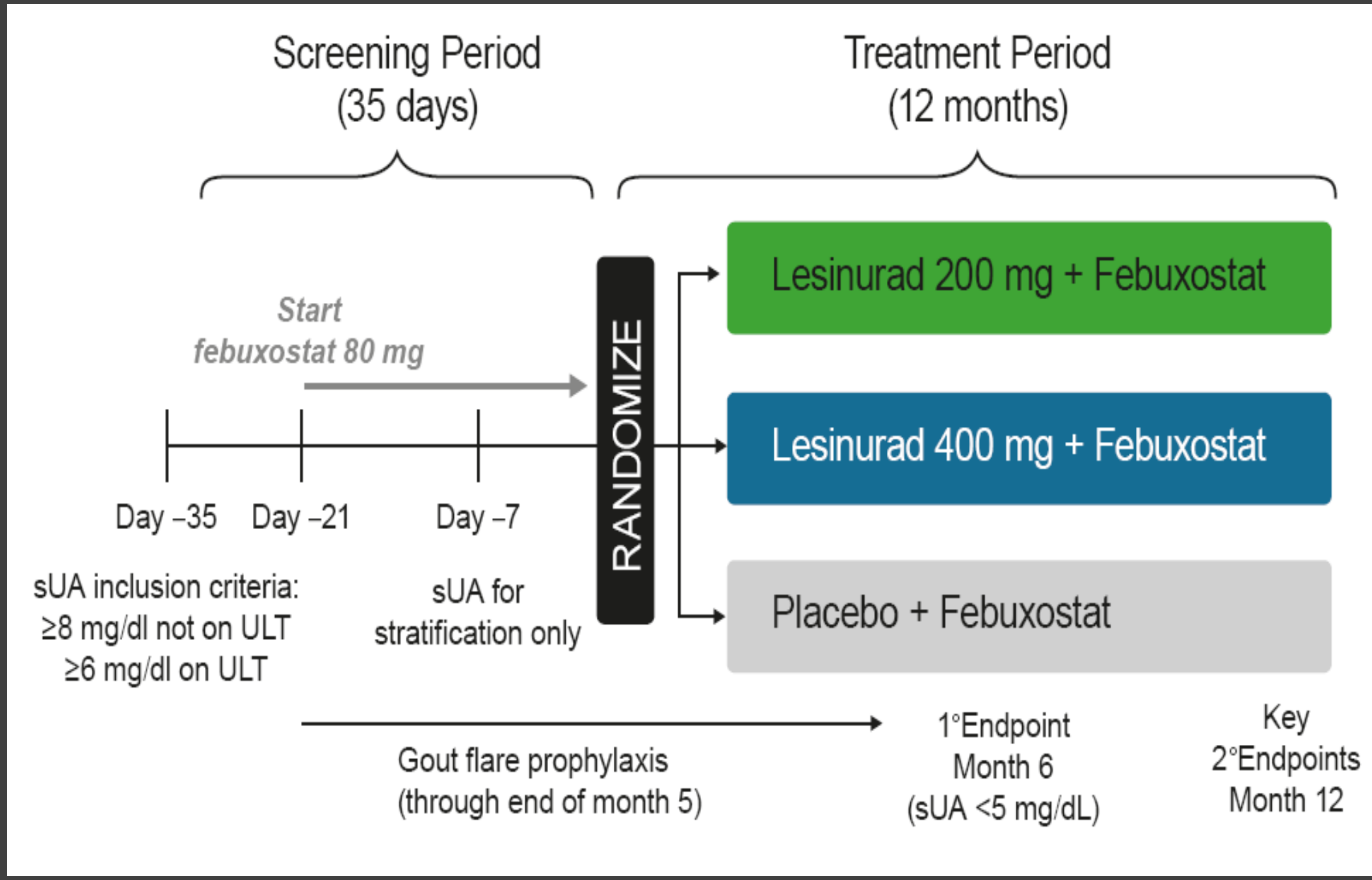

Screening Period
(35 days)
Treatment Period
(12 months)
Start
febuxostat 80 mg
RANDOMIZE
Lesinurad 200 mg + Febuxostat
Lesinurad 400 mg + Febuxostat
Placebo + Febuxostat
Day –35
Day –21
Day –7
sUA inclusion criteria:
≥8 mg/dl not on ULT
≥6 mg/dl on ULT
sUA for
stratification only
Gout flare prophylaxis
(through end of month 5)
1°Endpoint
Month 6
(sUA <5 mg/dL)
Key
2°Endpoints
Month 12

Table 1. Demographic and baseline clinical characteristics of the study patients, intent-to-treat population*

	Placebo plus febuxostat (n = 109)	Lesinurad 200 mg plus febuxostat (n = 106)	Lesinurad 400 mg plus febuxostat (n = 109)	Total (n = 324)
Age, mean ± SD years	54.6 ± 10.9	54.2 ± 11.0	53.3 ± 11.2	54.1 ± 11.0
Male, no. (%)	107 (98.2)	100 (94.3)	102 (93.6)	309 (95.4)
Race, no. (%)				
Asian	6 (5.5)	8 (7.5)	6 (5.5)	20 (6.2)
Black/African American	8 (7.3)	14 (13.2)	13 (11.9)	35 (10.8)
White	94 (86.2)	80 (75.5)	85 (78.0)	259 (79.9)
Other	1 (0.9)	4 (3.8)	5 (4.6)	10 (3.3)
Ethnicity, no. (%)				
Hispanic/Latino	9 (8.3)	7 (6.6)	5 (4.6)	21 (6.5)
Not Hispanic/Latino	100 (91.7)	99 (93.4)	104 (95.4)	303 (93.5)
Body weight, mean ± SD kg	99.4 ± 21.0	110.3 ± 19.5	98.8 ± 21.4	99.5 ± 20.6
Body mass index, mean ± SD kg/m^2	32.0 ± 5.6	32.4 ± 5.6	31.6 ± 5.7	32.0 ± 5.6
Duration since gout diagnosis, mean ± SD years	15.2 ± 10.9	15.8 ± 11.0	13.2 ± 10.6	14.7 ± 10.9
No. of target tophi at baseline, mean ± SD	1.9 ± 1.3	1.8 ± 1.3	1.8 ± 1.2	1.8 ± 1.2
Total area of target tophi at baseline, mean ± SD mm^2	291.1 ± 246.4	310.1 ± 227.9	280.3 ± 230.3	293.6 ± 234.6
No. of gout flares in previous 12 months, mean ± SD	6.1 ± 5.1	6.9 ± 11.2	7.0 ± 7.4	6.7 ± 8.2
Gout flare prophylaxis at baseline, no. (%)				
Colchicine	87 (79.8)	95 (89.6)	94 (86.2)	276 (85.2)
NSAIDs	22 (20.2)	9 (8.5)	15 (13.8)	46 (14.2)
Renal function (estimated CrCl) at baseline, no. (%)				
≥90 ml/minute	31 (28.4)	37 (34.9)	42 (38.5)	110 (34.0)
60 to <90 ml/minute	53 (48.6)	41 (38.7)	45 (41.3)	139 (42.9)
<60 ml/minute	25 (22.9)	28 (26.4)	22 (20.2)	75 (23.1)
Thiazide/thiazide-like diuretic at baseline, no. (%)	11 (10.1)	15 (14.2)	18 (16.5)	44 (13.6)
Serum UA, mean ± SD mg/dl				
At screening	8.8 ± 1.5	8.7 ± 1.6	8.6 ± 1.8	8.7 ± 1.6
At baseline	5.2 ± 1.5	5.4 ± 1.7	5.3 ± 1.6	5.3 ± 1.6
Any CV comorbidity or CV disease history (combined), no. (%)†	80 (73.4)	81 (76.4)	79 (72.5)	240 (74.1)
Hypertension	65 (59.6)	70 (66.0)	62 (56.9)	197 (60.8)
Hyperlipidemia	46 (42.2)	42 (39.6)	50 (45.9)	138 (42.6)
Diabetes mellitus	17 (15.6)	21 (19.8)	14 (12.8)	52 (16.0)
Myocardial infarction	7 (6.4)	5 (4.7)	7 (6.4)	19 (5.9)
Kidney stones	16 (14.7)	15 (14.2)	11 (10.1)	42 (13.0)

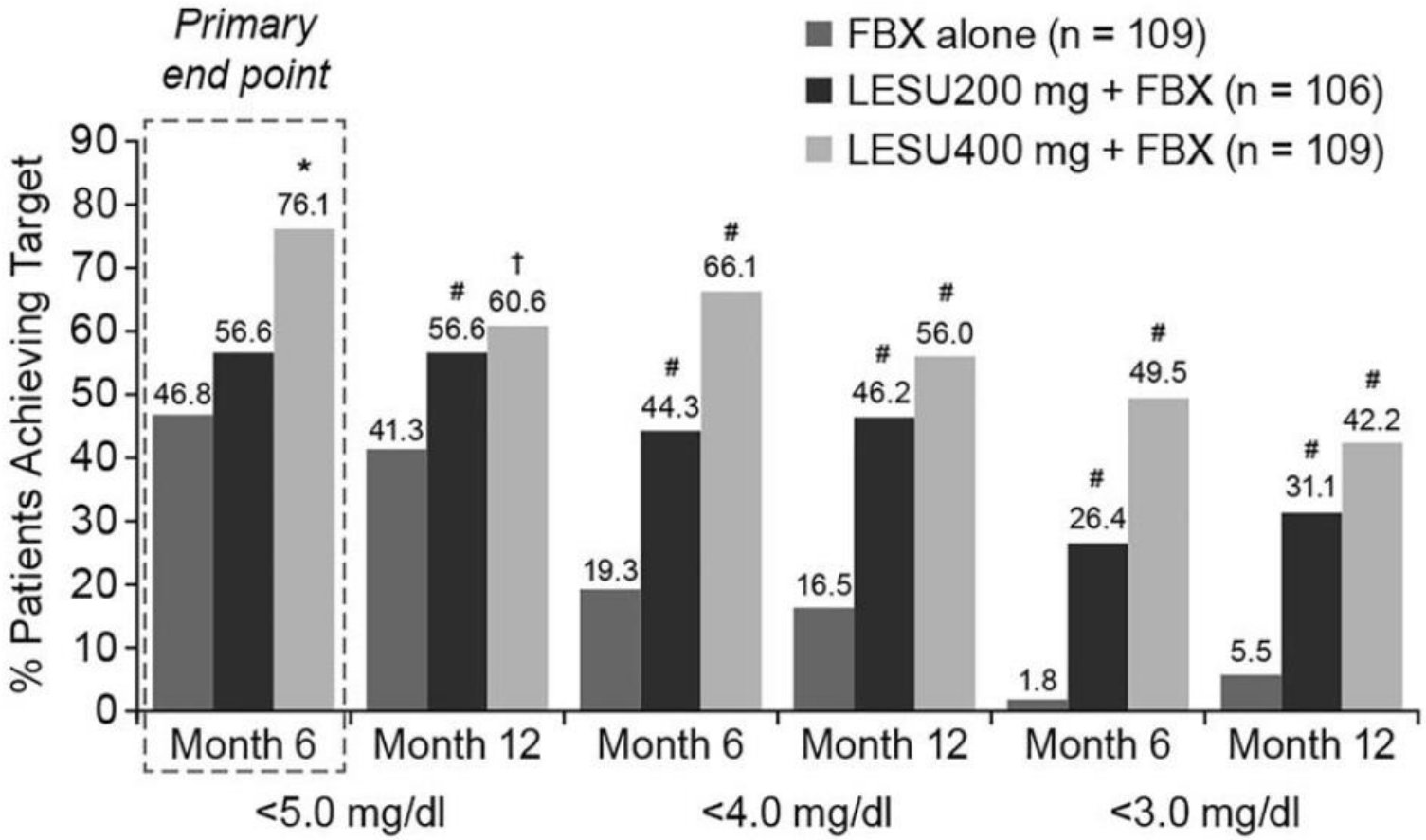
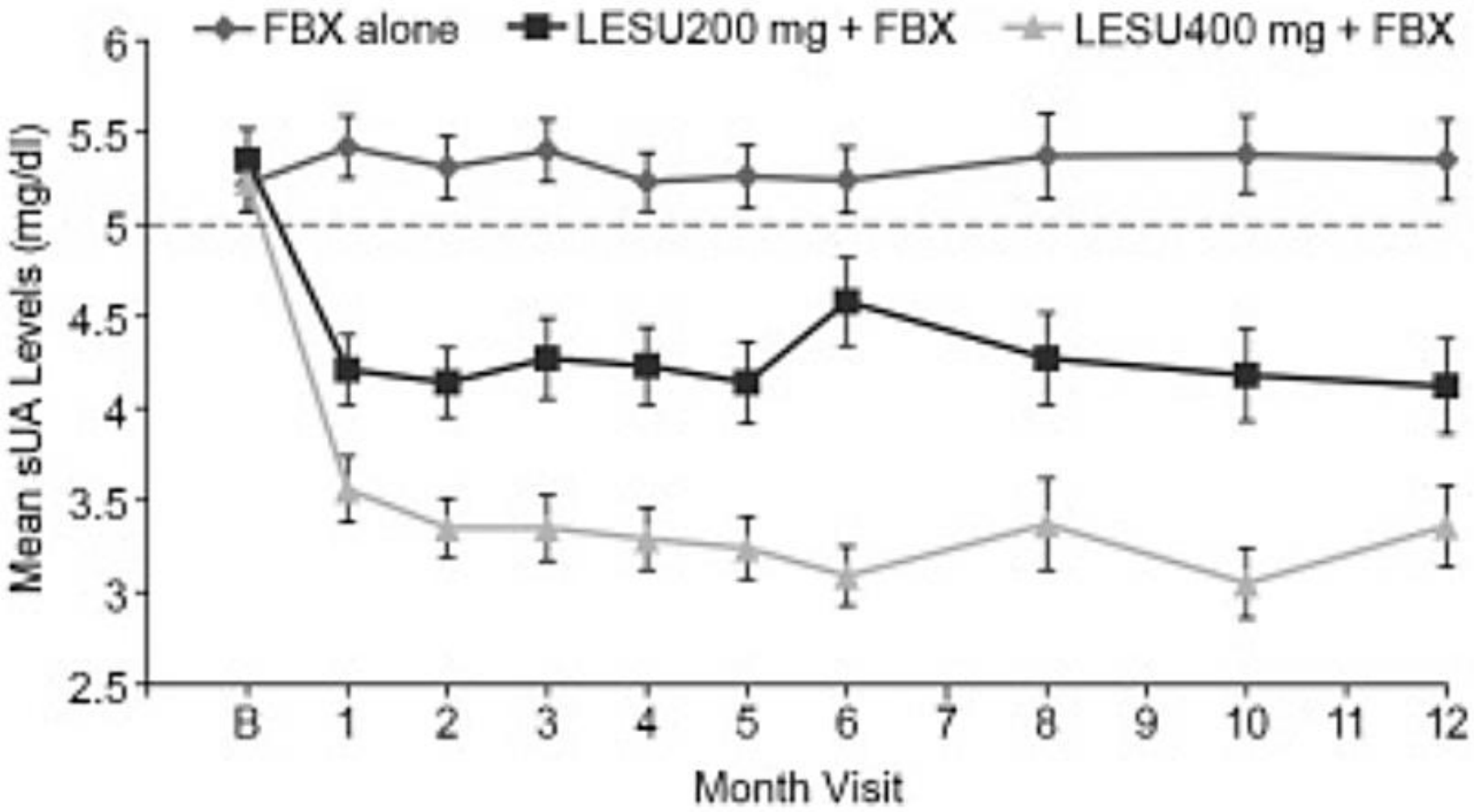
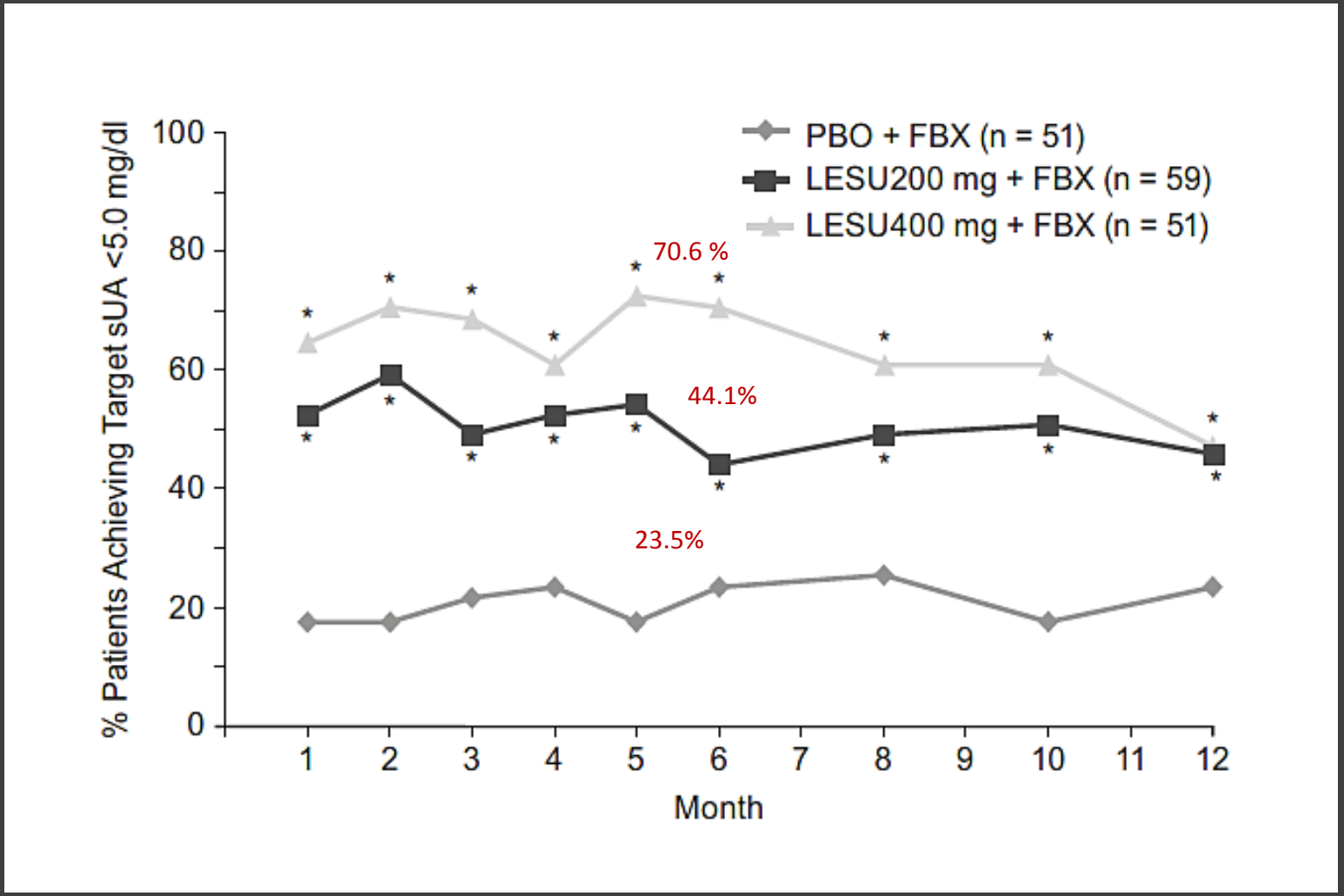


Figure 2. Proportion of patients achieving serum uric acid (UA) targets of <5.0 mg/dl, <4.0 mg/dl, and <3.0 mg/dl at month 6 and month 12 (intent-to-treat population). The primary end point was the proportion of patients achieving a serum UA level of <5.0 mg/dl at month 6, with non-responder imputation. * = $P < 0.0001$; # = $P < 0.0001$ versus febuxostat (FBX) alone, adjusted for multiple comparisons; † = $P < 0.01$ versus febuxostat alone, without adjustment for multiple comparisons. LESU = lesinurad.


FBX alone
LESU200 mg + FBX
LESU400 mg + FBX
Mean sUA Levels (mg/dl)
6
5.5
5
4.5
4
3.5
3
2.5
B
1
2
3
4
5
6
7
8
9
10
11
12
Month Visit



Supplemental Figure. Proportion of patients with a sUA <5.0 mg/dl by visit – Nonresponder imputation (ITT population subgroup with baseline sUA ≥5.0 mg/dl).

Secondary end points

l. Tophus resolution ≥1 target tophus at 12 months:

Treatment	Placebo + Febuxostat	Lesinurad 200 mg + Febuxostat 80 mg	Lesinurad 400 mg + Febuxostat 80 mg
Number of patients	109	106	109

- **Complete** :

  21.1% 25.5% 30.3%

- **Partial**:

  45.9% 49.1% 51.4%

- **No statically significant difference**

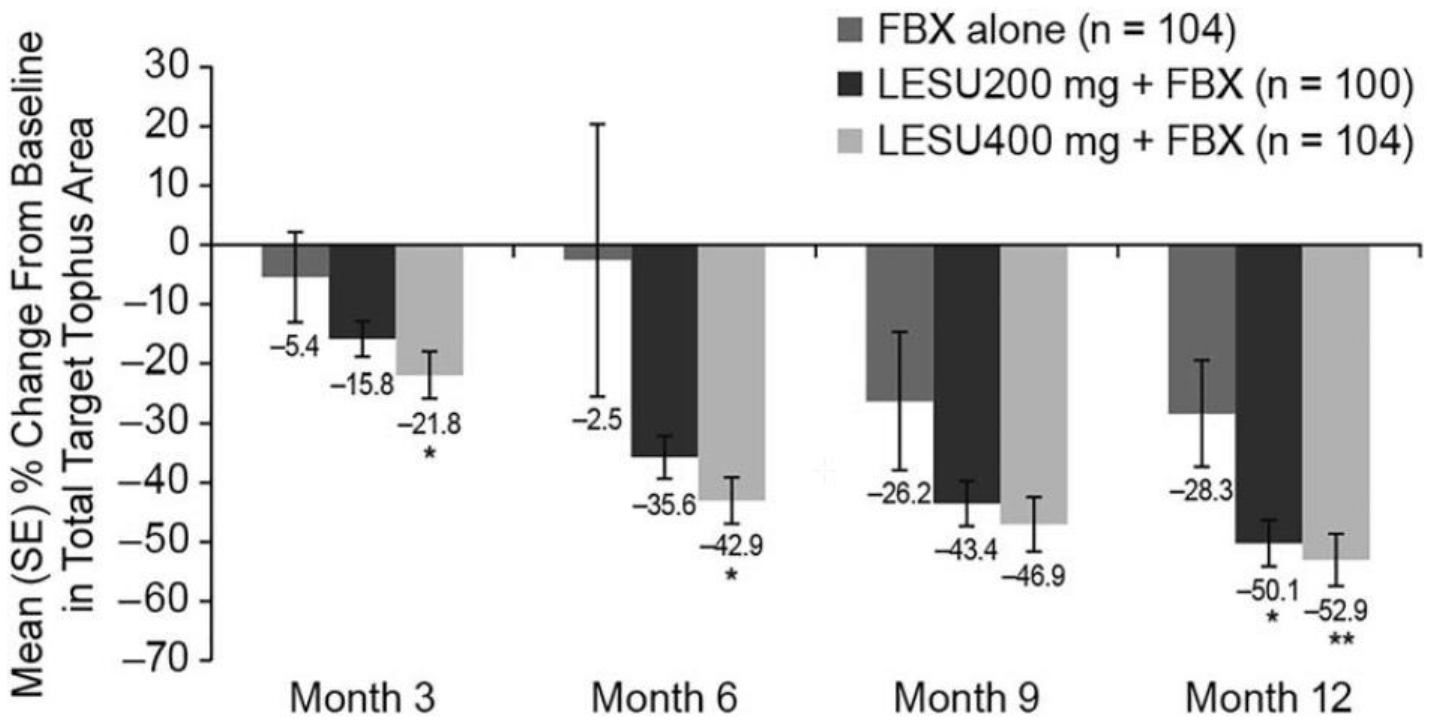


Figure 4. Percentage change in the sum of the areas of all target tophi versus baseline (mm^2) at each study visit in the last observation carried forward imputation (intent-to-treat population). Values are the mean ± SEM. $* = P < 0.05$; $** = P < 0.01$ versus febuxostat (FBX) alone. LESU = lesinurad.

II. Flares requiring treatment

Treatment	Placebo + Febuxostat	Lesinurad 200 mg + Febuxostat 80 mg	Lesinurad 400 mg + Febuxostat 80 mg
Number of patients	109	106	109

End of 6-12 months:

1.2±2.7 1.4±2.5 0.7±1.2

Table 2. Overall summary of treatment-emergent adverse events and renal-related adverse events (safety population)*

Adverse event category	Placebo plus febuxostat (n = 109)	Lesinurad 200 mg plus febuxostat (n = 106)	Lesinurad 400 mg plus febuxostat (n = 109)
Any TEAE	79 (72.5)	87 (82.1)	90 (82.6)
Any TEAE with RCTC toxicity of grade 3 or 4	13 (11.9)	11 (10.4)	11 (10.1)
Any TEAE possibly related to randomized study medication	22 (20.2)	25 (23.6)	28 (25.7)
Any serious TEAE	10 (9.2)	6 (5.7)	9 (8.3)
Any fatal TEAE	0	1 (0.9)	1 (0.9)
Any TEAE leading to discontinuation of randomized study medication	9 (8.3)	9 (8.5)	15 (13.8)
Any TEAE leading to study withdrawal	4 (3.7)	7 (6.6)	7 (6.4)
Renal-related AEs			
Any renal-related AEs	6 (5.5)	9 (8.5)	11 (10.1)
Serious renal-related AEs	1 (0.9)	0 (0)	2 (1.8)
Acute renal failure	1 (0.9)	0	1 (0.9)
Chronic renal failure	0	0	1 (0.9)
Kidney stones	4 (3.7)	1 (0.9)	2 (1.8)
Serum creatinine elevation			
≥1.5 times baseline†	3 (2.8)	5 (4.7)	11 (10.1)
Cases unresolved at last study visit†‡	0	1	1
≥2.0 times baseline	0 (0)	3 (2.8)	6 (5.5)
Cases unresolved at last study visit‡	0	1	1

- Serious Cardiovascular events:

Treatment	Placebo + Febuxostat	Lesinurad 200 mg + Febuxostat 80 mg	Lesinurad 400 mg + Febuxostat 80 mg
Number of patients	109	106	109
	0.9%	2.8%	3.7%

Conclusion

- Lesinurad in combination with an XOI, is an emerging option for the treatment of hyperuricemia in adults with gout who have not achieved target sUA levels with an XOI alone
- Combination with Lesinurad 400 mg is more potent
- Combination with Lesinurad 200 mg achieved SUA <5 within 12 month
- Results were minimally associated with improvements in flares and tophi resolution
- Regimen with Lesinurad 200 mg was generally well tolerated .

Limitations

- High percentage of pts achieving sUA <5 at randomization
- Relative short study time
- Predominance of males and white race

T H A N K Y O U